

Inter-variable Uncertainty In Decision Analytic Modeling: The Concept Of Second-order Sensitivity

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ABSTRACT

The constraint of the current methods of sensitivity analysis in decision analytic models is that those methods only show the sensitivity of the outcomes to a change through a range of potential values for one or more variables without taking into account the existing relationships between those variables. The present study presents various methods, which consider this type of inter-variable uncertainty for economic evaluations based on modeling techniques. We present initially a method assuming only uniform distributions, and subsequently various methods incorporating the real distributions. The results show that this second-order sensitivity of an input variable depends very much on the distribution of the other input variables. Overall our analysis showed that the most sensitive variables for the outcome of the model, were also the most sensitive for the second-order sensitivity of the other input variables.

Keywords: Sensitivity analysis; uncertainty; economic evaluation; cost; intervariable dependence.

Incertidumbre Entre Variables En Modelos De Decisión Analítica: El Concepto De Sensibilidad De Segundo Orden

RESUMEN

La limitación de los métodos actuales de análisis de sensibilidad en modelos de decisión analítica consiste en resolver solamente la sensibilidad de los resultados a un cambio a través de una gama de los valores potenciales para unas o más variables sin considerar las relaciones existentes entre esas variables. Este estudio presenta varios métodos que consideran este tipo de incertidumbre entre variables para evaluaciones económicas basadas en técnicas de modelización. Se presentan un primer método que asume solamente distribuciones uniformes y posteriormente varios métodos que incorporan distribuciones reales. Los resultados demuestran que esta sensibilidad de segundo orden de una variable input depende de manera importante de la distribución de las otras variables input. En conclusión, el análisis demuestra que las variables más sensibles para el resultado del modelo, eran también las más relevantes para la sensibilidad de segundo orden de las otras variables input.

Palabras clave: análisis de sensibilidad, incertidumbre, evaluación económica, coste, dependencia

JEL Classification: I 10.

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1. INTRODUCTION

There is growing evidence that health economic data is beginning to be used more widely to support decision makers in the health service for allocation of scarce health care resources (Drummond, 1999). The most evident impact of health economic studies is expected for reimbursement audiences because of the elaboration of economic reporting requirements. If economic evaluation is to be used for pricing and reimbursement issues by authorities or third party payers, it becomes important for the different stake holders (industry, government, health insurance) that these analyses are being performed according to generally accepted and standardised methods.

The handling of uncertainty in economic evaluation is an important area that remains relatively underdeveloped. Sensitivity analysis is currently the most widely used method to deal with uncertainty in economic evaluations. A sensitivity analysis is based on modification of the basic clinical and economic estimates of parameters to judge the effect on study results of alternative assumptions for the range of potential values for uncertain parameters (Task Force on Principles for Economic Analysis of Health Care Technology, 1995). The methods used, the choice of parameters and the range of these parameters must be stated and substantiated. If this procedure is followed for each estimate in turn, then we refer to it as a 'univariate sensitivity analysis' (Briggs 1999). In a multivariate sensitivity analysis, the effect of simultaneous changes in 2 or more variables is examined on the outcomes of the study. Probabilistic sensitivity analysis (PBA) is the most advanced method, which tries to obtain random distributions around each parameter and -- in conformity with the distributions -- then tries to arrive at a new estimate for each parameter (Briggs 1999).

The constraint of the above-mentioned methods for sensitivity analysis in decision analytic models is that those methods only show the sensitivity of the outcome of a model to a change through a range of potential values for one or more variables without taking into account the impact of an input variable on the sensitivity of another input variable.

The objective of this manuscript is to present various experimental methodologies, which consider this type of inter-variable uncertainty for economic evaluations based on decision analytic techniques. The concepts are illustrated using a Markov model, which compares the economic outcomes of a maintenance treatment with selective serotonin reuptake inhibitors (SSRIs) as the first choice therapy for depression over a one year follow up period. The general structural details of the Markov depression model have already been described in a previous paper and the specific details of the model with respect to depression are shown in figure 1 (Nuijten, 1997). The model in figure 1 defines four mutually exclusive states: no depression, mild depression, severe depression and chronic depression and the patient's progression through these states is divided into 6 cycles of 2 months each, which closely approximates the time of the sequential therapeutic stages. Chronic depression represents an absorption state, and after entering this state, a patient remains there. It is a valid health state

because of the short-term horizon of the current model. In case of extrapolation to a longer period of time, it probably would be better to stratify this health state into more health states.

The transition probabilities between the states are based on response rates to treatment and relapse rates after termination of treatment. A 2 months cycle time has been chosen, because this interval closely approximates the time of the sequential therapeutic stages: e.g. the initial 2-months trial of anti-depressant medication is followed by a continuation treatment in case the patient responded positively. Therefore the response rate was based on a meta-analysis of antidepressant medications in clinical trials with follow-up of approximately 2 months. Treatment given for 1 year or more after the acute phase is called continuation treatment and the aim of this treatment strategy is to prevent relapses of new depressive episodes. The relapse rates were derived from long-term clinical trials comparing continuation treatment with “no” continuation treatment (placebo). Further details of the sources for the clinical and economic data have been given in the previous article (Nuijten, 1997).

2. MEASUREMENT OF SENSITIVITY

Summary of concepts

A sensitivity analysis is based on the determination of the difference in a clinical or economic outcome when an input value is varied within its range and only depends on the range of a variable (Nuijten, 1997). This can be expressed as:

$$S_{v_1} = \Delta y = a \cdot \Delta v_1 \quad (\text{Eq. 1})$$

where S_{v_1} is the sensitivity of variable v_1 defined by the range Δy ; the slope a is derived from the sensitivity curve for v ($y = b_{v_1} + a_{v_1} \cdot v_1$) (Nuijten, 1997). In this formula the outcome is either the effectiveness or the costs associated with an initial treatment over a period of follow-up. In our depression model example the outcome was the total medical costs over a period of 1 year. The linear relationships in this manuscript were taken from two previous studies, in which those linear relationships were determined empirically by means of a one-way sensitivity analysis (Nuijten, 1997, Nuijten 1999). In this equation Δy and Δv_1 represent the range of the output and input values respectively. The sensitivity ($S_{v_1}, S_{v_2}, \dots, S_{v_k}$) for each input variable in the depression model is shown in Table 1. The *per diem* (*pdiem*) was the most sensitive variable using the presented method for sensitivity analysis. The sensitivity of an input variable v_1 in the current sensitivity analysis only depends on the range of that input variable v_1 , because the coefficient a seems a constant factor according to Eq. 1. However the coefficient a actually depends on all other input variables of the model, excluding v_1 .

$$a_1 = F(v_2, v_3, \dots, v_n) \quad (\text{Eq. 2})$$

Where coefficient a_1 of variable v_1 is a function of variables $v_2, v_3 \dots v_n$.

Consequently:

$$S_{v_1} = F(a_1; dv_1) = F(v_2, v_2, \dots, v_n; dv_1) \quad (\text{Eq. 3})$$

Hence the sensitivity of v_I depends on the range of v_I (dv_I) and the fixed input values of all other variables in the model (v_2, v_2, \dots, v_n). Thus the constraint of the standard one-way sensitivity analysis is that it shows the sensitivity of the outcomes to a change through a range of potential values for v_I without taking into account the existing relationships between this measure of sensitivity and the other variables (v_2, v_2, \dots, v_n). Although in a PBA the relationships between the input variables are taken into account, the results of a PBA only yield an overall figure of uncertainty, for example the standard deviation, but they do not show the impact of variable A on the sensitivity of variable B. The present study presents various methodologies which consider this type of inter-variable uncertainty for economic evaluations based on modeling techniques.

3. METHODS

A literature review did not yield any studies, which address this type of inter-variable uncertainty. Consequently the methods, which are described in this section, are novel and not related to published methodologies, and therefore only a limited number of bibliographic references are included.

3.1 Uniform distributions

This section presents a mathematical method to determine the dependence of the sensitivity of a variable on other input variables. Initially we assume that all variables have a uniform distribution with an absolute lower and upper limit (Table 1). The sensitivity of v_1 is determined at the lower value of another input variable v_2 ($S_{v_1 2 min}$) and subsequently at the upper value of v_2 ($S_{v_1 2 max}$). A measure of the impact of v_2 on the sensitivity of v_1 is the absolute value of the difference ($\Delta S_{v_1 2}$) between the sensitivity of v_1 , at the lower limit of v_2 , and the sensitivity at the upper limit of v_2 :

$$\Delta S_{v_1 2} = \text{abs}(S_{v_1 2 max} - S_{v_1 2 min}) \tag{Eq. 4}$$

This “sensitivity of the sensitivity”, is defined as second-order sensitivity for the remainder of this article. Consequently the traditional sensitivity of the outcome of a model to change of a variable is defined as a first-order sensitivity. Figure 2 shows the second-order sensitivity of $p1$ to the other input values of the model: this analysis shows that the sensitivity of $p1$ is most sensitive to the *per diem*. The results for all variables are shown in Table 2.

The above mentioned calculations were performed using TreeAge and Excel. Step 1: The fixed input value of v_2 is changed to the upper value; Step 2: A sensitivity analysis is performed for v_1 by varying the range between the upper and lower value of v_1 , which yields the range in the outcome for the upper value of v_2 ($S_{v_1 2 max}$); Step 3: The fixed input value of v_2 is changed to the lower value; Step 4: A sensitivity analysis is performed for v_1 by varying the range between upper and lower value of v_1 , which yields the range in the outcome for the lower value of v_2 ($S_{v_1 2 min}$); Step 5: the absolute difference $\Delta S_{v_1 2}$ is calculated between $S_{v_1 2 max}$ and $S_{v_1 2 min}$. Step 1, 2, 3, and 4 were performed in DataTreeAge and Step 5 was performed in Excel.

A disadvantage of the above-mentioned method is that the second-order sensitivity of variable v_1 to v_2 does not only depend on v_2 , but also on Δv_1 , which is shown in the following equations:

$$S_{v_1 2 max} = a_{max} \Delta v_1 \tag{Eq. 5}$$

$$S_{v_1 2 min} = a_{min} \Delta v_1 \tag{Eq. 6}$$

$$\Delta S_{v_1 2} = (a_{max} - a_{min}) \Delta v_1 = \Delta a \Delta v_1 \tag{Eq. 7}$$

Consequently, the second-order sensitivity of v_1 to v_2 is better reflected by the following equation:

$$SS_{v_1 v_2} = \Delta S_{v_1 v_2} / \Delta v_1 = \Delta a \quad (\text{Eq. 8})$$

Where $SS_{v_1 v_2}$ is the uniform second-order sensitivity of v_1 to v_2 . The results of this analysis are also shown in Table 2, which shows that this adjustment does not change the relative impact of the other variables on the sensitivity of another variable (e.g., $p1$), because all second-order sensitivity values are divided by the same value (e.g., $\Delta p1$). An advantage of this measure of second-order sensitivity is that it allows a comparison of the impact of one variable on the sensitivity of the other variables. The results in Table 2 can be judged horizontally and vertically: 1) the rows show which variable has the highest impact on the sensitivity of a variable (e.g., $pdiem$ has the highest impact on $p1$) and 2) the columns show the impact of a variable on the sensitivity of other variables (e.g., $pdiem$ has the highest impact on $p3$).

The second-order sensitivity of consultation does not depend on the *per diem*, while the *per diem* heavily influences the sensitivity of the other variables. This means that the sensitivity of all other variables depends heavily on the fixed input value of the *per diem*. For example, when $p1$ is varied between 0.5 and 0.7 the change in the outcome is US\$ 56501 using a *pdiem* of US\$ 500, which is the fixed input value in the model. However, when the same sensitivity analysis is performed varying $p1$ between 0.5 and 0.7 using a *per diem* of US\$ 800 instead of US\$ 500, the change in outcome is US\$ 9115. Thus the sensitivity of the model to a change in $p1$ is much larger, when the *pdiem* is US\$ 800 than when the *pdiem* is US\$ 500.

3.2 Real distributions

A limitation of the above-mentioned equation 1 is that it is based on the assumption that all input variables have a uniform distribution without taking into account the real distribution of the input variables. Therefore the original method for the determination of the second-order sensitivity was adjusted to include the real probability distributions of all variables. As a consequence a different outcome was defined for second-order sensitivity.

Standard deviation-based approach using linear relationships

The original equation (Eq. 1) is adjusted to:

$$S_m = a_m \cdot \Delta v_m \quad (\text{Eq. 9})$$

S_m is the sensitivity of variable v_m , which depends on the range of variable v_m , but also on the value of a_m , which is a function of all other variables, excluding v_m .

The following equation is determined:

$$a_m = k \cdot v_n + l \quad (\text{Eq. 10})$$

Where a_m is a function of variable v_n ; k and l are the coefficients. In this example when v_m is $p1$ and v_n is $pdiem$, k is -55.7 and l is 605 .

$$a_{p1} = -28257 \quad (\text{Eq. 11})$$

Consequently a at the fixed input value of $pdiem$ of 500 equals -28257 . Figure 3 shows that a linear relationship exists between a_{p1} and $pdiem$, which we also proved for the other relationships between the a values and the input values. A measure of second-order sensitivity of v_m to v_n is the standard deviation of a_m resulting from Eq. 12, which is a function of the standard deviation of v_n ($SD-v_n$).

$$SD-a_m = |k| SD-v_n \quad (\text{Eq. 12})$$

where $SD-a_m$ is the second-order sensitivity of variable v_1 to v_2 .

An adjustment to our example leads to the following formula:

$$SD-a_{p1} = |k| SD-pdiem_n = 57.7 \cdot 2,998 = 173$$

Thus the *per diem* leads to a standard deviation of 173 , which reflects the second-order sensitivity of $p1$ to $pdiem$. The standard deviations of the other variables are shown in Table 3, which shows that $pdiem$ has the highest impact on the sensitivity of $p1$ and all other variables, excluding consultation. Those results also allow us to determine the impact of each variable on the sensitivity of the other variables; in this example the *per diem* has highest impact on $p3$.

Point-sensitivity

The above-mentioned methods for the determination of second-order sensitivity are based on the distribution of variables, which assess simultaneously the impact of a fixed input value (mean) and its associated range on the sensitivity of another input variable.

$$S_m = \Delta y_m = a_m \cdot \Delta v_m \quad (\text{Eq. 13})$$

Equation 13 states that sensitivity of variable v_m depends on the range of v_m and the mean fixed input value of a_m only. Consequently it is reasonable to perform a sensitivity analysis, which shows only the impact of the fixed input value of a_m without including the impact of its range. In a previous article, we introduced the concept of point-sensitivity analysis, which measures the responsiveness of the outcome to the input value at a fixed point and does not include any associated range of the input (Nuijten, 1997). The definition of point-sensitivity was based on the concept of point-elasticity (Eq. 14) where x and y represent the fixed input value and the outcome respectively and η_s refers to point-elasticity, which describes the % change in the outcome, when the input variable changes 1%.

$$\eta_s = dy/dx \cdot x/y \quad (\text{Eq. 14})$$

In the case of a linear sensitivity relationship (Eq. 15) a more simple formula (Eq. 16) can be used:

$$y = a \cdot x + b \quad (\text{Eq. 15})$$

$$\eta_s = a \cdot x / (a \cdot x + b) \quad (\text{Eq. 16})$$

The concept of point sensitivity, was in the previous studies, applied to the first-order sensitivity of an input variable, but it can also be applied to determine the impact of the mean value of a_m on the second-order sensitivity of another input variable by adjusting the equations:

$$\eta_{m,n} = da_m / dv_n \cdot v_n / a_m \quad (\text{Eq. 17})$$

Where $\eta_{m,n}$ is the second-order point sensitivity of v_m to v_n . Because of the linear sensitivity relationship (Eq. 18) a more simple formula (Eq. 19) can be used:

$$a_m = k \cdot v_n + l \quad (\text{Eq. 18})$$

$$\eta_{m,n} = k \cdot v_n / (k \cdot v_n + l) \quad (\text{Eq. 19})$$

In this example when v_m is *p1* and v_n is *pdiem*, k is -57.7 and l is -607.7 , the second-order point sensitivity is $1,021$. Hence an increase of the *per diem* by 1% results in a 1.201% increase of a_{p1} . Figure 4 shows the point-sensitivity of *p1* to the other input variables, which shows that *p3* and *p4* now have become more sensitive variables than the *per diem*. Table 4 shows the results of the point-sensitivity analyses for all variables in the model for depression, which show that *p3* and *p4* have become the most sensitive variables for most of the input variables, while the impact of the *per diem* has become lower.

4. DISCUSSION

The constraint of the standard methods for sensitivity analysis is that those methods only show the sensitivity of the outcomes to a change through a range of potential values for one or more variables without taking into account the impact of an input variable on the sensitivity of another input variable. The present study describes various experimental methodologies, which consider this type of inter-variable uncertainty for economic evaluations based on decision analytic techniques. We initially presented a method for uniform distributions, and subsequently a method for real distributions of the input variables. The results show that this second-order sensitivity of an input variable can depend heavily on the distribution of other input variables. Overall our analysis showed that the most sensitive variables for the outcome of the model (first-order sensitivity) were also the most sensitive for the second-order sensitivity of the other input variables. Finally we presented a point-sensitivity analysis, which shows only the impact of the fixed input value of an input variable on sensitivity of another variable without including the impact of its range. The results from this type of second-order sensitivity analysis resulted in a different ranking of all variables according to their impact on the sensitivity of other variables. The difference in ranking of the variables results from the impact of the distribution of an input variable on the second-order sensitivity, which was excluded from the second-order sensitivity based on the point-sensitivity analysis. From a methodological point of view one may argue what is scientifically the most correct measure of second-order sensitivity: the second-order sensitivity based on the distributions of the input variables or on the fixed input value only.

The results from the second-order sensitivity analyses show that the most sensitive variables in the model also have the most impact on the sensitivity of the other input variables. Consequently one can argue that the reduction of uncertainty associated with the most sensitive variables in a model will lead to an overall reduction of uncertainty in the outcomes in the model because of a reduction in sensitivity of most variables. Hence it may be more important to investigate the uncertainty of the most sensitive variables of the model in more depth, e.g. by means of a meta-analysis, than to investigate the uncertainty associated with all variables. On the other hand, it may be worthwhile to reduce the sensitivity of the most sensitive variable by identifying the variables, which mostly influence its sensitivity by means of second-order sensitivity analyses. Although a more general mathematical proof is required to support those conclusions, which are based on empirical findings from a depression model, we may end with the following suggestions: 1) identify the most sensitive variables in the model by means of traditional sensitivity analysis (first-order sensitivity), 2) identify the variables, which have the most impact on the sensitivity of those most sensitive variables by means of a second-order sensitivity analysis, 3) reduce the uncertainty associated the variables, which have been identified in the previous two steps.

This so-called second-order sensitivity analysis could be a tool for investigating the uncertainty in the model during the analysis phase of the research, e.g. prioritizing further research for input data of the model and may subsequently reduce the uncertainty in the model. For example the clinical response rate was initially based on one few studies leading to a large variance, which may be reduced by including the results of more published studies or by performing a formal meta-analysis. The use of 2-order sensitivity analysis may further reduce the extra costs for the reduction of the uncertainty associated with this input variable. For example the 2-order sensitivity analysis may show that the uncertainty associated with the clinical response rate depends mainly on the hospitalization rate. Consequently the extra cost of exploring this response rate may be less than the extra costs for reducing the range of the response rate by means of additional meta-analysis.

The concept of second-order sensitivity should not be confused with co-variance between input variables. In this paper we assumed that there is no co-variance between the input variables, but that there is another relationship between input variables, which results from the model structure. This paper showed that, even when there is no co-variance between two input variables, $V1$ and $V2$, the value of input variable $V1$ still may have an impact on the sensitivity of the outcome of the model to the input variable $V2$ resulting from the model structure. In case of no co-variance between $V1$ and $V2$, the sensitivity of $V1$ is determined at the lower value of $V2$ (S_{V12min}) by varying the value of $V1$ from its lower to upper value within the range of $V1$. Subsequently, the sensitivity of $V1$ is determined at the upper value of $V2$ (S_{V12max}) by varying the value of $V1$ again from the same lower to the same upper value within the range of $V1$. The lower and upper values of $V1$ are independent from the value of $V2$, when there is no co-variance between $V1$ and $V2$. However, in case of co-variance between $V1$ and $V2$, the lower and upper values of $V1$ depend on the value of $V2$, and therefore 1) the sensitivity of $V1$ at the lower value of $V2$ (S_{V12min}) is based on a different range than at the upper value of $V2$ (S_{V12max}) and 2) consequently these ranges are smaller than the actual range for $V1$.

For, example, if we assume a hypothetical co-variance between $p1$ and *per diem*: a lower response rate is associated with higher *per diem*: at $p1$ is 0,5 the *per diem* varies between US\$ 500 and US\$ 800 and at $p1$ is 0,7 the *per diem* varies between US\$ 200 and US\$ 500. The resulting absolute value of the difference between the sensitivity of *per diem*, at the lower limit of $p1$, and the sensitivity at the upper limit of $p1$ (Eq. 4) becomes US\$ 3385 (US\$ 9463 – US\$ 6078), which is much lower than the base-case result of US\$ 6927.

We have to remark that current paper only focused on one-way sensitivity analysis, whereas the health authorities are increasingly requiring assessments that contain probabilistic sensitivity analysis, for example NICE. Whereas the results from a PSA are submitted to health authorities, a second-order sensitivity analysis should be considered more a tool in order to investigate the uncertainty in the model during

the analysis phase of the research, e.g. prioritizing further research. Consequently, the use of a second-order sensitivity analysis may reduce the variance in the results of the PSA.

Another reason why the outcomes of a second-order sensitivity cannot be used as final outcomes for uncertainty, is that the current methodology only focused on the total costs, which is only an intermediate outcome in a health economic study. The incremental cost-effectiveness ratio (ICER) should be considered the ultimate measure of cost-effectiveness and therefore the application of second order sensitivity to ICER may be explored.

Finally we end with a practical consideration, that the actual execution of the analyses was a time consuming exercise. The current software, does not contain an analysis tool for second-order sensitivity analysis, because it is a new type of analysis. The incorporation of such an analysis tool in current software would facilitate the execution of a second-order sensitivity analysis.

5. CONCLUSION

The constraint of the current methods of sensitivity analysis in decision analytic models is that those methods only show the sensitivity of the outcomes to a change through a range of potential values for one or more variables without taking into account the existing relationships between those variables. The present study presents various methods, which consider this type of inter-variable uncertainty for economic evaluations based on modeling techniques. This second-order sensitivity analysis should not be considered a substitute of existing methodologies for sensitivity analysis, but it may be an additional tool for dealing with uncertainty during the analysis phase of the research. It can help to minimize the extra burden and cost associated with further research by prioritizing the input variables, which may have a high impact on the model, but also on the sensitivity of other variables.

FIGURE LEGENDS

Figure 1: Markov states and possible transitions used in the depression model.

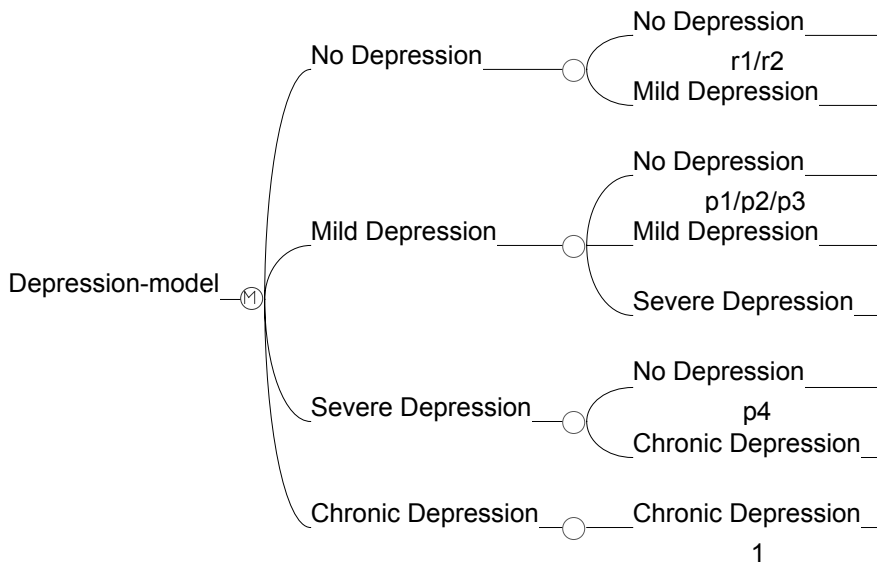


Figure 2: The second-order sensitivity of p1 to the other variables in the model.

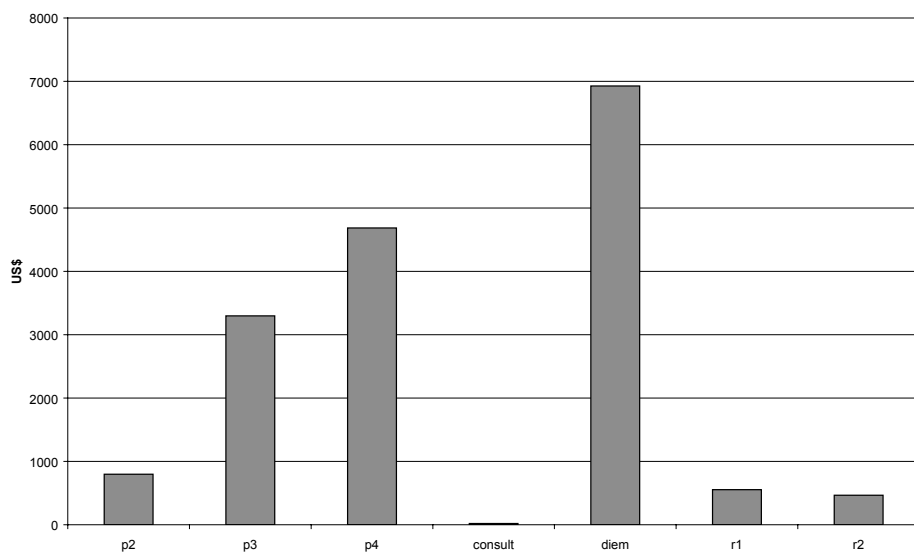


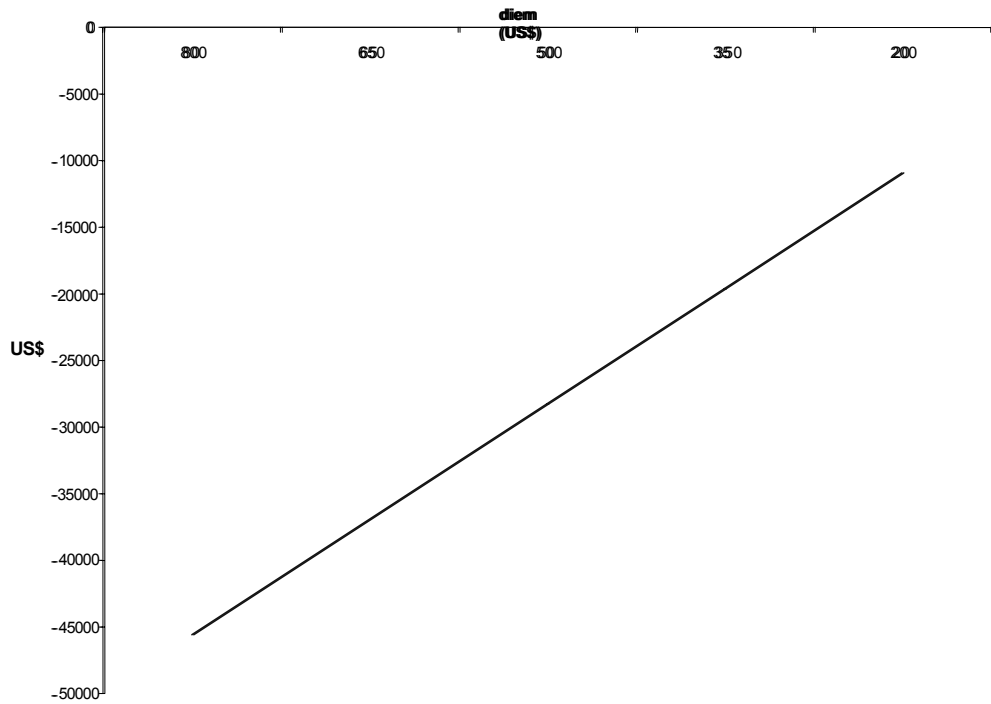
Figure 3: The relationship between a_{p1} and pdiem.

Figure 4: The second-order sensitivity of p1 to the other variables in the model using point-sensitivity analysis.

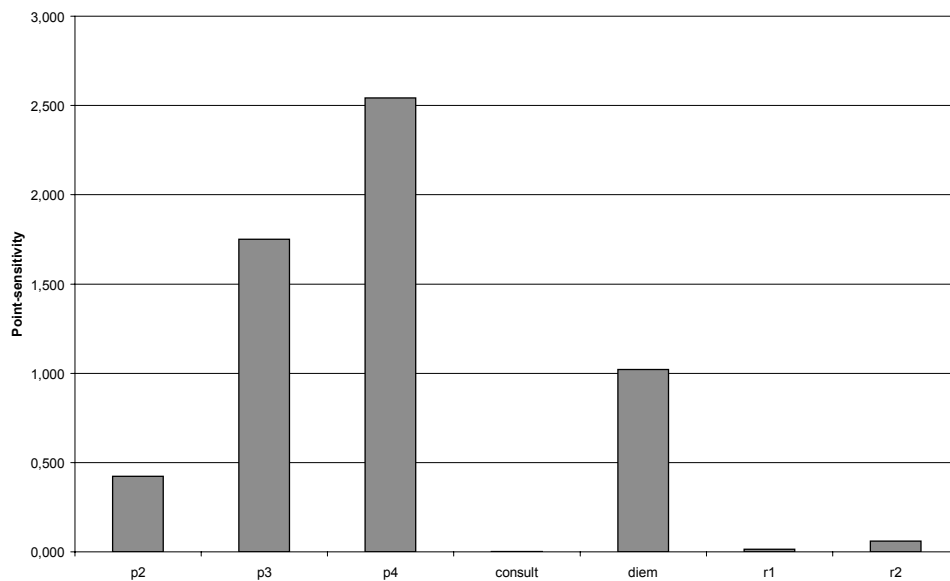


Table 1: Clinical and economic data: input values and range.

Variable†	Input values		Sensitivity (US\$)
	Fixed (SD)	Range	
Clinical probabilities			
Response rate to first-line treatment with an SSRI (p1)	0.60 (0.05)	0.50-0.70	56501
Response rate to TCA after SSRI treatment failure (p2)	0.30 (0.03)	0.25-0.35	8911
Response rate to another TCA after earlier TCA treatment failure p3)	0.30 (0.03)	0.25-0.35	7436
Response rate to hospitalisation (p4)	0.50 (0.04)	0.41-0.58	9850
Relapse rate during maintenance treatment with SSRI (r1)	0.04 (0.015)	0.02-0.06	1661
Relapse rate during no treatment after response to a TCA (r2)	0.10 (0.033)	0.07-0.16	932
Economic (\$US)			
Daily treatment cost of SSRI (DTC-SSRI)w	2 (0)	N.A. ‡	N.A.
Daily treatment cost of TCA (DTC-TCA)	0.19 (0)	N.A.	N.A.
Consultation tariff (consult)	50 (23.4)	10-90	526
Hospital per diem tariff (pdieem)	500 (173)	200-800	15621
Abbreviations: SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant			
† Further detail on data sources is given in a previous article (Nuijten 1997). Distributions of p, r1 and r2 have been changed compared with previous paper.			
‡: N.A. : not applicable.			

Table 2: The uniform second-order sensitivity for all variables in the model for depression.

	p1	p2	p3	p4	consult	Pdiem	r1	r2
ΔS_v								
p1	n.a.	797	3298	4686	20	6927	554	466
p2	797	n.a.	1028	1408	6	2159	244	173
p3	3298	1026	n.a.	5628	3	8916	977	501
p4	4687	1408	5628	n.a.	2	11822	573	9
consult	19	6	3	2	n.a.	0	9	53
pdiem	6927	2159	8927	11822	0	n.a.	2048	1076
r1	554	245	975	572	6	2111	n.a.	3
r2	467	174	501	8	53	1075	3	n.a.
Δa								
p1	n.a.	3985.0	16490.0	23430.0	100.0	34635.0	2770.0	2330.0
p2	7970.0	n.a.	10280.0	14080.0	60.0	21590.0	2440.0	1730.0
p3	32980.0	10260.0	n.a.	56280.0	30.0	89160.0	9770.0	5010.0
p4	27898.8	8381.0	33500.0	n.a.	11.9	70369.0	3410.7	53.6
consult	0.2	0.1	0.0	0.0	n.a.	0.0	0.1	0.7
pdiem	11.5	3.6	14.9	19.7	0.0	n.a.	3.4	1.8
r1	2359.5	1043.4	4152.5	2436.1	25.6	8990.6	n.a.	12.8
r2	3492.9	1301.4	3747.2	59.8	396.4	8040.4	22.4	n.a.

Table 3: The second-order sensitivity for all variables based on standard deviation of a , when using real distributions for input variables.

	p1	p2	p3	p4	consult	pdiem	r1	r2
p1	n.a.	1195.5	4947.0	5578.6	29.3	9986.4	177.0	575.1
p2	1992.5	n.a.	3084.0	3352.4	17.6	6225.1	155.9	427.0
p3	8245.0	3078.0	n.a.	13400.0	8.8	25707.8	624.1	1236.6
p4	6974.7	2514.3	10050.0	n.a.	3.5	20289.7	217.9	13.2
consult	0.1	0.0	0.0	0.0	n.a.	0.0	0.0	0.2
pdiem	2.9	1.1	4.5	4.7	0.0	n.a.	0.2	0.4
r1	589.9	313.0	1245.7	580.0	7.5	7785.0	n.a.	3.2
r2	873.2	390.4	1124.2	14.2	115.9	2318.3	1.4	n.a.

Table 4: The second-order sensitivity based on the fixed input value of a , without including the impact of its range. (point-sensitivity analysis).

	Two							
	p1	p2	p3	p4	consult	pdiem	r1	r2
p1	na	0.423	1.751	2.543	0.002	1.021	0.015	0.060
p2	1.325	na	1.710	2.389	0.002	0.998	0.026	0.074
p3	1.331	0.414	na	2.315	0.000	1.000	0.025	0.050
p4	1.427	0.429	1.714	na	0.000	1.000	0.010	0.001
consult	0.109	0.034	0.017	0.011	na	0.000	0.003	0.074
pdiem	1.330	0.415	1.714	2.315	0.000	na	0.025	0.051
r1	0.999	0.442	1.759	1.036	0.002	1.410	na	0.001
r2	1.501	0.566	1.610	0.025	0.035	0.961	0.001	na

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