SORT 28 (1) January-June 2004, 87-108

Incorporating patients' characteristics in cost-effectiveness studies with clinical trial data: a flexible Bayesian approach

F. J. Vázquez-Polo and M. A. Negrín-Hernández*

University of Las Palmas de G.C., Spain

Abstract

Most published research on the comparison between medical treatment options merely compares the results (effectiveness and cost) obtained for each treatment group. The present work proposes the incorporation of other patient characteristics into the analysis. Most of the studies carried out in this context assume normality of both costs and effectiveness. In practice, however, the data are not always distributed according to this assumption. Altervative models have to be developed.
In this paper, we present a general model of cost-effectiveness, incorporating both binary effectiveness and skewed cost. In a practical application, we compare two highly active antiretroviral treatments applied to asymptomatic HIV patients.
We propose a logit model when the effectiveness is measured depending on whether an initial purpose is achieved. For this model, the measure to compare treatments is the difference in the probability of success. Besides, the cost data usually present a right skewing. We propose the use of the log-transformation to carry out the regression model. The three models are fitted demonstrating the advantages of this modelling. The cost-effectiveness acceptability curve is used as a measure for decision-making.

MSC: 62F15, 62H12, 62P10

Keywords: Bayesian analysis, cost-effectiveness, Markov Chain Monte Carlo (MCMC), skewed cost distributions

1 Introduction

The frequentist approximation is the one most commonly adopted to compare different treatment options (Laska *et al.*, 1997, Stinnett and Mullahy, 1998, Tambour *et al.*

* *Address for correspondence:* Dept. of Quantitative Methods. University of Las Palmas de G.C. Fac. CC. Económicas. Campus de Tafira. 35017 Las Palmas de Gran Canaria, Spain.
E-mail: {fjvpolo or mnegrin}@dmc.ulpgc.es. Phone: +34 928 45 18 00 Fax: +34 928 45 82 25
Received: September 2003
Accepted: March 2004

1998, Van Hout *et al.*, 1994, Wakker and Klaassen, 1995, Willam and O'Brien, 1996). However, clinical research is fundamentally a dynamic process in which any study must be considered in the context of continual updating of the state of the art. The Bayesian method is of a dynamic nature in which initial beliefs, determined on the basis of a prior distribution, are modified by new data, using Bayes' theorem. A large body of literature has been published on Bayesian methods, chief among which are texts by Berry (1996), Box and Tiao (1973) and Gelman *et al.* (1995).

Spiegelhalter *et al.* (1994) and Jones (1996) were the first to discuss Bayesian approximation for statistical inference in the comparison of health technologies. Since then, many studies have proposed the Bayesian approach to compare treatment options by means of cost-effectiveness analysis (Al and Van Hout, 2000, Briggs, 1999, 2001, Heitjan, 1997, Heitjan *et al.*, 1999, O'Hagan *et al.*, 2001, O'Hagan and Stevens, 2001*a*, 2001*b*, 2002).

Most studies carried out in this field compare the effectiveness and the costs of the different treatment options analysed. This type of analysis assumes that the patients sampled and subjected to a particular treatment option present similar characteristics or, at least, that the differences between samples are not relevant to the analysis of cost and effectiveness, and so the variations between the treatment groups are only caused by the type of treatment applied. In the present paper, the above assumption is not made and so, in order to obtain the true effect of the type of treatment applied on costs and effectiveness a regression model is proposed. The use of regression models in cost-effectiveness analysis has recently been proposed by Hoch *et al.* (2002) and Willan *et al.* (2004) under a frequentist point of view. This paper presents the Bayesian solution, offering a more flexible framework for different measures of effectiveness and cost.

Sometimes effectiveness is not measured quantitatively but in a discrete way, depending on whether or not a particular objective has been attained. Therefore, we have developed two alternative regression models, a multiple linear regression model to be used when the effectiveness is measured by means of a continuous variable, and a logit discrete choice model when effectiveness is defined by a categorical variable.

Most published studies on cost-effectiveness analysis assume normality of the cost generation distribution (Laska, 1997, Stinnet and Mullahy, 1998, Tambour *et al.*, 1998, Willam and O'Brien, 1996, Heitjan *et al.*, 1999, O'Hagan *et al.*, 2001). In practice, however, costs usually present a high degree of skewness, and so the normality assumption is not valid. O'Hagan and Stevens (2001*b*) determined, from a practical application, the importance of dealing with skewed cost data, obtaining different results from those achieved under the assumption of normality.

The standard measure used to compare the cost and effectiveness of treatments is the incremental cost-effectiveness ratio (ICER). Nevertheless, this measure presents severe interpretational problems, as well as difficulties in estimating the confidence or credibility intervals. The incremental net benefit (INB) has been proposed as an alternative to ICER (Mullahy and Stinnett, 1998, among others). The INB of treatment

1 (new) versus treatment 0 (actual, or control) is defined as

$$INB(R_c) = R_c \cdot (\mu_1 - \mu_0) - (\gamma_1 - \gamma_0) = R_c \cdot (\Delta\mu) - (\Delta\gamma), \tag{1.1}$$

where μ's and γ's are the mean effectiveness and cost of the respective treatments. The value R_c is interpreted by O'Hagan and Stevens (2001a) as the cost that decision-makers are willing to accept in order to increase the effectiveness of the treatment applied by one unit. Thus, analysing whether the alternative treatment is more cost-effective than the control treatment is equivalent to determining whether $INB(R_c)$ is positive. In practice, it is not a simple matter for the decision-maker to determine a single R_c, and so a cost-effectiveness acceptability curve (CEAC) is constructed (Löthgren and Zethraeus, 2000). This curve provides a graphical representation of the probability of the alternative treatment being preferred ($\Pr(INB(R_c) > 0)$) for each value R_c. This interpretation of the CEAC, in terms of probability, is only possible when the Bayesian approach is adopted (Briggs, 1999).

Section 2 presents the regression models used in this study. These are selected depending on how the effectiveness is to be measured (qualitatively or quantitatively) and on the cost patterns generated. Section 3 provides a comparison of the different models created by means of a practical application using real data from a clinical trial comparing two alternative treatments for asymptomatic HIV patients. Section 4 presents a discussion of the results obtained and draws some conclusions.

2 Bayesian cost-effectiveness regression models incorporating covariates

2.1 Assumed normality of effectiveness and costs

Given a sample of N individuals participating in a clinical trial, we obtained effectiveness data (E_i) and cost data (C_i) for each patient i, $i = 1 \ldots N$. These N patients were given two different types of treatment, termed the control treatment and the new, or alternative treatment.

The results of the clinical trial, in terms of effectiveness and costs, are not determined only by the type of treatment received (X_T), and so it is necessary to consider a series of possible covariates that may influence the above results. Such covariates include the patient's age, state of health at the time of the clinical trial, gender and other characteristics that depend on the type of clinical trial under analysis (X). We define X as an $n \times (k + 1)$ matrix of covariates, where each column (X_i) refers to one covariate. The first column is a column of ones referring to the constant.

We seek, therefore, to explain the results obtained (E_i and C_i), as a linear combination of the k covariates considered (the patient's individual characteristics and the type of treatment received). For this purpose, we propose a Bayesian multiple linear regression model in which the perturbation term (u_i or v_i) is assumed to be Gaussian,

independent and identically distributed (i.i.d) with a mean of 0 and variances of σ_1^2 and σ_2^2 respectively.

$$E_i = \beta_0 + \beta_1 \cdot X_{1,i} + \beta_2 \cdot X_{2,i} + \ldots + \beta_{k-1} \cdot X_{k-1,i} + \beta_T \cdot X_{T,i} + u_i, \tag{2.1}$$

$$C_i = \delta_0 + \delta_1 \cdot X_{1,i} + \delta_2 \cdot X_{2,i} + \ldots + \delta_{k-1} \cdot X_{k-1,i} + \delta_T \cdot X_{T,i} + v_i, \tag{2.2}$$

where the vectors $\beta = (\beta_0, \beta_1, \beta_2, \ldots, \beta_{k-1}, \beta_T)'$, $\delta = (\delta_0, \delta_1, \delta_2, \ldots, \delta_{k-1}, \delta_T)'$, and the accuracy values $\tau_1 = 1/\sigma_1^2$ and $\tau_2 = 1/\sigma_2^2$ are the parameters of the model.

The k covariates considered for which data are available need not be explicative of both the effectiveness and the costs, and so the above general model could be corrected by eliminating those covariates that do not explain effectiveness and cost.

The first step to be taken in estimating the parameters is to determine the likelihood function, both of the effectiveness $\ell_e(E|\beta, \tau_1)$ and of the costs $\ell_c(C|\delta, \tau_2)$, where $E = (E_1, \ldots, E_N)'$ and $C = (C_1, \ldots, C_N)'$. In this stage both costs and effectiveness are assumed to present a normal distribution, and so the likelihood functions are represented by the following expressions:

$$\ell(E, C|\beta, \delta, \tau_1, \tau_2) = \ell_e(E|\beta, \tau_1) \cdot \ell_c(C|\delta, \tau_2), \tag{2.3}$$

where

$$\ell_e(E|\beta, \tau_1) \propto \tau_1^{\frac{N}{2}} \exp\left\{-\frac{\tau_1}{2}(E - X\beta)'(E - X\beta)\right\},$$

and

$$\ell_c(C|\delta, \tau_2) \propto \tau_2^{\frac{N}{2}} \exp\left\{-\frac{\tau_2}{2}(C - X\delta)'(C - X\delta)\right\}.$$

Assuming model (2.1)-(2.2) from a Bayesian point of view, we must specify the prior distribution for the $2 \cdot k + 4$ parameters of the model. The prior distribution represents expert information about the set of model parameters before the sample observations are analysed. We propose a normal/gamma form for the base prior and assume independence between the coefficients (β, δ) and precision terms (τ_1, τ_2). Obviously, the prior distributions used here are not the only possible choices and indeed, their independent conditional conjugate form is a suitable property to be considered by an expert.

$$\pi(\beta, \tau_1) = \pi_{e,1}(\beta) \cdot \pi_{e,2}(\tau_1), \tag{2.4}$$

$$\pi(\delta, \tau_2) = \pi_{c,1}(\delta) \cdot \pi_{c,2}(\tau_2), \tag{2.5}$$

where

$$\pi_{e,1}(\beta) \sim \mathcal{N}(\beta^0, V_1^{-1}), \qquad \text{and} \qquad \pi_{c,1}(\delta) \sim \mathcal{N}(\delta^0, V_2^{-1}),$$

and,

$$\pi_{e,2}(\tau_1) \sim \mathcal{G}(a_1, b_1), \qquad \text{and} \qquad \pi_{c,2}(\tau_2) \sim \mathcal{G}(a_2, b_2).$$

The symbols $\mathcal{N}$ and $\mathcal{G}$ denote the normal and gamma distributions, respectively, and the parameters β^0, V_1^{-1}, δ^0, V_2^{-1}, a_1, b_1, a_2 and b_2, which determine the prior distribution, are defined on the basis of the information available when the analysis begins. Thus,

the eliciting process plays an important role, by modelling the available empirical or historical evidence by means of the prior distribution (Chaloner and Duncan, 1983, Chaloner, 1995, Chaloner and Rhame, 2001, Freedman and Spiegelhalter, 1983, Kadane, 1980, Kadane and Wolfson, 1995, Kadane and Wolfson, 1998, Winkler, 1967, Wolpert, 1989).

The joint posterior distribution of the parameters $(\beta, \delta, \tau_1, \tau_2)$, given the data (E, C), can be calculated from equations (2.3-2.5), using Bayes' theorem.

$$\pi(\beta, \tau_1|E) \propto \tau_1^{\frac{N+2a_1}{2}-1} \exp\left\{-\tfrac{1}{2}\left[\tau_1(E - X\beta)'(E - X\beta) + (\beta - \beta^0)'V_1^{-1}(\beta - \beta^0) + 2b_1\tau_1\right]\right\}, \qquad (2.6)$$

$$\pi(\delta, \tau_2|C) \propto \tau_2^{\frac{N+2a_2}{2}-1} \exp\left\{-\tfrac{1}{2}\left[\tau_2(C - X\delta)'(C - X\delta) + (\delta - \delta^0)'V_2^{-1}(\delta - \delta^0) + 2b_2\tau_2\right]\right\}. \qquad (2.7)$$

Inferences about quantities of interest must be based on these posterior distributions. Unfortunately, these are not straightforward, thus the Gibbs sampling algorithm, in the context of the Markov Chain Monte Carlo (MCMC) simulation seems to be the most appropriate (Gelman *et al.*, 1995, Geman and Geman, 1984, Gilks *et al.*, 1996, Tweedie, 1998).

The treatment received is defined by means of a dichotomous variable (X_T) that is assigned a value of 0 for the control treatment and a value of 1 when the treatment received is a new treatment. The parameters corresponding to the latter variable are simple to interpret. The coefficient of the treatment variable in the effectiveness regression model (β_T) is interpreted as the mean increment in effectiveness derived from the new treatment in comparison with the control treatment. To obtain the cost increment corresponding to the new treatment, it is only necessary to estimate the coefficient δ_T.

The posterior cost-effectiveness acceptability curve describes the probability of the net benefit presenting positive values, that is, the posterior probability of the new treatmente being preferred to the control treatment, for each of the R_c considered:

$$Q(R_c) = \Pr\left(INB(R_c) > 0|E, C\right).$$

2.2 Binary effectiveness

On many occasions, the effectiveness data are not determined by a quantitative variable. An example of this is binary effectiveness, which is measured from a dichotomous variable $\{0, 1\}$ depending on whether or not a certain positive event has occurred.

Let us assume N binary random independent variables and that $Y_i, \ldots, Y_N$ are observed, where Y_i follows a Bernoulli distribution with a probability p_i of the event occurring. This probability p_i depends on a series of covariates that may be continuous or discrete. Let us define a binary regression model in a general way as $p_i = \mathcal{H}(X_i'\beta)$, $i = 1, \ldots, N$, where β is a vector of unknown parameters with dimension $(k + 1) \times 1$, and $X_i = (1, X_{1,i}, X_{2,i}, \ldots, X_{k,i})'$ is the vector of the known covariates. The logit model is

obtained when we assume that $\mathcal{H}$ is the logistic distribution. For a classical description of binary models, see Cox (1971), Nelder and McCullagh (1989), Maddala (1983) and McFadden (1974).

We now present the application of the logit model to cost-effectiveness studies. We describe the model corresponding to effectiveness, the cost model being identical to that analysed in Section 2.1.

We examined a sample of N individuals who took part in a clinical trial involving two alternative treatments, in which the effectiveness (E_i) of each was known, $i = 1, \ldots, N$.

$$E_i \sim Be(p_i), \tag{2.8}$$

where

$$p_i = \frac{e^{X_i' \cdot \beta}}{1 + e^{X_i' \cdot \beta}}.$$

The first step in the Bayesian analysis requires us to consider a likelihood function for the data, which in this case is the effectiveness. We apply the logit model, and so the likelihood function is specified as follows:

$$\ell_e(E|\beta) = \prod_{i=1}^{N} p_i^{E_i}(1 - p_i)^{1-E_i} = \prod_{i=1}^{N} \left(\frac{\exp[X_i' \cdot \beta]}{1 + \exp[X_i' \cdot \beta]} \right)^{E_i} \left(1 - \frac{\exp[X_i' \cdot \beta]}{1 + \exp[X_i' \cdot \beta]} \right)^{1-E_i}. \tag{2.9}$$

Having defined the likelihood function, we now propose a flexible model for the prior distribution. The normal multivariate distribution for the β parameters is flexible enough to include a large number of possible prior situations,

$$\pi(\beta) \sim \mathcal{N}(\beta^0, V_1^{-1}). \tag{2.10}$$

Estimation of the above binary response model was carried out using Gibbs sampling (Carlin and Polson, 1992, Albert and Chib, 1993).

We propose the use of the difference in the probability of success between treatments (Δp) as the measure to analyse the effectiveness. In a logit model the effect of a covariate on the probability of success depends on the level of the independents. Under the assumption that the sample is representative of the population, we can estimate the difference in probabilities of success between control and new treatment for each patient. The mean incremental effectiveness is estimated as the mean of the increase in the probability of success for the sample. The INB can be calculated as in the previous section where the value R_c is interpreted as the cost that decision-makers are willing to accept in order to increase the probability of success in 1%.

2.3 Skewed cost data: the log-normal model

The cost data obtained from the data of individual patients in health-care economic studies present, for the most part, a strongly asymmetrical distribution. Another

characteristic of many cost-effectiveness studies is the small sample size employed. These circumstances frequently oblige us to reject the normality assumption described in Section 2.1.

We now describe a model that reflects this skewed cost, using a non-normal likelihood function. In this sense, Al and Van Hout (2000) described a Bayesian approach to cost-effectiveness analysis showing how costs can be modelled under the assumption of a log-normal distribution. Such a distribution is a much more appropriate way of reflecting possible cost asymmetries.

It is now necessary to reformulate the cost model using a log-normal likelihood function, by which the cost model described in Section 2.1 is expressed as follows:

$$\log(C_i) = \delta_0 + \delta_1 \cdot X_{1,i} + \delta_2 \cdot X_{2,i} + \ldots + \delta_{k-1} \cdot X_{k-1,i} + \delta_T \cdot X_{T,i} + v_i, \tag{2.11}$$

where the vector $\delta = (\delta_0, \delta_1, \delta_2, \ldots, \delta_{k-1}, \delta_T)'$ and $\tau_2 = 1/\sigma_2^2$ are the parameters to be estimated.

The likelihood function of the logarithm of the costs $\ell_c(\log(C)|\delta, \tau_2)$ is:

$$\ell_c(\log(C)|\delta, \tau_2) \propto \tau_2^{\frac{N}{2}} \exp\left\{-\frac{\tau_2}{2}(\log(C) - X\delta)'(\log(C) - X\delta)\right\}.$$

A conditional-conjugate prior distribution is thus the normal-gamma distribution defined above:

$$\pi(\delta, \tau_2) = \pi_{c,1}(\delta) \cdot \pi_{c,2}(\tau_2), \tag{2.12}$$

where

$$\pi_{c,1}(\delta) \sim \mathcal{N}(\delta^0, V_2^{-1}) \qquad \text{and} \qquad \pi_{c,2}(\tau_2) \sim \mathcal{G}(a_2, b_2).$$

Under the assumption of lognormality, the parameter δ_T cannot be interpreted as the incremental cost and it is necessary to search for another means of comparing the two treatment options. In this case the ratio of the costs of the new treatment and those of the control treatment can be described by a simple expression, one that does not depend on the patients' individual characteristics,

$$\frac{C_i^1}{C_i^0} = \exp(\delta_T) \tag{2.13}$$

where C_i^1 is the cost of a patient *i* who has received the new treatment, and C_i^0 is the cost of the same patient *i* when the control treatment is applied.

Therefore, values greater than 1 for $\exp(\delta_T)$ indicate that the new treatment is more costly than the control treatment. Thus, $(\exp(\delta_T) - 1) \cdot 100\%$ shows the percentage increase in costs arising from the new treatment.

In comparison with the model described in Section 2.1, the INB presents the following expression:

$$INB = (R_c) \cdot \beta_T - (\exp(\delta_T) - 1), \tag{2.14}$$

where R_c is interpreted as the proportion of the cost increase that the decision-maker is willing to accept in order to increase effectiveness by one unit. Positive INB values show a preference for the alternative treatment. As in the previous sections, we can construct a posterior cost-effectiveness acceptability curve for each value of R_c.

3 Practical application

The data used in this section were obtained from a real clinical trial in which a comparison was made of two highly active antiretroviral treatment protocols applied to asymptomatic HIV patients (COSTVIR study, Pinto *et al.*, 2000).

We obtained data on the direct costs (of drugs, medical visits and diagnostic tests), on the effectiveness, based on clinical variables (percentage of patients with no detectable virus load) and on health-related life-quality variables, using EuroQol-5D.

EuroQol–5D is an instrument for the self-evaluation of personal health, consisting of five questions that investigate five aspects of health-related life quality, based on a visual analogue scale (VAS) (Brooks, 1996).

In this exercise we compared two three-way treatment protocols. The first of these (d4T + 3TC + IND) combines the drugs estavudine (d4T), lamivudine (3TC) and indinavir (IND); the second treatment protocol (d4T + ddl + IND) combines estavudine (d4T), didanosine (ddl) and indinavir (IND).

Two alternative measures of effectiveness were employed. The first of these was the improvement in the patient's life quality, measured as the improvement on a visual analogue scale (VAS). This scale simulates a thermometer with a minimum of 0 and a maximum of 100. The 0 represents the worst health state imaginable, and the 100, the best.

The second effectiveness measure considered was the percentage of patients who, at the end of the treatment programme, presented undetectable levels of viral load. The effectiveness, therefore, can only be expressed as one of two values, either 1 if the viral load is undetectable, otherwise 0.

Table 1 summarises the statistical data obtained. The d4T + ddl + IND treatment is more costly than the d4T + 3TC + IND treatment, by an average of 164.82 euros. When the VAS variation is used as the measure of effectiveness, the d4T + ddl + IND treatment is more effective because, on average, the patients who received this treatment experienced an improvement in their life quality of 4.94 units, while those who were given the d4T + 3TC + IND treatment only experienced a VAS improvement of 4.56 units. However, if the percentage of patients experiencing a reduction of the viral load to undetectable levels is used as the measure of effectiveness, then a better result is obtained for the d4T + 3TC + IND group (68%) than for those who received the alternative treatment (66%).

Table 1: *Statistical summary of costs (in euros) and effectiveness (change in VAS and percentage of patients with undetectable viral load).*

	d4T + 3TC + IND			d4T + ddl + IND		
Statistical measure	Cost	Change in VAS	% with undetectable VL	Cost	Change in VAS	% with undetectable VL
Mean	7142.44	4.56	0.68	7307.26	4.94	0.66
Stan. Devn.	1573.98	15.17	0.47	1720.96	13.98	0.48
N	$N_0 = 268$			$N_1 = 93$		

3.1 Assumption of normality in effectiveness and in costs

In this section, the increase in the VAS is used as the measure of the effectiveness of each treatment protocol. For this purpose, we applied the model described in Section 2.1, taking into account the effectiveness and cost of the treatment given to each patient, the individual characteristics of each patient and his/her clinical situation at the moment of the clinical trial.

The model's explanatory variables are the *age*, the *gender* (value 0 if the patient is male and value 1 for a female) and the existence of any concomitant illness (*cc1* with a value of 1 if a concomitant illness is present, otherwise 0; and *cc2* with a value of 1 if two or more concomitant illnesses are present, otherwise 0). The concomitant illnesses considered were hypertension, cardiovascular disease, allergies, asthma, diabetes, gastrointestinal disorders, urinary dysfunction, previous kidney pathology, high levels of cholesterol and/or triglycerides, chronic skin complaints and depression/anxiety. Also included in the model was the time (in months) elapsed since the *start* of the illness until the moment the clinical trial was performed. Finally, we included a dichotomous variable (*trat*) that was assigned a value of 1 if the patient received the (d4T + ddl + IND) treatment protocol and a value of 0 if the (d4T + 3TC + IND) treatment was applied. The linear model of the effectiveness and the costs, for the i-th patient is

$$E_i = \beta_0 + \beta_1 \cdot age_i + \beta_2 \cdot gender_i + \beta_3 \cdot cc1_i + \beta_4 cc2_i + \beta_5 \cdot start_i + \beta_T \cdot trat_i + u_i, \quad (3.1)$$

$$C_i = \delta_0 + \delta_1 \cdot age_i + \delta_2 \cdot gender_i + \delta_3 \cdot cc1_i + \delta_4 cc2_i + \delta_5 \cdot start_i + \delta_T \cdot trat_i + v_i. \quad (3.2)$$

3.1.1 Priors

For a fully Bayesian analysis, we must specify priors for the parameters of interest. The COSTVIR study was carried out in 1999 and it is not practical now to try to elicit the prior information. For the purpose of our illustrative analysis, we look at the reasoning behind the design of the study as an indication of what prior information we can use. For HAART regimens, there were no indications of differences in effectiveness because of age or gender. However, they showed better results for patients with concomitant

illnesses and for patients in the early stages of the illness. The d4T + ddl + IND treatment was expected to be on average more effective than the d4T + 3TC + IND treatment but with a prior interval of probability large enough to include negative values.

In cost terms, it was expected that the age, the fact to be female and the months of illness increase cost of HAART therapies. No effect of the existence of concomitant illnesses in cost was expected. Higher cost was expected for the treatment d4T + ddl + IND.

Mean and interval of probability were asked to the experts in an elicitation process to obtain the prior mean and variance of the parameters of interest. Diffuse information is assumed for the precision terms. Then, the prior elicitation is implemented by using the following parameter assignments:

$$\beta^0 = (0, 0, 0, 5, 10, -0.5, 2), \qquad V_1 = \text{diag}(10^{10}, 1, 1, 6.25, 6.25, 0.01, 2.25),$$
$$\delta^0 = (0, 10, 200, 0, 0, 5, 200), \qquad V_2 = \text{diag}(10^{10}, 25, 2500, 625, 625, 6.25, 2500),$$
$$a_1 = 0.5, \quad b_1 = 0, \quad a_2 = 0.5, \text{ and } b_2 = 0.$$

3.1.2 Results

For all models, simulations were done using WinBUGS (Spiegelhalter *et al.*, 1999). A total of 50000 iterations were carried out, after a burn-in period of 10000 iterations. The codes are available from authors upon request. Table 2 shows the posterior estimation of the parameters.

Table 2: *Posterior statistics and symmetrical interval of probability at 95% (normal model).*

	Mean	Standard deviation	95% CI
β_0	0.9514	3.9213	(-6.6991, 8.6842)
β_1	0.05458	0.1072	(-0.1549, 0.2629)
β_2	-0.3023	0.8701	(-2.0084, 1.3882)
β_3	3.5431	1.4382	(0.7186, 6.3673)
β_4	9.5387	1.7963	(6.0183, 13.0518)
β_5	-0.005698	0.008184	(-0.02176, 0.01038)
β_T	1.4080	1.1471	(-0.8494, 3.6707)
δ_0	6673.4	194.9	(6287.3, 7052.7)
δ_1	9.1532	4.6151	(0.0483, 18.2076)
δ_2	199.31	48.36	(103.84, 293.35)
δ_3	2.4683	24.7677	(-46.2720, 50.9167)
δ_4	-1.0110	24.9816	(-49.7648, 48.3937)
δ_5	1.0614	0.8412	(-0.5928, 2.7221)
δ_T	198.80	48.56	(103.39, 293.91)

Let us begin by analysing the effectiveness model. The age and gender coefficients (β_1 and β_2) are not statistically relevant, which means that these covariates do not affect

the final results for effectiveness. The existence of concomitant illnesses favours an increase in the patient's VAS, as shown by the positive signs of the corresponding coefficients. The months elapsed between the start of the illness and the moment of the clinical trial do not seem to affect the final effectiveness results.

The β_T coefficient indicates the incremental effectiveness of the new treatment. The coefficient has a value of 1.4080, which indicates that the patients who received the three-way treatment (d4T + ddl + IND), under conditions of *ceteris paribus*, reported an increase in their health state evaluation an average of 1.4080 units greater than the patients who were given the alternative treatment. Nevertheless, the 95% probability interval includes both positive and negative values, and so we cannot claim that the difference between the two treatment protocols, with regard to effectiveness, is statistically relevant. From the posterior marginal distribution of the β_T coefficient, it can be said that there exists a probability of 88.8% that the (d4T + ddl + IND) treatment is more effective than the (d4T + 3TC + IND) treatment.

With regard to costs, we found that the (d4T + ddl + IND) treatment is more expensive than the alternative, by an average of 198.80 euros, with an interval of probability of (103.39, 293.91).

The incremental cost-effectiveness ratio is calculated as the ratio of the increases in cost and effectiveness (δ_T/β_T). In the present study, the ICER was found to be 290.21. Figure 1 shows the joint posterior distribution of the incremental costs and effectiveness measured.

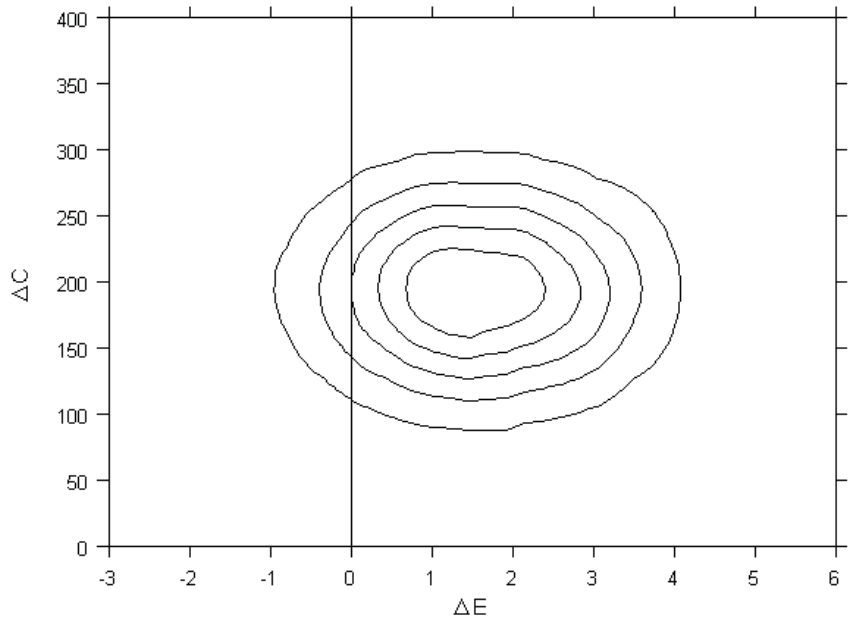

Figure 1: *Joint posterior distribution of costs and incremental effectiveness (normal model).*

In addition to the ICER, we obtained the value of the incremental net benefit (INB). Figure 2 shows the probability that the INB is positive for every possible value of R_c, that is, the cost-effectiveness acceptability curve.

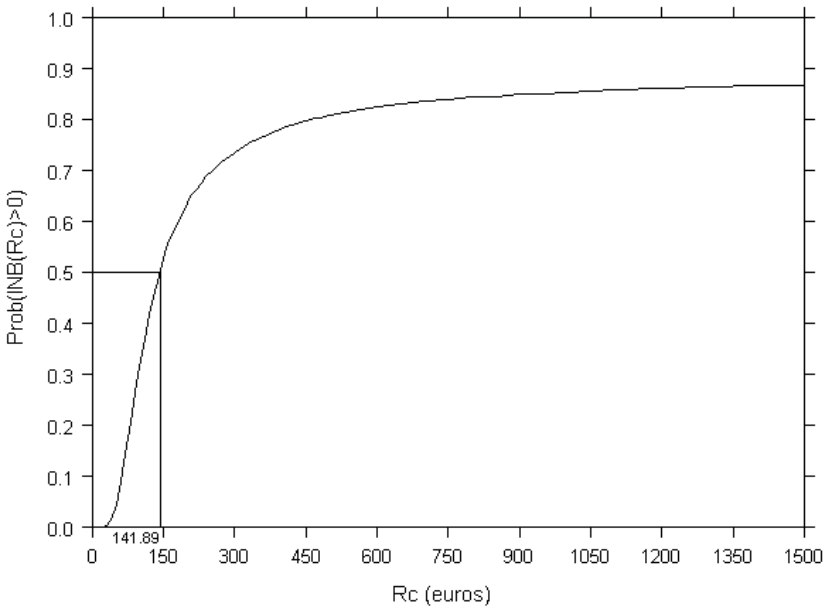

Figure 2: *Cost-effectiveness acceptability curve (normal model).*

At a willingness to pay of 141.89 euros or more, the decision-maker prefers the alternative treatment (d4T + 3TC + IND), because the probability of this preference is greater than 50%.

3.2 Binary effectiveness

We now consider the possibility of the effectiveness being measured by means of a binary variable, that is, the percentage of patients who, given a certain treatment option, achieve undetectable levels of viral load.

Table 1 shows that 68% of the patients achieved undetectable levels of viral load with the (d4T + 3TC + IND) treatment, versus 66% of those given the (d4T + ddl + IND) treatment. We now apply the logit regression model described in Section 2.2. This model enables us to determine whether the differences between the two treatment groups are due to the treatment itself or to individual characteristics of the patients.

The odds ratio (OR) is the most common measurement used to compare the probability of success between two categories of a qualitative variable in a logit model

(Deeks, 1998). Its main advantage over alternative measurements comparing treatments is its ability to measure independently of individual patient characteristics. Thus, when two categories 1 and 0, of a dichotomous variables are compared, indicating here the type of treatment received, the odds ratio is obtained as the relative probability of the success ratio between categories. Thus the final value obtained does not depend on the remaining individual patient characteristics:

$$\mathrm{OR} = \frac{\dfrac{p_i^1}{1-p_i^1}}{\dfrac{p_i^0}{1-p_i^0}} = \exp\left(\beta_T\right), \tag{3.3}$$

where p_i^1 is the probability of success of a patient i who has received the new treatment, and p_i^0 is the probability of success of the same patient i who has received the control.

Values greater than 1 for the odds ratio reflect a preference for the new treatment, as the relative probability of improvement is greater than in the case of the control treatment. The odds ratio has a very intuitive practical consideration, and the decision-maker who has a good statistical training should have no problem to assess it. We propose to use this feature in the elicitation process as shown in the following.

3.2.1 Priors

We include prior information about the value of the coefficients of the logit model. However, the coefficients have not a natural interpretation to be elicited. For that reason we asked the experts the prior beliefs about the mean and variance of the odds ratio for each covariate.

Assuming that the prior distribution of the vector of coefficients β is normal, the prior distribution of the odds ratio is log-normal. Thus, we can elicit the prior mean and variance using the following relationship:

$$\beta_k \sim \mathcal{N}(\beta_k^0, V_{1_{k,k}}^{-1}) \qquad \Longleftrightarrow \qquad \mathrm{OR}_k = \exp(\beta_k) \sim \text{log-}\mathcal{N}(\mathrm{OR}_k^0, V_{\mathrm{OR}_{k,k}}^{-1}),$$

where $\log-\mathcal{N}$ denotes the log-normal distribution and the two first moments are:

$$\mathbb{E}[\mathrm{OR}_k] = \mathrm{OR}_k^0 = \exp(\beta_k^0 + V_{1_{k,k}}^{-1}/2),$$

$$\mathrm{Var}[\mathrm{OR}_k] = V_{\mathrm{OR}_{k,k}}^{-1} = \exp(2\cdot\beta_k^0 + V_{1_{k,k}}^{-1})\cdot(\exp(V_{1_{k,k}}^{-1}) - 1).$$

The experts have prior information about the mean and variance of odds ratios. Solving the previous system of equations we can obtain prior information about the coefficients β.

Before the study was carried out, the experts expected lower probabilities to achieve undetectable viral load for women (odds ratio of 0.8), patients with concomitant illnesses (odds ratios of 0.7 and 0.5 for *cc1* and *cc2*) and for each additional month

of illness (odds ratio of 0.8). It is necessary to comment on the different signs of the coefficient for concomitant illnesses for the two measures of effectiveness considered. The HAART regimens improve the quality of life of the patients with concomitant illnesses attenuating the effect of these illnesses. However, the existence of these concomitant illnesses supposes an inconvenience in the goal of achieving undetectable viral load. There was no prior information about the difference between treatments. A small value of 0.01 was assigned to the prior variance for all the odds ratios. Then, the prior elicitation is implemented by using the following parameter assignments:

$$\beta^0 = (0, 0, -0.2301, -0.3667, -0.7124, -0.2301, 0),$$

and

$$V_1 = \text{diag}(10^{10}, 10^{10}, 0.0154, 0.02, 0.0385, 0.0154, 10^{10}).$$

3.2.2 Results

Table 3 shows some posterior moments of the parameters for the effectiveness regression estimated by means of MCMC simulation techniques.

Table 3: *Posterior statistics and symmetrical interval of probability at 95% (binary effectiveness).*

	Mean	Standard deviation	95% CI
β_0	1.5281	0.6020	(0.3998, 2.7534)
β_1	-0.0127	0.0162	(-0.0454, 0.0181)
β_2	-0.3174	0.1109	(-0.5359, -0.0972)
β_3	-0.3728	0.1244	(-0.6102, -0.1276)
β_4	-0.7451	0.1709	(-1.0760, -0.4078)
β_5	-0.000402	0.001304	(-0.002807, 0.002327)
β_T	-0.0367	0.2589	(-0.5392, 0.4722)
$\exp(\beta_T)$	0.9968	0.2631	(0.5832, 1.6041)
Δp	-0.002285	0.014085	(-0.030341, 0.024540)

The relative risk measure is usually employed to compare categories in logit discrete choice models. This measure is obtained by determining the ratio of the relative probabilities of success and failure of two categories. With regard to the type of treatment received, a patient given the (d4T + ddl + IND) treatment has an odds ratio of reducing the viral load to undetectable levels of 99.7% with respect to another, with the same characteristics, who receives the (d4T + 3TC + IND) treatment. There is a probability of 44.7% that the new treatment (d4T + ddl + IND) is more effective than the first-named one (d4T + 3TC + IND). The regression coefficients corresponding to the costs are the same as in the previous section.

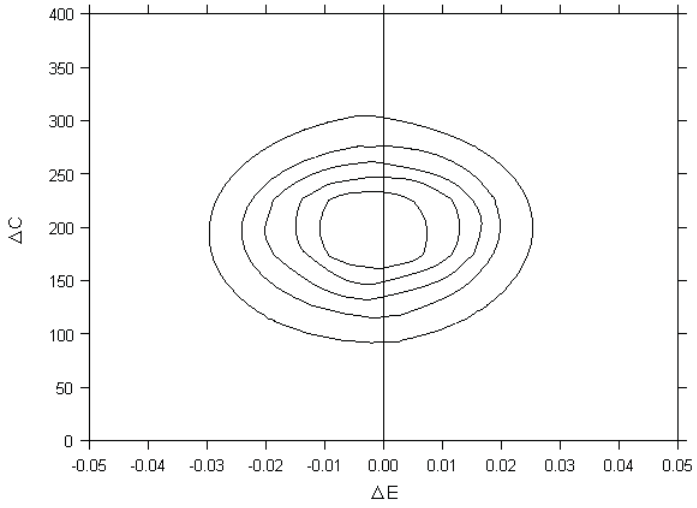

Figure 3: *Joint posterior distribution of costs and relative risk (binary effectiveness).*

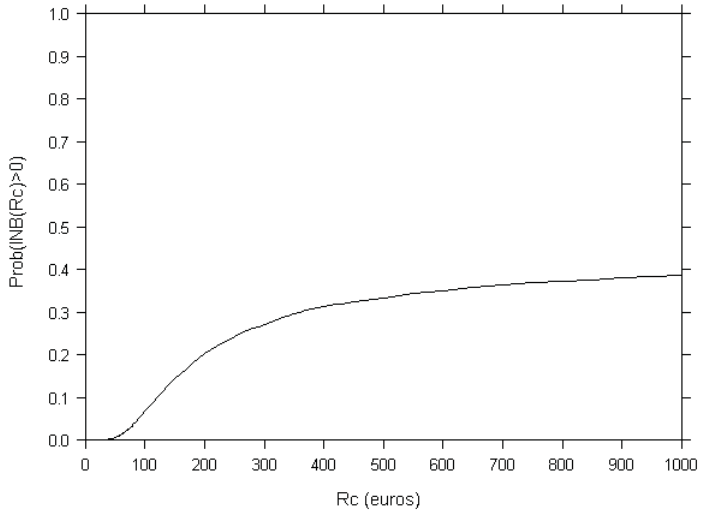

Figure 4: *Cost-effectiveness acceptability curve (binary effectiveness).*

Besides the odds ratio, we estimate the mean difference in the probability of success between treatments. The mean incremental change in probability is estimated as -0.229%, with a Bayesian interval of $(-3.03\%, 2.45\%)$.

Figure 3 shows the joint posterior distribution of the increase in probability and of the incremental cost.

The cost-effectiveness acceptability curve is shown in Figure 4. From the cost-effectiveness acceptability curve, we see that the new treatment (d4T + ddl + IND) is not preferred, in all cases, to the control treatment (d4T + 3TC + IND).

3.3 Cost asymmetry: log-normal model

Most statistical models assume normality in effectiveness and in costs (O'Hagan *et al.*, 2001, O'Hagan and Stevens, 2002). In practice, however, costs tend to present severe asymmetry, and this should be taken into account in the analysis. Evidence of skewing is shown in Figure 5, which contains a histogram of the residuals from the normal model of Section 3.1. Due to this skewness, it is more appropriate to consider a log-transformation. The analysis of the effectiveness is similar to that of Section 3.1.

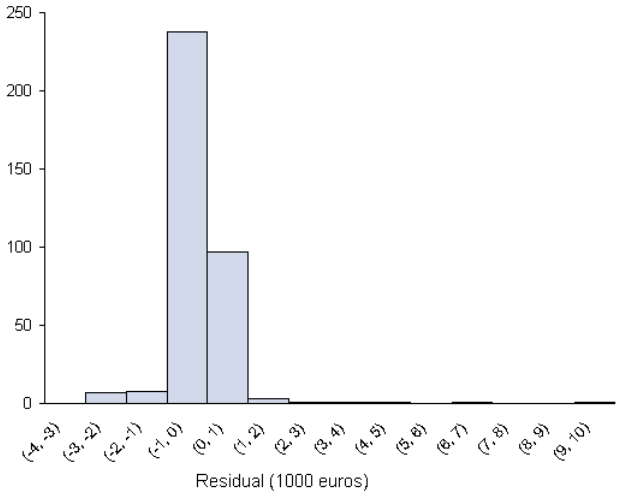

Figure 5: *Histogram of residuals of the normal model.*

The coefficients of the log-normal model does not have a natural interpretation and it is necessary to search for another means of comparing the effect of a covariate. In this case, the ratio of the costs of having or not a characteristic can be described by the exponential of the coefficient. We use this property to define our prior information:

$$\exp(\delta_k) = \frac{C(X_k = 1)}{C(X_k = 0)} = \frac{C(X_k = 1) - C(X_k = 0)}{C(X_k = 0)} + 1 = \frac{\Delta C}{C(X_k = 0)} + 1,$$

where $C(X_k = 1)$ is the cost of a patient in the treatment group and $C(X_k = 0)$ is the cost of a patient in the reference group.

3.3.1 Priors

We can elicit the prior mean and variance of the exponential of each coefficient β using the prior information shown in Section 3.1.

$$\mathbb{E}[\exp(\delta_k)] = \frac{E(\Delta C)}{C(X_k = 0)} + 1 \qquad \text{and} \qquad \text{Var}[\exp(\delta_k)] = \frac{\text{Var}(\Delta C)}{(C(X_k = 0))^2}.$$

Using as $C(X_k = 0)$ the sample mean of the cost for the reference group we obtain the prior mean and variance for the exponential of the coefficients. For continuous covariates as *age* or *start* we use as reference group the total of the sample. With this information and similarly to the previous section we can obtain the prior information about the coefficients:

$$\beta^0 = (0, 1.39060 \cdot 10^{-3}, 2.76073 \cdot 10^{-2}, -6.12301 \cdot 10^{-6}, -6.02103 \cdot 10^{-6},$$
$$\cdot 6.93488 \cdot 10^{-3}, 2.75936 \cdot 10^{-2}),$$

and

$$V_1 = \text{diag}(10^{10}, 4.80952 \cdot 10^{-7}, 4.64127 \cdot 10^{-5}, 1.22460 \cdot 10^{-5}, 1.20421 \cdot 10^{-5},$$
$$\cdot 1.19405 \cdot 10^{-7}, 4.63492 \cdot 10^{-5}).$$

3.3.2 Results

The new treatment is 2.78% more expensive than the control one, with an interval of probability of 95% of (1.48%, 4.06%).

Table 4: *Posterior statistics and symmetrical interval of probability at 95% (log-normal model).*

	Mean	Standard deviation	95% CI
δ_0	8.785	0.02294	(8.74, 8.829)
δ_1	0.000961	0.000585	(-0.000190, 0.002107)
δ_2	0.02548	0.006382	(0.01285, 0.03784)
δ_3	0.000862	0.003448	(-0.005887, 0.007592)
δ_4	-0.000138	0.003429	(-0.00685, 0.006563)
δ_5	0.000423	0.0000858	(0.000259, 0.000596)
δ_T	0.027411	0.006416	(0.0147, 0.03977)
$\exp(\delta_T) - 1$	0.02781	0.006594	(0.01481, 0.04057)

Figure 6 shows the joint posterior distribution of the incremental effectiveness and the relative incremental cost ($\exp(\delta_T) - 1$).

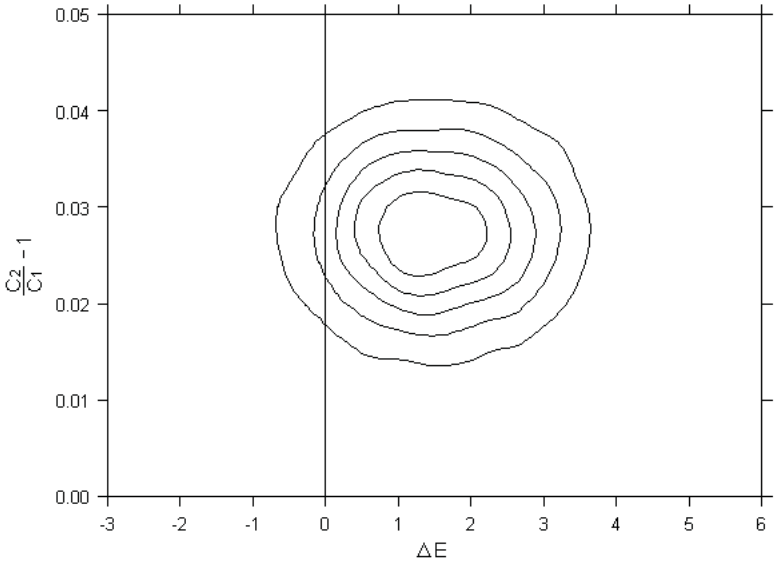

Figure 6: *Joint posterior distribution of incremental effectiveness and of the ratio between costs (log-normal model).*

The cost-effectiveness acceptability curve is shown in Fig. 7.

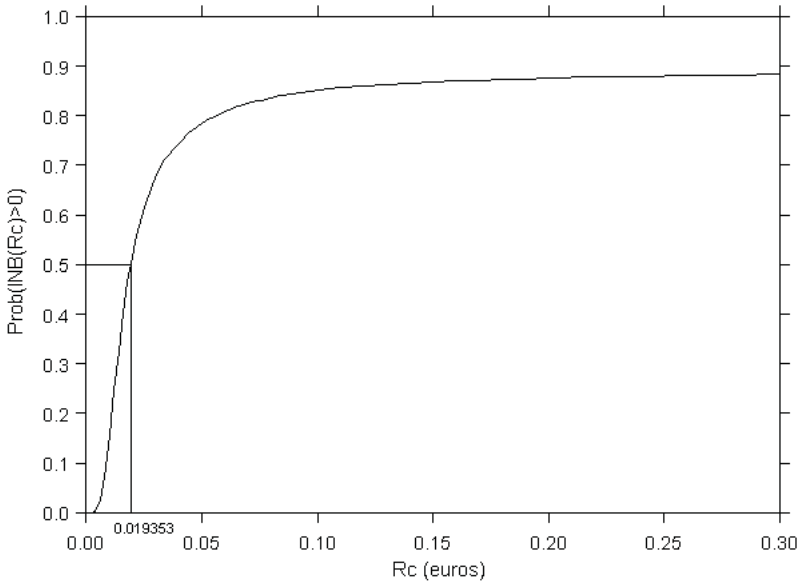

Figure 7: *Cost-effectiveness acceptability curve (log-normal model).*

The critical value is 0.019353. When the decision-maker is prepared to increase costs by 1.9353% or more in order to increase effectiveness by one unit, then the new treatment (d4T + ddl + IND) will be preferred. If we take the cost of the control treatment as its mean value (7142.44 euros), an increase of 1.9353% is equivalent to 138.23 euros. In Section 3.1, with the assumption of normality, this critical value was calculated to be 141.89 euros. The greater the degree of asymmetry in costs, the greater is the divergence between the results obtained by the normality assumption and the log-normal assumption.

4 Conclusions

This paper presents a flexible methodology to carry out cost-effectiveness analysis, developed from a Bayesian perspective. The assumption common to all models is that the effectiveness and cost differences between alternative treatment options may not be due solely to the type of treatment received. Sample differences between the groups given one or other of the two treatments may be relevant and influence the final results for effectiveness and cost. Therefore, a valid comparison of two alternative treatments is only possible if we are able to isolate the effect of the type of treatment received on the variables of interest (effectiveness and cost). In order to achieve this, we must create a regression model that includes the other explanatory variables and a dichotomous variable that is assigned a value of 0 or 1 depending on the type of treatment received. On the basis of these models, we can generate the different cost-effectiveness decision-making measures described in the literature.

The initial model is normal-normal, in which both effectiveness and costs are assumed to follow a normal distribution. This assumption may be justified by the central limit theorem, in the case of large sample sizes.

However, on some occasions the effectiveness measure is not determined by a quantitative variable. For example, effectiveness may be measured by whether or not a certain objective has been achieved. Taking this into account, we have developed an alternative model that uses the difference in the probability of success as measure of effectiveness.

Moreover, costs often present severely asymmetrical distributions, or the sample size may be limited, which would invalidate the assumption of normality. In such cases, it is necessary to assume an alternative cost distribution, one that is flexible to the existence of extreme values. Such a requirement is met by the log-normal distribution, and the ratio of costs is then used to compare different treatments.

All the models described here have been developed from a Bayesian perspective, which enables us to incorporate prior information (if it exists) in a natural, flexible way, and to interpret the results in terms of probability. For the purposes of our illustrative analysis, we obtained prior information from the consensus of the experts

who participated in the study. A different elicitation process is proposed for each model, and this process plays an important role in the analysis of the results. For future research more efforts have to be carried out to elicit the prior information and to analyse the robustness of the models. The cost-effectiveness acceptability curve is shown to be a natural measure and one that is easy for the decision-maker to interpret.

Acknowledgments

The authors are very grateful to an executive editor and two anonymous referees for their constructive and helpful comments, which have significantly improved the paper. This research is partially funded by grants Beca Bayer (Asociación de Economía de la Salud and Química Farmacéutica Bayer, S.A.) and MCyT (Ministerio de Ciencia y Tecnología, Spain, Project BEC2001/3774). We would like to thank Professor Badía (Health Outcomes Research Europe, Spain) for allowing us to use the COSTVIR data archive. Any responsability for the further analysis of the data is ours.

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Resum

La major part de les publicacions que comparen diverses opcions de tractament, es redueixen a comparar els resultats (eficàcia i cost) obtingudes per cada grup. Aquest treball proposa la incorporació d'altres característiques dels pacients en l'anàlisi. La major part dels estudis duts a terme en aquest context suposen que tant el cost com l'eficàcia són normals. A la pràctica les dades no sempre es distribueixen d'acord amb aquesta hipòtesi. Cal desenvolupar models alternatius. En aquest article presentem un model general que incorpora una mesura de l'eficàcia binària i un cost asimètric. En un aplicació pràctica, comparem dos tractaments antiretrovirals altament actius donats a pacients VIH asimptomàtics. Proposem un model logit on l'eficàcia es mesura d'acord amb si s'ha aconseguit un determinat propòsit inicial. Per a aquest model, la mesura per comparar els tractaments es la diferència en la probabilitat d'èxit.

A més, les dades de cost són usualment asimètriques cap a la dreta. Proposem usar la transformació logarítmica per a dur a terme el model de regressió. Els tres models es condueixen demostrant els avantatges d'aquest model. La corba d'acceptabilitat cost-eficàcia s'utilitza com a mesura per prendre les decisions.

MSC: 62F15, 62H12, 62P10

Paraules clau: anàlisis baiesiana, eficàcia-Cost, Markov chain Monte Carlo (MCMC), distribucions de cost asimètriques