A Decision-Theoretic Framework for the Application of Cost-Effectiveness Analysis in Regulatory Processes

Gianluca Baio\textsuperscript{1,2} and Pierluigi Russo\textsuperscript{3}

\textsuperscript{1} University of Milano Bicocca, Milan, Italy
\textsuperscript{2} University College London, London, UK
\textsuperscript{3} Agenzia Italiana del Farmaco, Rome, Italy

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 the regulatory process is often limited by some critical barriers, and decisions in clinical practice are frequently influenced by factors that do not contribute to efficient resource allocation, leading to inappropriate drug prescription and utilization. Moreover, most of the time there is uncertainty about the real cost-effectiveness profile of an innovative intervention, with the consequence that it is usually impossible to obtain an immediate and perfect substitution of a product with another having a better cost-effectiveness ratio.

The objective of this article is to propose a rational approach to CEA within regulatory processes, basing our analysis in a Bayesian decision-theoretic framework and proposing an extension of the application of well known tools (such as the expected value of information) to such cases. The regulator can use these tools to identify the economic value of reducing the uncertainty surrounding the cost-effectiveness profile of the several alternatives. This value can be compared with the one that is generated by the actual market share of the different treatment options: one that is the most cost effective and others in the same therapeutic category that, despite producing clinical benefits, are less cost effective.

Since the milestone paper by Weinstein and Stason,\textsuperscript{1,1} cost-effectiveness techniques have long been established in the healthcare 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 formalization,\textsuperscript{2,3} increasingly often under a Bayesian statistical approach.\textsuperscript{4-9}

However, the application of this technique to real practice decision making has found several critical barriers (outlined in the next section) in different countries. In Italy, for instance, cost effectiveness is hardly considered when deciding about marketing, reimbursement or pricing of new technologies.\textsuperscript{10} In effect, the decisions in clinical practice are frequently influenced by factors that do not contribute to an efficient resource allocation, leading to inappropriate drug
prescription and utilization. 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 authorization 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—cannot 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 article is to propose a rational approach to the analysis of the cost-effectiveness of several products in the same homogeneous therapeutic category (i.e. a new vs an already available medicine or class of medicines). This issue is relevant when the regulator has to decide about reimbursement of a new drug, negotiate its price, or decide on a formulary structure. 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.

1. 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 terms of QALYs in cost-utility analysis. 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 the 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 maximization of health benefits for the overall population, while minimizing the impact on expenditure.

However, the application of CEA to decision-making has faced several critical barriers. A first aspect is related to the transferability of results into clinical practice. In fact, the particular healthcare system may be too resistant to change, preventing the effective resource re-allocation suggested by CEA. A second critical aspect is the choice of a threshold value for the cost per QALY. In some local regulatory contexts (e.g. in the UK), a threshold value (or a range of values) is used to define the reimbursement of new medicines. However, the stringent application of the cost per QALY approach to decision making may be controversial for both theoretical and practical reasons.

From a theoretical point of view, there is much debate about a context specific versus a social-value of a cost-per-QALY threshold. 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 a higher 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). Finally, while it is plausible that individuals with worse health are willing to pay more to improve their own quality of life, from the societal perspective, the decision to devote almost all the resources to people in worse positions on the QALY scale is controversial.

From a practical point of view, the introduction of new cost-effective interventions on the market can have a critical impact on healthcare budgets, 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 in information from budget impact analyses, although only few have developed guidelines on this. Furthermore, although the
ranking of several treatment options into league tables according to their incremental cost-effectiveness ratio (ICER) has been recognized as a simple and transparent tool for resource allocation, it presents some methodological constraints that have limited its widespread use (i.e. the comparison between ICERs obtained from studies based on different assumptions, and the choice of comparators, discount rate, time horizon and population subgroups).[17]

A third critical aspect is the influence of CEA on the acquisition price of new drugs. On the one hand, the use of CEA in licensing decisions may favour both transparent decision making and more efficient relative pricing. However, on the other hand, in a specific regulatory context where there is no freedom to set a 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 regulation. For this reason, several authors have suggested that the main fourth hurdle effect (after efficacy, quality and safety) represented by CEA is not that of pricing of the single medicine, but rather derives from rationalization in the use of medicines available for the treatment of the same therapeutic indication.[18]

Despite these criticisms, interest in the relevance of CEA in decision processes has been recently renewed. As suggested by Detsky and Laupacis,[19] the application of cost effectiveness should consider the regulators’ perspective in decision making, for example by using a cost-consequence approach in the presentation of the ICER. 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 both accessibility to medicines and their appropriate use. Later in the regulatory process, other players in the overall healthcare system (e.g. regions and local health units) are also involved in decisions, until the final stage represented by a medical prescription to the patient.

Arguably, the crucial aspect in the decision process is market authorization. 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 experiments. As a consequence, cost-effectiveness results for a new medicine can be unreliable a posteriori, after the appearance of conflicting evidence during phase IV (e.g. clinical effectiveness lower than expected clinical efficacy as estimated by randomized trials, inappropriate use of the new medicine in clinical practice, unexpected adverse drug reactions).

In summary, during the premarket authorization phase, the regulator has to decide whether to grant reimbursement to a new product – and in some countries also sets the price – on the basis of uncertain evidence, regarding both clinical and economic outcomes. After market authorization, 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 overall access to the new treatment. Apart from the exception of new evidence forcing the withdrawal of a particular drug from the market or limitation of its use (this decision depends only on the regulatory authority or on the pharmaceutical company), after market authorization several factors are involved 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.

2. A Model for the Integration of Cost-Effectiveness Analysis within the Regulatory Context

The main issue that we address with our model is that usually it is impossible to obtain an immediate and perfect substitution of the market share of an existing product with that of another having a better cost-effectiveness ratio. This is due to (possibly a combination of) the following factors.
1. Generally there are small differences among cost-effectiveness ratios of drugs in the same homogeneous therapeutic category (e.g. statins, proton pump inhibitors).

2. The introduction of a new product can modify the overall cost-effectiveness profile of the treatments for a single therapeutic indication. If this condition holds, the new product might be only marginally better than those currently licensed for the same indication.

3. The allocation of market share among available products licensed for the same therapeutic indication could at least in part reflect the respective cost-effectiveness ratios. This relationship may be modified either by the introduction of a new chemical entity, or by the withdrawal of a marketed medicine, or by the patent 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:

(a) 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). We consider the future health economic response as \( y = (e, c) \), where \( e \) is a measure of effectiveness (for instance measured in terms of QALYs) and \( c \) is the costs associated with the application of treatment \( t \). Then, a common form of utility is the monetary net benefit\(^{[20]}\)

\[
u(y, t) = ke - c \quad \text{(Eq. 1)}
\]

where \( k \) is a ‘willingness to pay’ (WTP) parameter used to put clinical benefits and costs on the same scale.

(b) Define a probability distribution to describe the individual variability of the future (yet unobserved) health economic response \( y \). This distribution is typically a function of a set of relevant population parameters \( \theta \). In the Bayesian framework, the current uncertainty about the parameters is formally described by a probability distribution. This is computed starting from a (possibly subjective) prior distribution to describe the state of science about the parameters before observing any data, which is updated into the posterior distribution by the observed evidence, applying Bayes’s Theorem.

(c) For each possible treatment, calculate the overall expected utility

\[
U^t = E[u(Y, t)] \quad \text{(Eq. 2)}
\]

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

(d) Provided that the function \( u(y, t) \) actually describes the utility of interest, treat the entire homogeneous (sub)population with the most cost-effective treatment, i.e. the one that is associated with the maximum expected utility \( (U^*) \)

\[
U^* = \max_t U^t \quad \text{(Eq. 3)}
\]

We set up the following simple fictional model – see Baio and Dawid\(^{[21]}\) for a detailed specification. For the sake of simplicity, we assume a joint multivariate Normal model for the future health economic response \( y = (e, c) \), with parameters \( (\theta', S') \). The elements of \( \theta' = (\theta'_e, \theta'_c) \) represent, respectively, the population average benefits and costs associated with the application of treatment \( t \), while \( S' \) is the population covariance matrix (assumed known). This is probably the most basic joint model for \( (e, c) \) [see for instance van Hout et al.\(^{[22]}\)].

As for \( \theta \), let us assume that a posterior distribution is available, conditionally on the observation of some evidence \( \mathcal{E} \), such as that obtained by previous studies or, in the case of \( t = 0 \), recent years’ experience. Again for the sake of simplicity we assume independence between the population parameters among the different treatments and between average costs and benefits for the same treatment. Consequently, we can model
\[ p(\theta^t_c | \mathcal{E}) \sim \text{Normal}(\mu^t_c, \tau^t_c) \quad \text{and} \quad p(\theta^t_e | \mathcal{E}) \sim \text{Normal}(\mu^t_e, \tau^t_e) \] (Eq. 4)

independently for each treatment \( t \).

Finally, we assume that the quantities \((\mu^t_c, \tau^t_c)\) and \((\mu^t_e, \tau^t_e)\), which represent respectively the mean and the variance for \( \theta^t_c \) and \( \theta^t_e \), are fixed to encode the available knowledge about the parameters, conditionally on background information. For instance, let us take
\[
(\mu_c^0, \mu_e^0) = (0.5; 11000), \quad (\mu_c^1, \mu_e^1) = (1; 22000)
\]
\[
(\tau_c^0, \tau_e^0) = (0.15; 60 \times 10^5), \quad (\tau_c^1, \tau_e^1) = (0.10; 61 \times 10^5)
\] (Eq. 5)

Clearly, real-world health economic models (both for the observable variables and for the parameters) are actually much more complex than the one shown here. For instance, Normality is rarely a reasonable assumption for costs (that are typically skewed); also, the assumption of independence between the parameters might not be justifiable. However, we stress that the results that we show throughout the article using this simple structure are replicable with more appropriate distributional assumptions.

We performed a simulation exercise on this model, the results of which are described in Table I. For each of the \( N=1000 \) iterations, we simulate a value of the parameters \( \theta^1 = (\theta^1_c, \theta^1_e) \) and \( \theta^0 = (\theta^0_c, \theta^0_e) \) from the distributions defined in equation (1). For each simulation the quantity
\[ U(\theta^t) = k \theta^t_c - \theta^t_e \] (Eq. 6)
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 \( k=\€25000 \); 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 I) accounts for the variability in the parameter distribution, thus providing the overall expected utility for each treatment. As one can see, the expected utilities are computed as \( U^1 = 3641.00 \) and \( U^0 = 1413.89 \). Consequently, in this case we have \( U^* = U^1 = 3641.00 \) and therefore, given the current state of knowledge, treatment \( t=1 \) should be selected by the decision maker to replace the standard option \( t=0 \).

### 2.1 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 sensiti-

<table>
<thead>
<tr>
<th>Iteration (s)</th>
<th>Simulated values</th>
<th>Expected utility(^a)</th>
<th>Maximum utility</th>
<th>Opportunity loss(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \theta^t_c )</td>
<td>( \theta^t_e )</td>
<td>( \theta^0_c )</td>
<td>( \theta^0_e )</td>
</tr>
<tr>
<td>1</td>
<td>1.040</td>
<td>22.771</td>
<td>0.332</td>
<td>6920</td>
</tr>
<tr>
<td>2</td>
<td>1.376</td>
<td>21.907</td>
<td>0.056</td>
<td>13917</td>
</tr>
<tr>
<td>3</td>
<td>0.941</td>
<td>23.793</td>
<td>0.627</td>
<td>11428</td>
</tr>
<tr>
<td>4</td>
<td>0.957</td>
<td>22.281</td>
<td>0.272</td>
<td>16348</td>
</tr>
<tr>
<td>5</td>
<td>0.970</td>
<td>19.944</td>
<td>0.913</td>
<td>11145</td>
</tr>
<tr>
<td>6</td>
<td>1.226</td>
<td>26.010</td>
<td>0.614</td>
<td>7727</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>1000</td>
<td>1.154</td>
<td>19.135</td>
<td>0.414</td>
<td>11806</td>
</tr>
<tr>
<td>Average over all iterations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Obtained for a fixed value of \( k=\€25000 \).

\(^b\) Obtained at each iteration as \( U^* (\theta) - U(\theta^t) \).

\( c \) = costs; \( e \) = effects; \( \text{EVDI} \) = expected value of (distributional) information; \( k \) = willingness to pay of a decision maker; \( U \) = expected utility; \( U^* \) = maximum utility; \( \theta \) = a set of relevant population parameters.

Table I. Expected utility, maximum utility and opportunity loss for the introduction of a new treatment \((t=1)\) to a market where there is one existing treatment \((t=0)\); 1000 iterations of the simulation model.

© 2009 Adis Data Information BV. All rights reserved.
vity analysis (PSA), which is explicitly required by organizations such as the National Institute for Health and Clinical Excellence (NICE) in the UK.\textsuperscript{23}

A purely decision-theoretic tool to manage the uncertainty in the decision process through PSA is based on value of information analysis,\textsuperscript{24} an increasingly popular method in health economic evaluations.\textsuperscript{2,25-32} 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 pharmaco-economic assessment of the new intervention.

The value of (distributional) information (VDI) is defined as

\[ VDI(\theta) = U^*(\theta) - U^* \quad (\text{Eq. 7}) \]

where \( U^*(\theta) \) is the maximum utility that is obtained if the uncertainty on the parameters is resolved (table I). 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 on 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 that loss (table I). Therefore, this measure gives us an appropriately integrated indication of: (i) how much we are likely to lose if we take the ‘wrong’ decision; and (ii) how likely it is that we take it.

Figure 1 shows the analysis of the expected value of information as a function of the WTP parameter \( k \). When the value of the threshold \( k \) is very low (less than \( €10,000 \)), the derived utility function is not affected very much 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

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Expected value of information as a function of willingness to pay (WTP) where the preferred treatment (the option with the highest overall utility – either \( t=1 \) or \( t=0 \)) is the only treatment option.}
\end{figure}
the best option becomes higher, and so does the value of information to reduce it, which goes up to about €4000.

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 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. This can be due to the fact that in this interval the value of the WTP is large enough to limit the impact of undesired consequences.

### 2.2 Expected Value of Information for Mixed Strategies

In real practice it is rare that a treatment proves to be cost effective over the entire population, therefore justifying that the market includes more than one treatment option. In addition, implementing an intervention is typically associated with some risks such as irreversibility of investments, thus justifying that the decision-maker might want to temporize, in order to have more reliable evidence on which to base the final decision. Moreover, the market usually takes some time to ‘adjust’ to the new configuration generated by the innovative drug just introduced.

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 interventions [indexed by \( t \)] that are not the option that maximizes the expected utility) cannot be all set to zero.

Under this constraint, the actual expected utility in the overall population can be computed as

\[
\bar{U} = \sum_t q_t U^t = q_0 U^0 + q_1 U^1 \tag{Eq. 8}
\]

assuming that \( q_0 \) and \( q_1 (\approx [1 - q_0]) \) are the market share that will be obtained in the future by the two treatments considered earlier. Notice that the situation can be easily extended to the case where, say, \( T+1 \) alternatives are present on the market; in this case, we would have a vector of market shares

\[
q = (q_0, q_1, \ldots, q_T), \text{ with } q_T = 1 - (q_0 + \ldots + q_{T-1}) \tag{Eq. 9}
\]

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 shows the expected value of information computed for some arbitrary different choices of the market shares \((q_0, q_1)\), that is for different combinations of the use of the two treatments. In this sense, we effectively perform a deterministic sensitivity analysis on the vector \( q = (q_0, q_1) \).

In the situation when one of the treatments is only cost effective among a specific subgroup of patients, a possible rationale for the definition of \((q_0, q_1)\) might be to set them according to the proportion of each subgroup in the population.

The analysis of figure 2 is incremental with respect to the ‘ideal’ situation where the option with the highest overall utility is chosen (which, in this example, amounts to setting \( q_t = 0 \) for \( k < €21,550 \) and \( q_t = 1 \) for \( k \geq €21,550 \)), 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 \( t = 0 \) \((k < €22,550)\), the mixed strategy produces an increase in the value of reducing uncertainty. That is because the non-optimal option is being used 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 \( k = 0 \), when 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, \( k = €22,550 \)), 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 \( k = 22,500 \)). 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 coloured line in figure 2 shows the situation where the new treatment becomes market leader (with a share of 80%). Obviously, this produces higher losses when \( t = 0 \) should be selected, but lower losses when \( k \) is greater than the break-even point. Moreover, the multivariate case can be assessed in much the same way, although the graphical representation shown in figure 2 would be less helpful (as defined in more than 2 dimensions).

A possible extension to this model is to consider formally the uncertainty about future market share. In this case, the vector \( q \) should be associated with a suitable probability distribution (for instance a Beta distribution, in the simple case of two treatments, or a Dirichlet distribution in the multivariate case), to encode any knowledge about the future market dynamics. Under this modified framework, \( q \) would become one of the stochastic parameters subject to PSA; this can be easily implemented in the Bayesian model.

### 2.3 Implications for the Regulatory Process

The framework just described suggests a way of managing a decision-making process in the presence of mixed strategies. In the regulatory

---

**Fig. 2.** Expected value of information as a function of willingness to pay (WTP) where the two treatment options (either \( t = 1 \) or \( t = 0 \)) have varying market share (\( q \)). **EVDI** = expected value of distributional information.
context, this should start from the current market 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 than 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 derived from the use of the already available treatments with that same indication.

Let us consider a WTP equal to $k = €35\,000$; 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 coloured line) and that associated with the decision to leave on the market both the alternative treatments (upon varying the respective market shares).

Generally, the pharmaceutical company has 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, despite the old treatment being 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 €8368.8.

This value of the uncertainty surrounding the optimal decision is due to the following two circumstances:

1. The pharmaceutical company proposes 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 approximately €3900 (that is the value corresponding to the EVDI associated with the optimal strategy).

Fig. 3. Expected value of information as a function of willingness to pay (WTP) where the two treatment options (either $t=1$ or $t=0$) have varying market share ($q$). EVDI = expected value of distributional information.
2. The decision to keep the old treatment (competitor) on the market, despite it not being cost effective, introduces a further layer of uncertainty about the optimal decisional scenario whose value is €4474.3 (i.e., €8368.8 – €3894.5). This uncertainty can be attributed to the pharmaceutical company that distributes the competitor, and it also depends on the national health service that does not disinvest from a non-cost-effective treatment (that is, unless the regulator has the possibility of re-evaluating the reimbursement profile of a given drug).

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 than 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 (i) establish the amount of investment for clinical research that would be cost effective to reduce the uncertainty about optimal decision; (ii) determine the proposed reimbursed retail price, in terms of reduction of proposed reimbursed price; or (iii) represent the payback value from the pharmaceutical company to the decision maker.

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

3. Conclusions

In this article we presented an extended framework that allows the direct incorporation of CEA precepts in to the regulatory processes. As discussed earlier, while CEA is established in the health economics literature as one of the standard economic analyses 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.

Acknowledgements

Neither Dr Russo nor Dr Baio reported any potential conflicts of interest. Furthermore, the article reflects the personal view of Dr Russo and does not represent the official perspective of the Italian Medicine Agency.

The authors wish to thank Carlo Lucioni and Francesco Saverio Mennini for their suggestions and critical revision, and two anonymous referees for their insightful comments on a previous version.

References

10. Russo P. Pharmacoeconomics evaluations in the Italian regulatory context: a qualiquantitative analysis of pricing
and reimbursement dossiers. Pharmacoeconomics – Italian Research Articles 2008; 10 (2): 59-75


27. Claxton K. Bayesian approaches to the value of information: implications for the regulation of new pharmaceutical. Health Econ 1999; 8: 269-74


