The consequences of ignoring correlations between model input parameters in value of information analyses

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Abstract

Stochastic decision models are developed to estimate the mean incremental net benefit of a new technology versus its comparator(s), and the associated probability distribution. The model converts a set of defined distributions of input parameters (for example, treatment response rates, utilities and costs) into a probability distribution on the output parameter (incremental net benefit). In such models, inputs are commonly assumed to be independent, either for the sake of parsimony or due to lack of data on the covariance structure. In this paper we show the impact of not taking into account correlation between input parameters on the estimate of mean incremental net benefit, the variance, and hence the expected value of perfect information and expected value of sample information.

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1. Introduction

Stochastic decision models (i.e. Monte Carlo simulations of Markov or other model structures) are recommended to estimate the cost-effectiveness of interventions, and of capturing the uncertainty around the mean.[1]

In such models, inputs (for example response rates to treatments, resource quantities and utilities) are commonly assumed to be independent as "…analysts … have no data on the covariance structure and so choose not to model covariance…".[2] This is due to the nature of decision analytic modelling: a single trial is unlikely to provide all necessary data for decision making. It is therefore necessary to draw on a variety of summary data from numerous sources.[3 4] Even for those modelling studies drawing on one primary study for effectiveness data, resource use data are usually extracted from other sources, and any correlations between resource use and other model inputs (e.g. response rate) are therefore unknown.

Of recent economic evaluations published in the journal 'Pharmacoeconomics' employing decision analytic modelling and probabilistic sensitivity analysis, a number had access to individual patient level data from one (or more) primary source(s) and so incorporated the correlation structure between (some) variables, most usually the treatment effect (see Appendix for full details). For example:

- Reed et al.[5] modelled the cost-effectiveness of imatinib versus interferon alpha (IFNa) in patients with newly diagnosed chronic phase chronic myeloid leukaemia, drawing on a meta-analysis of two RCTs. In the model, survival in the treatment (imatinib) arm was modelled as survival in control (IFNa) multiplied by a 'calibration constant' corresponding to a percentage reduction in the hazard ratio. From the report it is unclear from where resource use data were drawn.

- Ramsey and colleagues[6] developed a Markov model drawing on data from a single trial of atorvastatin vs no statin in the primary prevention of cardiovascular (CV) events in type 2 diabetes (T2DM). Risk of a CV event with atorvastatin was expressed as a hazard ratio relative to baseline (no statin), using data observed in the CARDS trial. The hazard ratio was assigned a normal distribution, and the baseline risk was that observed from an epidemiological study of the United States T2DM population. Costs were estimated from a separate source.

However, other studies maintained independence between variables:

- Bojke et al.[7] estimated the cost effectiveness of pharmacotherapy versus surgery (laparoscopic fundoplication) for gastro-oesophageal reflux disease (GORD). Key variables (e.g. outcome of surgery, risk of complications, probability of stable maintenance on medical management) were estimated from a fixed-effects metaanalysis of the literature, and incorporated into the model as independent beta distributions. Resource use was estimated from a survey of five hospitals involved in a concurrent comparative trial (the REFLUX trial), and resulting cost inputs were modelled as independent gamma distributions.

- Teerawattananon and colleagues[8] report a comparison of three treatments for cytomegalovirus retinitis (eye infection) in HIV/AIDS patients: systemic (either oral or intravenous) ganciclovir (O/IV), intravitreal injection (IVI), or intraocular implantation (IMP). The model is a decision tree populated with data from a systematic review. All inputs are modelled independently. For example variables U2 (unilateral infection, risk of complications with IVI) and U9 (unilateral infection, risk of complications with IMP) are modelled as independent betas.

The first point to note is that even in the first two cases, dependencies between variables are limited to treatment effect between intervention and control (response in one arm is modelled as a function of response in the other): other inputs are modelled as independent distributions. Secondly, a crucial difference between the Reed[5] & Ramsey[6] papers and the Bojke[7] and Teerawattananon[8] papers is that the first two are modelling one drug versus another, and thus the model structure between the two arms is identical. For the latter two however, the model structure is fundamentally different between the arms,

Where model arms are of identical structure, treatment effect of one drug can be modelled as a function of the treatment effect on the other: $P_n=f(P_o)$, where P_n is response on new, P_o response on old. For example, a commonly used relationship is $P_n=P_o.RR$ where RR is relative risk.

In this paper, we consider the impact of including or excluding correlations between model input parameters on model output (incremental net benefit), and resulting value of information statistics (EVPI, EVPPI and EVSI). It should be noted that we are concerned with the incorporation of dependencies between *input* parameters in a decision analytic model, and not correlations between *output* parameters.

2. The model

We set up a simple illustrative model concerning a new treatment for disease 'X'. With current treatment ('Old') for disease X, evidence suggests an annual mortality risk, P_o, of 0.20. The new treatment ('New') reduces the annual mortality risk to 0.15. Call this P_n. The relative risk (RR) is therefore 0.75. At this stage we do not specify the source of this evidence. It could be anything ranging from expert opinion, two independent case series, or an RCT.

A simple two-state Markov model with transition period of one year and time horizon 15 years is developed to determine the cost-effectiveness of New versus Old (Figure 1). Variables in the model are summarised in Table 1. Costs and outcomes are discounted at 3.5%.

Firstly, we analyse this model deterministically (section 2.1). We then analyse the model probabilistically, assuming independence between input parameters (section 2.2.1), and again assuming a specific relationship between P_o and P_n (section 2.2.2). We consider differences in estimated incremental net benefit, expected value of perfect information and expected value of sample information between 2.2.1 and 2.2.2.

2.1 Deterministic modelling

2.1.1 Deterministic analysis 1 (independent inputs)

First consider a deterministic modelling approach: the input parameters are inserted into the model at their point estimates and the model calculated for 15 transitions. The resulting ICER is £18,834 (Table 2).

Given a willingness to pay threshold of £20,000 per QALY, New would be considered cost-effective compared with Old. Rearranging the inequality, we calculate an incremental net benefit of £1,191.60 (Formulae 1 & 2). As this is positive, we would adopt New as a cost-effective treatment compared with Old. Uncertainty around this point estimate can be captured by means of one- and multi-way sensitivity analyses.

2.1.2 Deterministic analysis 2 (dependent inputs)

Instead of estimating Po and Pn independently, we can express Pn as a function of Po, changing the inputs to those in Table 3. It should be evident that this makes no difference to the deterministic modelling approach, and our estimate of the ICER and INB are unchanged.

2.2 Probabilistic modelling

The limitations of the deterministic approach centre around the characterisation of uncertainty: one-way sensitivity analysis, by definition, only shows how one model parameter affects the ICER / INB, and hence decision. Two-way analysis improves on this by showing how uncertainty in two parameters together affects the ICER / INB, but interpretation becomes rather more awkward, especially as multi-way analyses start to be considered.[9] An alternative is probabilistic sensitivity analysis, where uncertainty in all input parameters is propagated through a model to determine the impact on the ICER / INB. Essentially, inputs are defined in terms of a probability distribution. The model, via Monte Carlo simulation, is a means of combining sampled values from these distributions together to estimate an output distribution (around INB). NICE recommend PSA as the standard approach to sensitivity analysis.[1]

To make the example probabilistic, we assign distributions to each input parameter. Suppose the data informing the economic evaluation are from an RCT comparing New vs Old, of sample size 100 in each arm, and an outcome of survival at 1 year (Table 4). These survival data are used as estimates of P_o and P_n.

The relative risk of death is (15/100)/(20/100) = 0.75. Assuming a lognormal distribution around relative risk, the 95% confidence interval is estimated at (0.408, 1.379) (Formula 3). As the interval includes 1, this result would not be considered statistically significant, given a standard frequentist statistical approach at 95% confidence.

As in the deterministic analysis, we can model these data either as independent annual probabilities of death, P_o and P_n, or as baseline risk (P_o) and relative risk with New (RR), such that $P_n=P_o*RR$.

2.2.1 Probabilistic analysis 1 (Independent inputs)

In the former case, the inputs are as per Table 5 (for the purpose of this example, assume costs and utility data are known with absolute certainty). Beta distributions possess desirable characteristics making them suitable to model probabilities.

The model is simulated with repeated random draws from the two beta distributions, and recording of the outputs, E_n, E_o, C_n and C_o each time (where E_i and Ci are QALYs and cost of intervention i respectively [i = n, o]). The ICER and incremental net benefit, based on the mean values of each output parameter (E_n etc) is calculated after 1000 iterations. This is contrasted with the deterministic case, where the ICER is calculated from E_n, E_o, C_n and C_o generated when each input is at its mean. In this case we estimate an ICER of £20,001 (INB of -£1 at a willingness to pay of £20,000 per QALY gained; Table 6).

Note that these results are similar, but not identical to the deterministic results. This is because the deterministic results are evaluated with the inputs at their mean values, whilst we *should* be interested in the expected value of the outputs.[10] Briggs et al.[10] state that "…in all but the most nonlinear models, the difference between the

expectation over the output of a probabilistic model and that model evaluated at the mean values of the input parameters, is likely to be modest, suggesting the bias in the latter approach is usually not a major concern.". In this example the difference is indeed small, but straddles the threshold (£20,000), implying the decision is sensitive to whether or not a deterministic or probabilistic approach is chosen.

An explanation for the difference could simply be random noise due to insufficient iterations of the Monte Carlo simulation. However, examination of the cumulative estimate of INB shows that the estimate settles down fairly quickly after the first 50 or so iterations, with very little variation after 500 or so, suggesting 1000 iterations is more than enough to obtain a reliable estimate of the INB (Figure 2).

Upon examining uncertainty in the mean results, a scatter plot of incremental cost and QALYs shows a clear positive correlation between incremental cost and incremental QALYs (not unexpected: in this model the longer you live, the more you cost), with the majority of points in the NE quadrant, where New is both more expensive and more effective than Old (Figure 3). The cost-effectiveness acceptability frontier shows that a threshold of £20,000 per QALY, Old has the highest expected net benefit, with a 50.6% probability of yielding the highest net benefit. The per-patient expected value of perfect information at the £20,000 threshold is £7,777 (Figure 4).

EVPPI

In calculating the EVPPI, we have two uncertain parameters which we are assuming to be independent: response rate on old and response on new. Given a willingness to pay of £20,000, the expected value of perfect parameter information on response with old and response with new is approximately equal (£5000 each), which is to be expected given the data for each are based on the same sample size (n=100 in each case), with similar variances (Figure 5).

EVSI

EVSI provides the necessary condition for future research to be worthwhile and is conditional upon the proposed sample size of a study (EVSI|n). The hypothesised trial in this case is essentially two concurrent prospective observational studies, one looking at risk of death with old, and one at risk of death with new. Figure 6 shows the per patient EVSI yielded from the observational studies of n in each arm. (To be useful for decision making, this would need multiplying by the present and future incident population, and netted from the cost of conducting the observational studies to calculate the expected net benefit of sampling. The sample size which maximises the ENBS is the optimal study sample size.) In this case, the per patient EVSI of two prospective case series of size 2n=200 is £4882.

Summary

To summarise the results, the model estimated using two independent beta distributions shows an expected ICER of £20,001. Given a threshold of £20,000, the expected incremental net benefit is therefore -£1. This is less than zero so New would be rejected. However, there is a 49.4% probability that New has a higher net benefit than Old, so by choosing Old, we would be wrong 49.4% of the time. Given a willingness to pay of £20,000 per QALY gained, the expected value of perfect information is £7,777 per patient, and the per patient EVSI of two prospective case series of, for example, size 2n=200 is £4882.

2.2.2 Probabilistic analysis 2 (Correlated inputs)

Now we revisit the model, this time modelling Po as before, but defining Pn = Po*RR, and ln(RR)~N(ln(0.75),0.097). The parameters for the distribution are extracted from the trial data, and the inputs are now as per Table 7.

For the purposes of comparison, we have used exactly the same 1000 sampled values of Po as in probabilistic analysis 1, but recalculated Pn as Po*RR, where RR is sampled from a lognormal distribution.

This model results in slightly different results from probabilistic analysis 1 (Table 8). Note that the cost and QALYs of Old are identical to the previous analysis (the same sampled values are used for Po, and all the other variables are constant), but New now appears more expensive and more effective than it was previously. This leads to a slightly lower ICER of £18,288 (vs £20,001). Examination of cumulative mean INB shows this difference is not random as the two simulations converge on different values (Figure 7).

Correlating Po and Pn systematically reduces the estimate of the ICER. This is due to the mean of retransformed samples from the lognormal distribution not being equal to the original relative risk (i.e. use of the lognormal distribution to sample relative risk is biased). The variance is also reduced, reflected in the CEAC being shifted vertically upwards (Figure 8).

Critically, the EVPI is also reduced when the Po and Pn are correlated, although interestingly at low thresholds, EVPI based on the correlated analysis is higher than for the uncorrelated (Figure 9).

EVPPI & EVSI

[At time of writing these analyses are underway, but early indications suggest the EVPPI and EVSI are reduced compared with probabilistic analysis 1.]

Summary

To summarise the results, the model estimated with a specific dependency between Po and Pn shows an expected ICER of £18,288, the difference most likely being attributable to use of the log normal distribution to estimate relative risk. Given a threshold of £20,000, the expected incremental net benefit is £1712. On this basis new would be accepted. It appears that the EVPPI and EVSI will be reduced compared with probabilistic analysis 1 (results pending).

3. Discussion

These are initial results, and are not guaranteed error free at this stage.

In this analysis we compared the results of a decision analytic model analysed probabilistically assuming independent inputs and reanalysed with a dependency assumed between two input parameters, Po and Pn. Furthermore we assumed that the dependence was characterised by relative risk (RR). Relative risk itself was assumed independent of baseline risk (Po).

The results show that incorporating correlations between parameters reduces uncertainty, reflected in a shifting up of the CEAC, and corresponding decrease in EVPI. It is reasonable to assume that input parameters will exhibit dependencies of one form or another, therefore assuming zero correlations leads to an overestimation of uncertainty and value of information. Overestimating EVPI is not of particularly severe consequence: an EVPI greater than zero is a necessary but not sufficient condition for further research. However, overestimating the EVSI is a problem as this could result in the recommendation of inefficient research.

We assumed a very specific form of dependency between the two parameters, Po and Pn, that is Pn=Po*RR, with RR modelled as a lognormal distribution. There are two issues here.

Firstly, the lognormal distribution leads to a biased estimator of relative risk: the mean of the retransformed samples is not equal to the original mean (in this case the mean of the 1000 samples was about 0.78, not 0.75). This leads to a biased estimate of the incremental net benefit. There are several ways by which this could be corrected. For example, use of a normal distribution in place of lognormal. Other methods of correcting odds ratios,[11] or estimating relative risks from odds ratios[12] could also be drawn on. Refinement of this work should include a bias-corrected estimator of relative risk.

Secondly (and more importantly), the assumed relationship between Po and Pn (Pn=Po*RR) is by no means the true relationship: RR may be a function of Po, or some other functional form may be more appropriate. Unfortunately, it is impossible to estimate this as to do so requires knowledge of the counterfactual: if a patient (or indeed the entire population) responds well on one treatment, it is plausible that they will also respond well on the other (a high value of Po is more likely to lead to a high value of Pn). Whilst given sufficient data, a relationship between Po and RR could be estimated via a meta-regression, the only way this could truly be quantified is if the same patient (or population) could be simultaneously observed taking both treatments separately *ceteris paribus*. This is not physically possible.

In this example we restricted dependency to that between two variables: Po and Pn. Studies in the literature frequently limit dependencies to the key efficacy/effectiveness variables too.[5 6] Given access to patient level data, more sophisticated dependencies could be modelled via the Cholesky decomposition. This allows correlated draws to be taken from the distributions of each of the relevant parameters. However, this does not solve the problem described above as it can only apply to variables observable within patients, not between patients. For example the relationship between response

rate and risk of side effect within one patient can be estimated, but not the response rate of the patient on drug A and response rate on drug B.

Finally, if modelling some relationship between Po and Pn is considered preferable to assuming independent response rates, then it is unclear how to apply this when the structure of the decision model is fundamentally different between arms of a study. For example, Bojke et al.[7] compared surgery with medical management, and so the input variables differed between the arms. It is not clear how a variable representing 'response rate' in one arm directly links to an equivalent in the other arm.

Further discussion points:

- It is reasonable to hypothesise that incorporating dependency within a model reduces uncertainty and hence the value of information. However could part (all?) of the difference observed in this example be due to the problem of using the lognormal distribution for RR? The VoI is a function not only of the variance of INB, but the mean too.
- An iterative approach gradually generalising the relationship between Po and Pn should be explored. For example:
    1. $Po \sim \beta(a,b)$, $Pn \sim \beta(x,y)$
    2. $Po \sim \beta(a,b)$, $Pn = Po.RR$. $RR = 0.75$ (constant)
    3. $Po \sim \beta(a,b)$, $Pn = Po.RR$. $RR \sim LogN(\mu_{rr}, \sigma^2_{rr})$
    4. $Po \sim \beta(a,b)$, $Pn = f(Po)$
    5. $Po \sim D(\theta)$, $Pn \sim D(f(\theta))$
- An issue we have not yet discussed in detail is that gathering information on one parameter leads to reduction in value of further information on a closely correlated one. This requires exploration.
- What exactly are we comparing in the EVSI calculations? We've defined it as two observational studies to estimate Po and Pn versus an RCT to estimate Po and RR. Is this appropriate?

4. Conclusion

In this paper we illustrated, by means of a simple example, the consequences of ignoring dependencies between parameters in a decision analytic model: the variance is overestimated and hence the value of additional information too is overestimated.

Correlations between variables simultaneously observable in one patient can be estimated from patient level data. However, decision analytic modelling (and hence value of information analysis) requires knowledge of correlations between a variable observed in a patient taking one treatment and that same variable had the patient taken the other, i.e. the counterfactual. This is not observable, therefore such dependencies can only be assumed, yet these assumptions are not themselves testable.

Formulae

Formula 1: Incremental Net Benefit

$$\lambda(\overline{E}_2 - \overline{E}_1) - (\overline{C}_2 - \overline{C}_1)$$

λ = shadow price of a QALY / threshold
E_i = QALYs gained on treatment i
C_i = Cost of treatment i

Formula 2: Calculating incremental net benefit

(£20,000 * 1.022) - £19,254 = £1,191.60

Formula 3: Equation for confidence interval around RR

$$e^{\ln(0.75) \pm 1.96 * \sqrt{\left(\frac{1}{15} - \frac{1}{15+85} + \frac{1}{20} - \frac{1}{20+80}\right)}}$$

Figures

Figure 1: Model structure

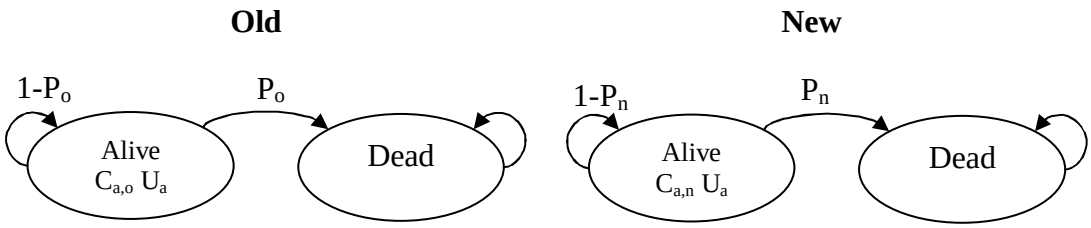


Figure 2: Cumulative estimate of INB by number of iterations

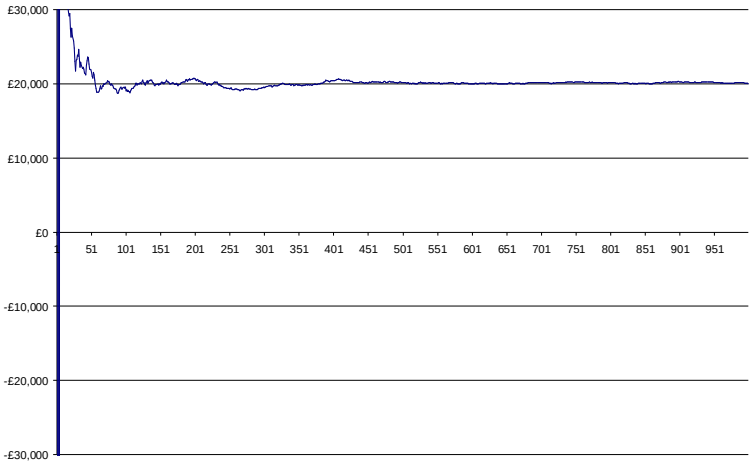


Figure 3: Scatter plot of C-E pairs

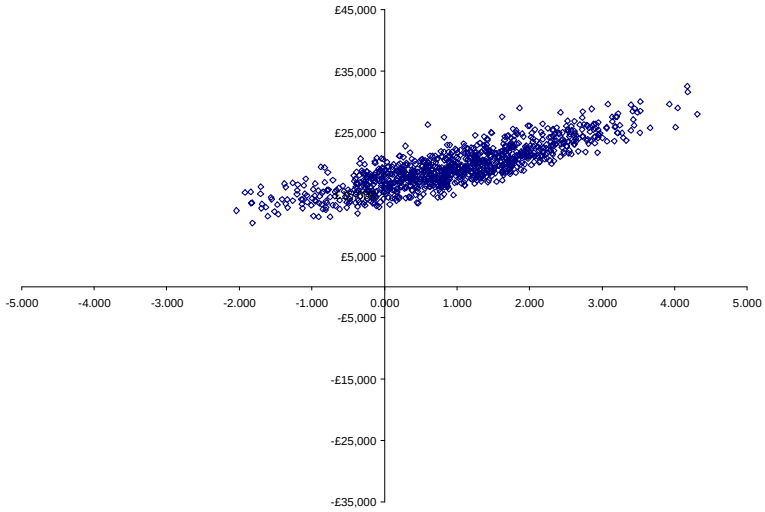


Figure 4: CEAF, CEAC and EVPI

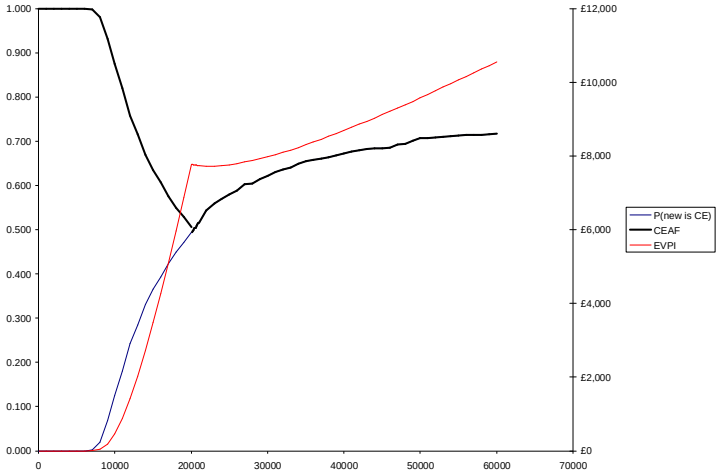


Figure 5: EVPPI and EVPI

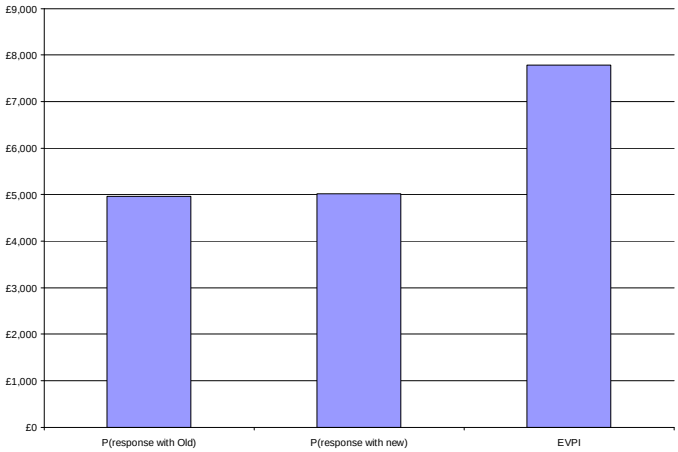


Figure 6: EVSI of two concurrent observational studies of equal sample size

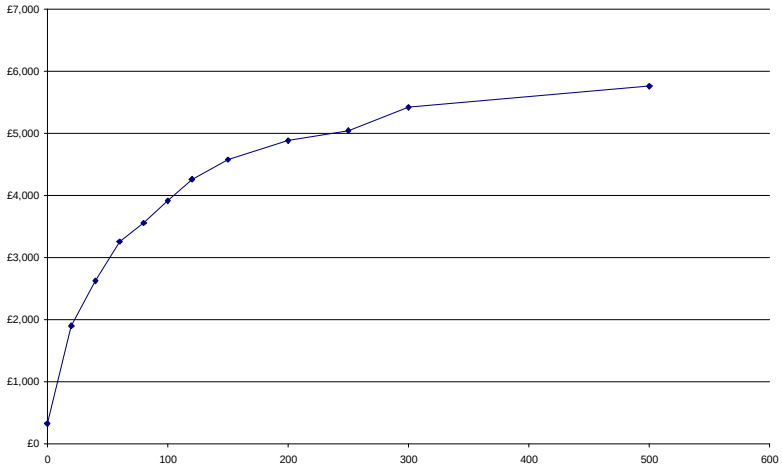


Figure 7: Cumulative estimate of INB by number of iterations

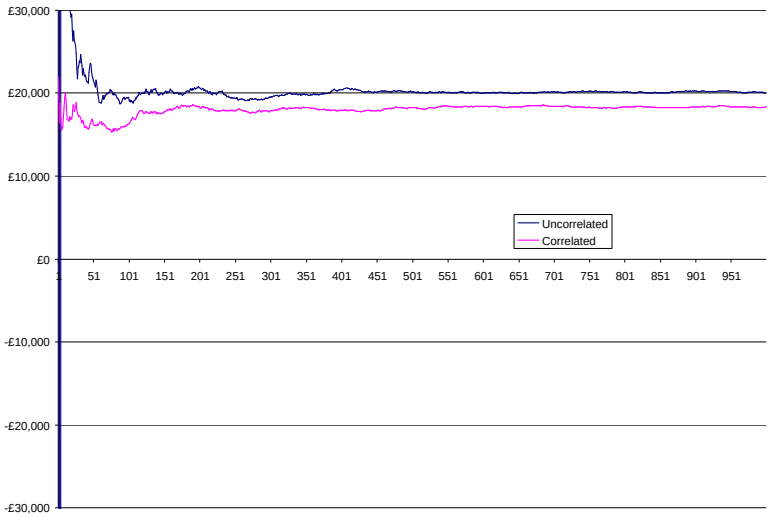


Figure 8: Cost-effectiveness acceptability curves

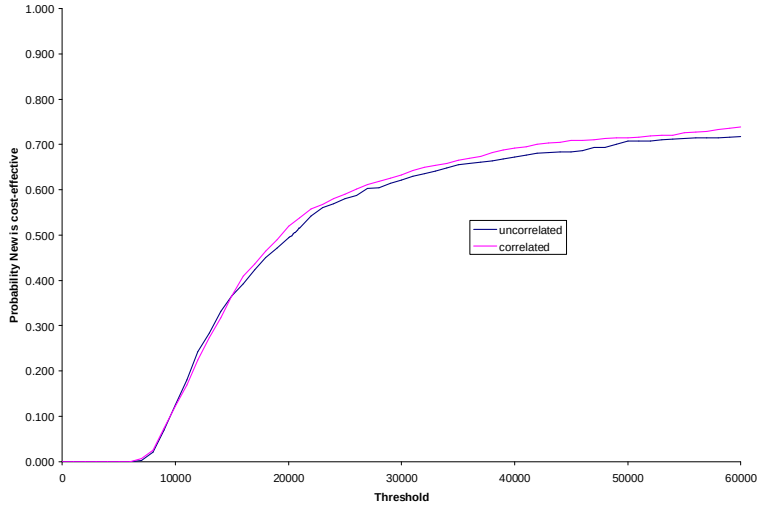
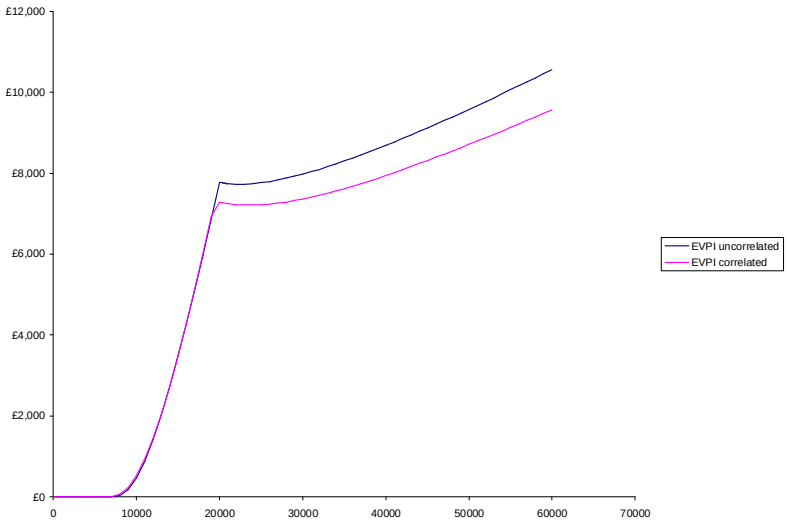


Figure 9: EVPI



Tables

Table 1: Model parameters

Parameter	Description	Point estimate
Po	Annual prob of death, Old	0.2
Pn	Annual prob of death, New	0.15
Ca_o	Annual cost, Old	£500
Ca_n	Annual cost, New	£4,000
Ua	Utility Alive	1
Ud	Utility Dead	0

Table 2: Results: deterministic modelling

Results	Cost	QALY
New	£21,420	5.355
Old	£2,166	4.333
Increment	£19,254	1.022
ICER	£18,834	

Table 3: Model parameters (alternative expression)

Parameter	Description	Point estimate
Po	Annual prob of death, Old	0.2
RR	Relative risk death, New vs Old	0.75
Pn	Annual prob of death, New	= Po*RR = 0.15
Ca_o	Annual cost, Old	£500
Ca_n	Annual cost, New	£4,000
Ua	Utility Alive	1
Ud	Utility Dead	0

Table 4: Source data

Event \ Exposure	New	Old
Dead	15	20
Alive	85	80

Table 5: Model parameters (independent inputs)

Parameter	Point estimate	Distribution	A	B	Name
Annual prob of death, Old	0.2	Beta	20	80	P_o
Annual prob of death, New	0.15	Beta	15	85	P_n
Annual cost, Old	£500	Constant			Ca_o
Annual cost, New	£4,000	Constant			Ca_n
Utility Alive	1	Constant			U_a
Utility Dead	0	Constant			U_d

Table 6: Probabilistic results (independent inputs)

Results	Cost	QALY
New	£21,673	5.418
Old	£2,223	4.446
Increment	£19,450	0.972
ICER	£20,001	

Table 7: Model inputs

Parameter	Point estimate	Distribution	Variance	A	B	Name
Annual prob of death, Old	0.2	Beta		20	80	Po
RR death New vs Old	0.75	LogNormal	Exp(0.097)			RR
Annual prob of death, New	=Po*RR					Pn
Annual cost, Old	£500	Constant				Ca_o
Annual cost, New	£4,000	Constant				Ca_n
Utility Alive	1	Constant				Ua
Utility Dead	0	Constant				Ud

Table 8: Probabilistic analysis 2 mean results

Results	Cost	QALY
New	£22,140	5.535
Old	£2,223	4.446
Increment	£19,917	1.089
ICER	£18,288	

Appendix: Search Strategy

A search of Pubmed with the key term 'economic evaluation model', limited to the journal 'Pharmacoeconomics' and publication date between 1998 and 2008 generated 120 hits. Review by title reduced this to 88. The ten most recent economic evaluations comprising decision analytic modelling and probabilistic sensitivity analysis are summarised in Table A1.

Table A1: Summaries of Economic Evaluations

REFERENCE	COMPARATORS	DISEASE	PERSPECTIVE	KEY VARIABLES	SOURCE OF EVIDENCE	MODELLING APPROACH	CHARACTERISATION OF UNCERTAINTY	DEP / INDEP PARAMETERS?	NOTES
Reed et al. 2008.[5]	imatinib vs interferon-a	newly diagnosed chronic phase CML	healthcare system	5 year survival	meta-analysis of 2 RCTs (update of previous model with new evidence)	Markov chain?	survival dependent on complete cryogenic response (CCyR). Hazard ratio of CCyR vs not CCyR for IFNa+LDAC modelled as lognormal. Imatinib group hazard ratio multiplied by the 'calibration constant' (i.e. % reduction in hazard ratio).	Dependent	
Ramsey et al. 2008.[6]	atorvastatin vs no statin	primary prevention of CV events in T2DM	US payor	risk of CV event	single trial (CARDS trial)	Markov model	atorvastatin effect modelled as hazard ratio from CARDS trial, applied to US T2DM population	Dependent	
Bojke et al. 2007.[7]	pharmacotherapy vs surgery (lap. Fundoplication)	GORD	UK NHS	outcome of surgery, risk of complications, prob of stable maintenance on medical management	Fixed effects metaanalysis of literature	Markov model	Probabilistic sensitivity analysis	Independent	Arms of model fundamentally different, so cannot apply a 'treatment effect' to a single variable as such.
Cohen et al. 2007[13]	continuous subcutaneous insulin infusion vs mutliple daily insulin injections	T1DM	Australian health payor	%change HbA1c and absolute change in BMI with CSII vs MDI @ 1 year	meta-analysis of insulin pump therapy.	CORE' model (Patient level Markov model)	Probabilistic sensitivity analysis, but also set of scenario analyses using different means reported in different trials (?why not just combine the trials?)	Dependent (eg baseline HbA1c less % change due to CSII)	
Wolowacz et al. 2007.[14]	pegaptamib vs best supportive care	age related macular degeneration	UK govt	risk of disease progression along one of 12 Markov states corresponding to declining Visual Acuity defined by Snellen scores	single trial (VISION trial)	Markov model	PSA and univariate SA	Dependent	Cholesky decomposition from trial data on transition probabilities. Utilities modelled as independent betas
Shih et al. 2007.[15]	salmeterol/fluticasone as single inhaler vs fluticasone ICS vs non-fluticasone ICS vs LTRAs	persistent asthma	US Managed Care Organisation payor	% symptom free with each tx, rescue med and exacerbation free etc.	review of trials and other studies, expert opinion	Decision tree model	univariate and PSA	independent (note mentions relationship between adherence and effectiveness - this is different)	trials selected for inclusion so long as included >=1 of the 4 treatment comparators.
Teerawattananon et al. 2007.[8]	IV or oral vs intravitreal injectionvs intraocular implantation	cytomegalovirus in HIV+ patients.	Thai health care system (also societal)	probability of spread to other eye, risk of complications, spread to other organs	systematic review, hospital survey & patient interviews	Decision tree model	PSA	independent	
Tilden et al. 2007.[16]	pioglitazone vs rosiglitazone	T2DM	UK NHS	glycaemic & lipid control	single trial	Markov linked to UKPDS model	univariate & scenario analysis	n/a	Model is first order MCMC, but not second order.
Lamotte et al. 2006.[17]	omega-3 polyunsaturated fatty acids vs no n-3 PUFAs	secondary prevention post MI	Health care payor (multi country analysis)	risk of events over 3.5 years (non-fatal MI or stroke, revascularisation, CV/non-CV death)	single trial (GISSI-P). costs from literature	Decision tree model	1-way & PSA	dependent (N-3 PUFAs risk= baseline * RR). Normal distributions for RRs. Triangular for costs	time horizon 3.5 years (same as GISSI-P trial), but life expectancy also calculated
Schadlich et al. 2006.[18]	enoxaparin vs no enoxaparin vs subcutaneous unfractionated heparin	prophylaxis against venous thromboembolic ccs in acutely ill medical patients	hospital perspective, Germany	diagnosis & Tx of VTEs, episodes of major bleeding, 2o pneumonia following pulmonary embolism, resource use.	two trials plus metaanalysis & hospital survey	Decision tree model	1-way & PSA	Independent	appear to have used normal & lognormal dbns for probabilities.

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