A decision-theoretic framework for the application of cost-effectiveness analysis in regulatory processes

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Abstract

Cost-effectiveness analysis (CEA) represents the most important tool in the health economics literature to quantify and qualify the reasoning behind the optimal decision process in terms of the allocation of resources to a given health intervention. However, the practical application of CEA in real regulatory process is often thwarted by some critical barriers and decisions in clinical practice are frequently influenced by factors that do not contribute to an efficient resources allocation, including inappropriate drug prescription and utilisation. We propose in this paper an approach that is firmly based in a Bayesian decision-theoretic approach and that combines the use of well known tools (such as the expected value of information) to the regulatory process.

Key words: Bayesian decision theory, Health economic evaluation, Sensitivity analysis, Regulatory process.
1 Introduction

Since the milestone paper by Weinstein & Stason (1977), cost-effectiveness techniques have long been established in the health care arena. At present, this type of economic analysis (as well as the very much related cost-utility analysis) is the most frequently used in the evaluation of new biomedical technologies (pharmaceutical drugs and procedures), and much literature has been devoted to its formalisation (Briggs et al. 2006, Willan & Briggs 2006), increasingly often under a Bayesian statistical approach (Briggs 2001, O’Hagan & Stevens 2001, O’Hagan et al. 2001, Parmigiani 2002, Spiegelhalter & Best 2003, Spiegelhalter et al. 2004).

However, the application of this technique to real practice decision making has found several critical barriers: in Italy, for instance, cost-effectiveness is hardly considered when deciding about marketing, reimbursement or pricing of new technologies. In effect, the decisions in clinical practice are frequently influenced by factors that do not contribute to an efficient resource allocation, including inappropriate drug prescription and utilisation. In this sense, the assumption that the market is able to determine the optimal mix (in terms of health benefits) is hardly reasonable.

From a different point of view, the regulator is frequently involved in decisions on the authorisation of new drugs having a low incremental effectiveness with respect to already available ones, at a more than proportional incremental cost. Furthermore, clinical practice — and the regulator’s decisions in particular — can not move towards a rapid substitution of the available therapeutic options with a new one that is more cost-effective. In fact, although it could be exceeded by a new innovative intervention, a therapeutic option used for a long time remains effective and often cost-effective at least for a smaller group of patients (or patient subgroup).

The objective of this paper is to propose a rational approach to the analysis of cost-effectiveness of several products having indication in the same homogeneous therapeutic category, with particular reference to the regulatory process. We base our analysis in a Bayesian decision-theoretic framework and we propose an extension of the application of well known tools such as the expected value of information. The paper is structured as follows: in section 2 we discuss the main criticisms to the application of cost-effectiveness analysis in the regulatory process, while in section 3 we present our model to incorporate decision-theoretic tools in the analysis and finally in section 4 we discuss our main conclusions.

2 Cost-effectiveness analysis and the evaluation process of a new chemical entity

Formally, cost-effectiveness analysis (CEA) is a systematic approach that enables the comparison of two or more alternative options based on the joint evaluation of costs and consequences, typically expressed as physical measures or in term of quality-adjusted life years (QALYs) in cost-utility analysis (Berger
The main purpose of CEA is to support decision makers in the identification of priorities in resource allocation among alternative treatments or health programmes. In presence of budget constraints, such as expenditure caps, the efficient allocation of available resources represents the most rational approach, and it is instrumental to the maximisation of health benefits for the overall population, while minimising the impact on expenditure.

However the application of CEA to decision making has also found several critical barriers. A first aspect is related to the utilisation of the results obtained by means of this analysis. In fact, although efficient scenarios of resource allocation are directly addressed, the real transfer to clinical practice may be contrasted by several rigidities in the health care organisation, which prevent an effective resource reallocation (Donaldson et al. 2002).

A second critical aspect is represented by the identification of a new technology as cost-effective, according to a threshold value of cost per QALY. In some local regulatory contexts, a specific value of cost per QALY is recognised as the reference in the definition of the reimbursement properties of new interventions. On the contrary, in other contexts it is used simply to address pharmaco-prescription. Despite the recognition of a representative value of cost per QALY is widely considered as a crucial issue, its stringent application to decision making may be frequently difficult for both theoretical and practical reasons.

- From the theoretical point of view, the dispute about the search of a context specific— as opposed to a social-value of QALYs (EuroQol 2008, Brouwer et al. 2008) is a recent matter of debate. Actually, in a specific local context, it might be preferable to gain QALYs in certain areas rather than in others (according to patients’ health condition and disease prognosis), for instance because of concerns with health equity. Therefore the decision maker may prefer interventions with lower cost-effectiveness ratio, if they produce a more valuable gain in QALYs. Furthermore, depending on the specific local health priorities, the decision maker may prefer health gains in some subgroups of the population to those in others (broader equity, Brouwer et al. 2008). Finally, while it is plausible that individuals with worse health are willing to pay more to improve their own quality of life, moving from the individual to societal perspective, the decision to devote almost all the resources to people in worse positions on the QALYs scale is a controversial topic (Brouwer et al. 2008).

- From the practical point of view, the introduction of new cost-effective interventions on the market can determine a critical budget impact, which can even be unsustainable. This is one of the reasons why many regulatory authorities (especially those involved in the governance of domestic pharmaceutical expenditure) are interested on information from budget impact analyses, although only few have developed guidelines on this (Trueman et al. 2001). Furthermore, although the ranking of several treatment options into league tables according to their incremental cost-effectiveness ratio has been recognized as a simple and transparent tool for resource
allocation, it presents some methodological constraints that has limited its widespread utilisation so far (Mauskopf et al. 2003).

A third critical aspect is represented by the influence of CEA on price definition of new drugs. On the one hand, the use of cost-effectiveness evaluation in licensing decisions may favour both a transparent decision making and a more efficient relative pricing. However, on the other hand in specific regulatory context where there is no free retail price, this economic approach may conflict with real available options in the definition of reimbursable price for the national health service provided by national normative and rules. For this reason, several authors have suggested that the main fourth hurdle effect (over efficacy, quality and safety) represented by CEA is not that on pricing of the single medicine, but rather derives from the rationalisation in the use of medicines available for the treatment of the same therapeutic indication (Taylor et al. 2004).

Despite these criticisms, interest in the relevance of CEA in decision processes has been recently renewed. As suggested by Detsky & Laupacis (2007), the application of cost-effectiveness should also consider others factors involved in the regulatory process (e.g. expenditure caps, national investments, market shares, etc.), as simpler modalities of utilisation of pharmacoeconomic results under the regulators’ perspective. In particular, the decision perspective depends on the position of the new drug within the regulatory process. At an earlier stage, the main actors are the national regulatory authorities, which are involved in general decisions influencing the prescription and utilisation of the new medicine. Later in the regulatory process other players in the overall health care system (e.g. Regions and local health units, in Italy) are also involved in decisions, until the final stage where the physician is called to prescribe a specific treatment to a given patient.

Arguably, the main drift in the decision process is the market authorisation. Before this stage, the assessment of new interventions is informed by (often incomplete) data on efficacy, while the alternative treatment strategies available in clinical practice could be different from that considered in phase III clinical experimentations. As a consequence, cost-effectiveness results for a new medicine can be unreliable a posteriori, after the appearance of conflicting evidences during phase IV (e.g., clinical effectiveness lower than expected clinical efficacy as estimated by randomized trials, inappropriate utilisation of the new medicine in the clinical practice, unexpected adverse drug reactions, etc.).

In summary, during a pre-market authorisation phase, the regulator should decide whether to grant reimbursement to a new product — and in some Countries also about the price — on the basis of uncertain evidence, regarding both clinical and economic outcomes. After market authorisation, although it is possible to answer some unresolved questions, relevant decisions in the public health perspective have been already taken, such as that on reimbursement which determines the overall access to the new treatment. With the exception of new evidence forcing the withdrawal of a particular drug from the market, or the limitation of its use, (this decision depends only on regulatory authority or on the pharmaceutical company), after market authorisation several actors are in-
volved in decisions that generally influence the market share of the new medicine with respect to the other treatments available for the same therapeutic indication (or disease). At this stage, CEA informs decision makers about treatment priority, leaving to the market the decision on the optimal mix of products for the treatment of a specific clinical condition.

3 A model for the integration of cost-effectiveness analysis within the regulatory context

The model that we propose takes into account the following basic assumptions.

1. It is impossible to obtain an immediate and perfect substitution of the market share of a product with that of another one having a better cost-effectiveness ratio;

2. Generally there are small differences among cost-effectiveness ratios of drugs in the same homogeneous therapeutic category (e.g., statins, proton pump inhibitors, etc.);

3. The introduction of new products can modify the overall cost-effectiveness level in the treatment of the therapeutic indication, but also the relative cost-effectiveness level of new drugs with respect to those currently licensed with the same indication can change;

4. The allocation of market shares among available products, useful in the context of the same homogeneous therapeutic category, could at least in part reflect the respective cost-effectiveness ratio. This relationship may be modified either by the introduction of a new chemical entity, or by the withdrawn of a marketed medicine, or by the patent’s expiration of a branded product.

We proceed here with a worked example to better explain how to account for these issues in a decision-theoretic framework, based on CEA. Suppose for simplicity that a particular disease is only treated by two different molecules, \( t = 0, 1 \). Treatment \( t = 0 \) is established on the market as the gold standard and has been the only available treatment up to now. Treatment \( t = 1 \) is about to enter the market as an innovative intervention.

According to the precepts of Bayesian decision theory, the process by which the decision maker arrives at the final decision on which treatment should be selected is the following:

1. Define a utility function, which describes the quality of the future decision \( t \) (i.e., the recommendation of the “best” treatment for the management of the disease under study). A common form of utility is the monetary net benefit (Stinnett & Mullahy 1998)

\[
  u(y, t) = ky - c,
\]
where $k$ is a “willingness to pay” (WTP) parameter used to put benefits ($e$) and costs ($c$) on the same scale.

b) For each possible treatment, calculate the expected utility

$$U^t := E[u(Y, t)],$$

that is the average value of the utility function, obtained averaging out the uncertainty about both the parameters and the individual variations.

c) Provided that the function $u(y, t)$ actually describes the utility of interest, treat the entire homogenous (sub)population with the most cost-effective treatment, i.e. the one which is associated with the maximum expected utility

$$U^* = \max_t U^t.$$

We set up a simple fictional model — see Baio & Dawid (2008) for a detailed specification of the statistical assumptions used for the observable variables and the population parameters. Table 1 shows the result of a simulation exercise developed for this model. For each of the $N = 1000$ iterations, we simulate a value of the parameters $\theta^1 = (\theta_{e1}, \theta_{c1})$ and $\theta^0 = (\theta_{e0}, \theta_{c0})$ from their distributions. From the definition of the model, these represent the population averages for the suitable measure of effectiveness and for the costs, for each available treatment. Therefore, for each simulation the quantity $U(\theta^t) = k\theta_{et} - \theta_{ct}$ represents the expected utility of treatment $t$ that would be obtained if the uncertainty about the parameters were resolved to the simulated values (for the sake of simplicity, we selected here a fixed value of $k = 25 000$. As is obvious, this analysis can — and should! — be replicated for any relevant value of $k$).

Taking the average over the large number of simulations (the rows of Table 1), accounts for the variability in the parameters distribution, thus providing the overall expected utility for each treatment. As one can see, the expected utilities are computed as $U^1 = 3 641.00$ and $U^0 = 1 413.89$. Consequently, in this case we have $U^* = U^1 = 3 641.00$ and therefore treatment $t = 1$ should be selected by the decision maker to replace the standard option $t = 0$.

### 3.1 Standard analysis: the expected value of information

Under the Bayesian approach, this procedure automatically accounts for uncertainty in the estimation of the parameters. However, a large part of the health economics literature suggests that the impact of this uncertainty in the final decision should be taken into account thoroughly, by means of a process known as Probabilistic Sensitivity Analysis (PSA), which is explicitly required by organisations such as NICE in the UK (Claxton et al. 2005).
Table 1: For each intervention and for each iteration of the model, the maximum expected utility (i.e. the optimal intervention) is typeset in italics – source: Baio & Dawid (2008)

A purely decision-theoretic tool to manage the uncertainty in the decision process through PSA is based on the value of information analysis (Howard 1966), an increasingly popular method in health economic evaluations (Felli & Hazen 1998, Felli & Hazen 1999, Claxton 1999, Claxton et al. 2001, Claxton et al. 2002, Ades et al. 2004, Brennan & Kharroubi 2005, Briggs et al. 2006, Fenwick et al. 2006). This is useful in order to minimize the negative consequences of uncertainty on the current decision, informing the decision maker about the most critical elements of uncertainty (unreliable clinical endpoint, unrepresentative comparators, short duration of follow-up, etc.), which may influence the overall pharmacoeconomic assessment of the new intervention.

The value of information is defined as

$$\text{VDI}(\theta) := U^*(\theta) - U^*,$$

where $U^*(\theta)$ is the maximum utility that is obtained if the uncertainty on the parameters is resolved — see Table 1. Taking the expectation of this quantity with respect to the distribution of the parameters, we obtain the expected value of (distributional) information (EVDI). This is necessarily non-negative and it places an upper limit to the amount that we would be willing to pay to obtain any information, perfect or imperfect, about $\theta$.

By construction, the EVDI measures the weighted average opportunity loss induced by the decision that we make based on the expected utilities, the weight being the probability of incurring in that loss. Therefore, this measure gives us an appropriately integrated indication of: a) how much we are likely to lose if we take the “wrong” decision, and b) how likely it is that we take it.

Figure 1 shows the analysis of the expected value of information as a function of the willingness to pay parameter $k$. When the value of the threshold $k$ is very low (less than € 10,000), the derived utility function is actually not much affected by the uncertainty. In this case, the preferred option turns out to be the standard treatment $t = 0$ (calculations not shown) and as is easy to see, the
value of reducing information is actually quite limited. With $k$ increasing up to around €20,000 uncertainty as to whether $t = 0$ is indeed the best option becomes higher, and so does the value of information to reduce it, which goes up to about €4,000.

At the point $k = €21,550$, the optimal decision changes and above that threshold (i.e. if the decision maker is willing to allocate at least that budget to the treatment of the disease under study) the preferred option becomes $t = 1$. From this point on, the relevant uncertainty is that about whether $t = 1$ is indeed the best alternative. As one can see, the value of reducing uncertainty in this case is almost constant, slightly decreasing for values of $k$ in the interval €[22,550; 35,000] and then slightly increasing again.

3.2 Expected value of information for mixed strategies

In real practice it is hardly the case that a treatment proves to be cost-effective over the entire population, therefore justifying the fact that the market always includes more than one option. Moreover, from a different point of view it can be argued that completely withdrawing a molecule from the market just because it is not cost-effective would be unfair to the pharmaceutical company, possibly leading to unpleasant consequences in terms of incentives to research. This is mainly due to the fact that implementing an intervention is typically associated with some risks such as the irreversibility of investments, thus justifying the fact
that the decision makers might not want to fully commit to a single treatment, completely withdrawing the others.

Consequently, we are faced with the problem of balancing the optimal decision (i.e. implementing the most cost-effective treatment) with the constraints represented by the fact that the market shares of the other molecules already present on the market (i.e. all $t$ different from the option that maximises the expected utility) can not be all set to zero. Under this constraint, the actual expected utility in the overall population can be computed as the mixture

$$\bar{U} = \sum_t q_t U_t$$

$$= q_0 U^0 + q_1 U^1,$$

where $q_0$ and $q_1 = (1 - q_0)$ are the market share that will be obtained in the future by the two treatments. It is possible to measure the impact of uncertainty in the decision process, where the mixed strategy turns out to be actually chosen by the decision maker (that is when both $t = 0$ and $t = 1$ are on the market, with shares $q_0$ and $q_1$, respectively).

Figure 2: Analysis of the expected value of information for the mixed strategy and for different values of the market shares

Figure 2 also shows the expected value of information computed for different choices of the market shares ($q_0$, $q_1$), that is for different combination of the use of the two treatments. The analysis should be incremental with respect to the
“ideal” situation where the option with the overall highest utility is chosen, which is represented by the solid bold line.

Let us consider the case where treatment $t = 0$ maintains 60% of the market, represented graphically by the dashed line in Figure 2. For values of $k$ for which the preferred option is $t = 0$ ($k < \mathcal{E} 22550$), the mixed strategy produces an increase in the value of reducing uncertainty. That is due to the fact that in this case the non-optimal option is being used (in fact in 40% of the cases).

Clearly, the less uncertain the cost-effectiveness of an option, the larger the “loss” produced by the mixed option (which does not make exclusive use of the optimal treatment). Consequently, for $k = 0$, where the cost-effectiveness of $t = 0$ is virtually certain (as the expected value of information is close to 0), there is a large loss derived by the mixed option that grants 40% of the market to the other treatment.

When $k$ gets closer to the “break even point” (i.e. the point of indifference between the two alternatives, $k = \mathcal{E} 22550$), uncertainty as to whether either of the treatment is cost-effective is at its maximum (as confirmed by the fact that the expected value of information is maximum). Consequently, using any mixed strategy produces a lower loss, which will eventually be 0 at the break even point (as one can see, all curves coincide for $k = \mathcal{E} 22500$). Interestingly, when $k$ is greater than the break even point, suggesting that $t = 1$ becomes the preferred option, the mixed strategy where treatment $t = 0$ still retains most of the market produces increasingly higher losses.

A similar analysis can be replicated for any combination of the two treatments on the market. For instance, the solid light line shows the situation where the new treatment becomes market leader (with a share of 80%). Obviously, this produces higher losses when in fact $t = 0$ should be selected, but lower losses when $k$ is greater than the break even point.

3.3 Implications for the regulatory process

The framework just described suggests a way of managing a decision-making process in presence of mixed strategies. In the regulatory context, this should start from the typical scenario and information available. For example, let us consider the assessment of a new chemical entity, never marketed before, which proves to be more effective but also more expensive, with respect to the standard option. Taking into account the therapeutic indication(s) of the new drug, the regulator has knowledge of the current WTP of the national health service for each unit of benefit deriving from the use of the already available treatments with that same indication.

Let us consider a WTP equal to $k = \mathcal{E} 35000$; from Figure 3, we can identify the expected value of information for both the optimal decision-theoretic scenario (i.e. the situation of perfect substitution of the “old” treatment with the new one, the bold line) and that associated with the decision to leave on the market both the alternative treatments (upon varying the respective market shares).
Expected value of information at individual level (€)

Figure 3: Analysis of the expected value of information for the mixed strategy and for different values of the market shares with a fixed monetary willingness to pay threshold of € 35 000

Generally, the pharmaceutical company have some knowledge of the potential market share that can be gained after the introduction of the new product. Let us consider a potential share of 40%. As a consequence we obtain that, despite the fact that the old treatment is less effective (but also less expensive), it still maintains a market share of 60%. As shown in Figure 3, this scenario produces an expected value of information of about € 8 368.8. This value of the uncertainty surrounding the optimal decision is due to the following two circumstances:

1. The pharmaceutical company propose a new treatment strategy without eliminating (or reducing significantly, i.e. virtually a zero EVDI) the overall uncertainty on the cost-effectiveness of its product. In this case, the value of the pharmaceutical-company-related uncertainty is about € 3 900 (that is the value corresponding to the EVDI associated with the optimal strategy);

2. The decision to keep the old treatment (competitor) on the market, despite it is not cost-effective, introduces a further layer of uncertainty about the optimal decisional scenario whose value is € 4 474.3 (i.e. € 8 368.8 minus € 3 894.5). This uncertainty depends on the pharmaceutical company that distribute the competitor, and it also depends on the national health
service that do not disinvest from a non cost-effective treatment.

These values can be used in several different ways, according to the perspective of the subject affected by this uncertainty: the pharmaceutical company proposing the new treatment at the predicted market share \(q_1\); or the pharmaceutical company distributing the already available treatment, less cost-effective with respect to the new one, at the corresponding market share \(q_0 = (1 - q_1)\).

In both cases, the value of the uncertainty could be used in order to: (a) establish the amount of investment for clinical research that would be able to reduce the uncertainty about optimal decision; (b) determine the proposed reimbursed retail price, in terms of reduction of proposed reimbursed price; or (c) represent the payback value from the pharmaceutical company to the regional provider.

This last case could be considered after the marketing of the new product, since it depends on the market shares really associated with all the alternative options.

4 Conclusions

In this paper we presented an extended framework that allows the direct incorporation of cost-effectiveness analysis precepts in regulatory processes. As discussed earlier, while CEA is established in the health economics literature as one of the standard economic analysis to be used when aiming at an efficient allocation of resources, its application in regulatory decision making can be sometimes problematic. Our analysis is based on standard Bayesian decision-theoretic tools, such as the expected value of information, extending their interpretation to the problem of negotiation between the regulator and both the pharmaceutical company producing the new cost-effective intervention and those marketing older, less efficient alternatives. Using this framework it would be possible to quantify and qualify the increase in the uncertainty produced by allowing non cost-effective products on the market. This can generate returns for all the actors: on the one hand, the national health system can negotiate a payback price, which could be invested for further research, or for the treatment of other diseases. On the other hand, companies producing less cost-effective drugs can still be on the market.

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