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**Published paper**

Brennan, Alan, Kharroubi, Samer, O'Hagan, Anthony and Chilcott, Jim (2007)  
Calculating Partial Expected Value Of Perfect Information Via Monte-Carlo  
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1 **Calculating Partial Expected Value Of Perfect Information Via Monte-Carlo Sampling**  
2 **Algorithms.**

3  
4 Alan Brennan, MSc<sup>(a)</sup>

5 Samer Kharroubi, PhD<sup>(b)</sup>

6 Anthony O'Hagan, PhD<sup>(c)</sup>

7 Jim Chilcott, MSc<sup>(a)</sup>

8  
9 (a) Health Economics and Decision Science, School of Health and Related Research, The University of  
10 Sheffield, Regent Court, Sheffield S1 4DA, England.

11 (b) Department of Mathematics, University of York, Heslington, York YO10 5DD, England.

12 (c) Department of Probability and Statistics, The University of Sheffield, Hounsfield Road, Sheffield S3  
13 7RH, England.

14 Reprint requests to:

15 Alan Brennan, MSc

16 Director of Health Economics and Decision Science,

17 School of Health and Related Research,

18 The University of Sheffield,

19 Regent Court,

20 Sheffield S1 4DA,

21 England.

22 [a.brennan@sheffield.ac.uk](mailto:a.brennan@sheffield.ac.uk)

23 **ABSTRACT**

24

25 Partial EVPI calculations can quantify the value of learning about particular subsets of uncertain  
26 parameters in decision models. Published case studies have used different computational approaches.  
27 This paper examines the computation of partial EVPI estimates via Monte-Carlo sampling algorithms.  
28 Our mathematical definition shows two nested expectations, which must be evaluated separately because  
29 of the need to compute a maximum between them. A generalised Monte-Carlo sampling algorithm uses  
30 nested simulation with an outer loop to sample parameters of interest and, conditional upon these, an  
31 inner loop to sample remaining uncertain parameters. Alternative computation methods and ‘shortcut’  
32 algorithms are discussed and mathematical conditions for their use are considered. Maxima of Monte-  
33 Carlo estimates of expectations are biased upwards, and we demonstrate that using small samples results  
34 in biased EVPI estimates. Three case studies illustrate (i) the bias due to maximisation, and also the  
35 inaccuracy of shortcut algorithms (ii) when correlated variables are present and (iii) when there is non-  
36 linearity in net-benefit functions. If relatively small correlation or non-linearity is present, then the  
37 ‘shortcut’ algorithm can be substantially inaccurate. Empirical investigation of the numbers of Monte-  
38 Carlo samples suggest that fewer samples on the outer level and more on the inner level could be  
39 efficient and that relatively small numbers of samples can sometimes be used. Several remaining areas  
40 for methodological development are set out. Wider application of partial EVPI is recommended both for  
41 greater understanding of decision uncertainty and for analysing research priorities.

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43

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53 **INTRODUCTION**

54

55 Quantifying expected value of perfect information (EVPI) is important for developers and users of  
56 decision models. Many guidelines for cost-effectiveness analysis now recommend probabilistic  
57 sensitivity analysis (PSA)<sup>1,2</sup> and EVPI is seen as a natural and coherent methodological extension<sup>3,4</sup>.  
58 Partial EVPI calculations are used to quantify uncertainty, identify key uncertain parameters, and inform  
59 the planning and prioritising of future research<sup>5</sup>. Many recent papers recommend partial EVPI, for  
60 sensitivity analysis rather than alternative ‘importance’ measures<sup>6,7,8,9</sup>, or for valuing research studies in  
61 preference to ‘payback’ methods, but do not discuss computation methods in any detail. Some of the  
62 few published EVPI case studies have used slightly different computational approaches<sup>10</sup> and many  
63 analysts, who confidently undertake PSA to calculate cost-effectiveness acceptability curves, still do not  
64 use EVPI.

65

66 The concepts of EVPI are concerned with policy decisions under uncertainty. A decision maker’s  
67 ‘adoption decision’ should be that policy which has the greatest *expected* pay-off given current  
68 information<sup>11</sup>. In healthcare, we use monetary valuation of health ( $\lambda$ ) to calculate a single expected  
69 payoff e.g. expected net benefit  $E(NB) = \lambda * E(QALYs) - E(Costs)$ . Expected value of information  
70 (EVI) is a Bayesian<sup>12</sup> approach that works by taking current knowledge (a prior probability distribution),  
71 adding in proposed information to be collected (data) and producing a posterior (synthesised probability  
72 distribution) based on all available information. The *value* of the additional information is the difference  
73 between the expected payoff that would be achieved under posterior knowledge and the expected payoff  
74 under current (prior) knowledge. ‘Perfect’ information means perfectly accurate knowledge i.e. absolute  
75 certainty about the values of parameters, and can be conceptualised as obtaining an infinite sample size,  
76 producing a posterior probability distribution that is a single point, or alternatively, as ‘clairvoyance’ –  
77 suddenly learning the true values of the parameters. For some values of the parameters the adoption  
78 decision would be revised, for others we would stick with our baseline adoption decision policy. By

79 investigating the pay-offs associated with different possible parameter values, and averaging these  
80 results, the ‘*expected*’ value of perfect information is quantified. Obtaining perfect information on *all*  
81 the uncertain parameters gives ‘overall EVPI’, whereas ‘Partial EVPI’ is the expected value of learning  
82 the true value(s) of an individual or subset of parameters. Calculations are often done per patient, and  
83 then multiplied by the number of patients affected over the lifetime of the decision to quantify  
84 ‘population EVPI’.

85  
86 Reviews show that several methods have been used to compute EVPI. The earliest healthcare  
87 literature<sup>13</sup> used simple decision problems and simplifying assumptions, such as normally distributed net  
88 benefit, to calculate overall EVPI analytically via standard ‘unit normal loss integral’ statistical tables<sup>14</sup>,  
89 but gave no analytic calculation method for partial EVPI. In 1998 and 2003<sup>15</sup>, Felli and Hazen gave a  
90 fuller exposition of EVPI method, with a suggested general Monte-Carlo random sampling procedure for  
91 partial EVPI calculation and a ‘shortcut’ simulation procedure for use in certain defined circumstances.  
92 We review these procedures in detail in the next section. In the late 1990s, some UK case studies  
93 employed different algorithms to attempt to compute partial EVPI<sup>16,17,18</sup>, but these algorithms actually  
94 computed “expected opportunity loss remaining” given perfect information on a subset of parameters,  
95 which is not the same as partial EVPI and can give substantially different results<sup>10,19</sup>. In 2002, a UK  
96 event helped to produce work resulting in a series of papers providing guidance on EVI method<sup>10,19,20</sup>.  
97 UK case studies since that time have used the two level Monte-Carlo sampling approach we examine in  
98 detail here<sup>21,22</sup>. Coyle et al. have used a similar approach<sup>23</sup>, though sometimes using quadrature (taking  
99 samples at particular percentiles of the distribution) rather than random Monte-Carlo sampling to speed  
100 up the calculation of partial EVPI for a single parameter. Development of the approach to calculate  
101 expected value of sample information (EVSI) is also ongoing<sup>20,24,25,26</sup>.

102

103 The EVPI literature is not confined to health economic policy analysis. A separate literature examines  
104 information gathering as the actual intervention e.g. a diagnostic or screening test that gathers

105 information to inform decisions on individual patients<sup>27,28</sup>. Risk analysis is the other most common  
106 application area. Readers with a wider interest are directed to a recent review of risk analysis  
107 applications<sup>29</sup>, which showed, for example, Hammitt and Shlyakhter<sup>30</sup> building on previous authors'  
108 work,<sup>31,32,33,34</sup> setting out similar mathematics to Felli and Hazen, and using elicitation techniques to  
109 specify prior probability distributions when data are sparse.

110  
111 The objective of this paper is to examine the computation of partial EVPI estimates via Monte-Carlo  
112 sampling algorithms. In the next section, we define partial EVPI mathematically using expected value  
113 notation. We then present a generally applicable nested 2 level Monte-Carlo sampling algorithm  
114 followed by some variants which are valuable in certain circumstances. The impact of sampling error on  
115 these estimates is covered including a bias caused by maximisation within nested loops. We lay out the  
116 mathematical conditions when a 'short-cut' 1 level algorithm may be used. Three case studies are  
117 presented to illustrate (i) the bias due to maximisation, (ii) the accuracy or otherwise of the shortcut  
118 algorithm when correlated variables are present and (iii) the impact of increasingly non-linear net-  
119 benefit functions. Finally, we present some empirical investigations of the required numbers of Monte-  
120 Carlo samples and the implications for accuracy of estimates when relatively small numbers of samples  
121 are used. We conclude with the implications of our work and some final remarks concerning  
122 implementation.

## 123 124 **MATHEMATICAL FORMULATION**

### 125 126 **Overall EVPI**

127 We begin with some notation. Let,

128  $\theta$  be the vector of parameters in the model with joint probability distribution  $p(\theta)$ .

129  $d$  denote an option out of the set of possible decisions; typically,  $d$  is the decision to adopt  
130 or reimburse one treatment in preference to the others.

131  $NB(d, \theta)$  be the net benefit function for decision  $d$  for parameters values  $\theta$ .

132 Overall EVPI is the value of finding out the true value of the currently uncertain  $\theta$ . If we are not able to  
 133 learn the value of  $\theta$ , and must instead make a decision now, then we would evaluate each strategy in turn  
 134 and choose the baseline adoption decision with the maximum expected net benefit, which we denote  
 135  $ENB_0$ .  $ENB_0$ , the expected net benefit given no additional information, is given by

$$136 \quad ENB_0 = \max_d [E_\theta \{NB(d, \theta)\}] \quad (1)$$

137  $E_\theta$  denotes an expectation over the full joint distribution of  $\theta$ , that is in integral notation:

$$138 \quad E_\theta[f(\theta)] = \int_\theta f(\theta) p(\theta) d\theta$$

139

140 Now consider the situation where we might conduct some experiment or gain clairvoyance to learn the  
 141 true values of the full vector of model parameters  $\theta$ . Then, since we now know everything, we can  
 142 choose with certainty the decision that maximises net benefit i.e.  $\max_d \{NB(d, \theta_{true})\}$ . This naturally  
 143 depends on  $\theta_{true}$ , which is unknown before the experiment, but we can consider the expectation of this  
 144 net benefit by integrating over the uncertain  $\theta$ .

$$145 \quad \text{Expected net benefit given perfect information} = E_\theta \left( \max_d [NB(d, \theta)] \right) \quad (2)$$

146 The overall EVPI is the difference between these two (2)-(1),

$$147 \quad EVPI = E_\theta \left( \max_d [NB(d, \theta)] \right) - \max_d [E_\theta \{NB(d, \theta)\}] \quad (3)$$

148 It can be shown that this is always positive.

149

## 150 **Partial EVPI**

151

152 Now suppose that  $\theta$  is divided into two subsets,  $\theta^i$  and its complement  $\theta^c$ , and we wish to know the  
 153 expected value of perfect information about  $\theta^i$ . If we have to make a decision now, then the expected

154 net benefit is ENB0 again, but now consider the situation where we have conducted some experiment to  
 155 learn the true values of the components of  $\theta^i = \theta^i_{\text{true}}$ . Now  $\theta^c$  is still uncertain, and that uncertainty is  
 156 described by its conditional distribution, conditional on the value of  $\theta^i_{\text{true}}$ . So we would now make the  
 157 decision that maximises the expectation of net benefit over that distribution. This is therefore  $\text{ENB}(\theta^i_{\text{true}})$

158  $= \max_d \left[ E_{\theta^c | \theta^i_{\text{true}}} \{ \text{NB}(d, \theta) \} \right]$ . Again, this depends on  $\theta^i_{\text{true}}$ , which is unknown before the experiment, but

159 we can consider the expectation of this net benefit by integrating over the uncertain  $\theta^i$ .

160 Expected Net benefit given perfect info only on  $\theta^i = E_{\theta^i} \left( \max_d \left[ E_{\theta^c | \theta^i} \{ \text{NB}(d, \theta) \} \right] \right)$  (4).

161 Hence, the partial EVPI for  $\theta^i$  is the difference between (4) and ENB0, i.e.

162  $\text{EVPI}(\theta^i) = E_{\theta^i} \left( \max_d \left[ E_{\theta^c | \theta^i} \{ \text{NB}(d, \theta) \} \right] \right) - \max_d \left[ E_{\theta} \{ \text{NB}(d, \theta) \} \right]$  (5)

163 This is necessarily positive and is also necessarily less than the overall EVPI.

164

165 Equation (5) clearly shows two expectations. The inner expectation evaluates the net benefit over the  
 166 remaining uncertain parameters  $\theta^c$  conditional on  $\theta^i$ . The outer evaluates the net benefit over the  
 167 parameters of interest  $\theta^i$ . The conditioning on  $\theta^i$  in the inner expectation is significant. In general, we  
 168 expect that learning the true value of  $\theta^i$  could also provide some information about  $\theta^c$ . Hence the correct  
 169 distribution to use for the inner expectation is the conditional distribution that represents the remaining  
 170 uncertainty in  $\theta^c$  after learning  $\theta^i$ . The exception is when  $\theta^i$  and  $\theta^c$  are independent, allowing the  
 171 unconditional (marginal) distribution of  $\theta^c$  to be used in the inner expectation. The two nested  
 172 expectations, one with respect to the distribution of  $\theta^i$  and the other with respect to the distribution of  $\theta^c$   
 173 given  $\theta^i$ , may seem to involve simply taking an expectation over all the components of  $\theta$ , but it is very  
 174 important that the two expectations are evaluated separately because of the need to compute a maximum  
 175 between them. It is this maximisation between the expectations that makes the computation of partial  
 176 EVPI complex.

177

178 **COMPUTATION**

179

180 Three techniques are commonly used in statistics to evaluate expectations. The first is when there is an  
 181 analytic solution to the integral using mathematics. For instance, if  $X$  has a normal distribution with  
 182 mean  $\mu$  and variance  $\sigma^2$  then we can analytically evaluate the expectation of functions  $f(X) = X$  or  $X^2$  or  
 183 of  $\exp(X)$  i.e.  $E[X] = \mu$ ;  $E[X^2] = \mu^2 + \sigma^2$ ;  $E[\exp(X)] = \exp(\mu + \sigma^2/2)$ . This is the ideal but is all too often  
 184 not possible in practice. For instance, there is no analytical closed-form expression for  $E[(1 + X^2)^{-1}]$ .

185 The second common technique is quadrature, also known as numerical integration. There are many  
 186 alternative methods of quadrature which involve evaluating the value of the function to be integrated at a  
 187 number of points and computing a weighted average of the results<sup>35</sup>. A very simple example would  
 188 evaluate the net benefit function at particular percentiles of the distribution (e.g. at the 1<sup>st</sup>, 3<sup>rd</sup>, 5<sup>th</sup> ... 99<sup>th</sup>  
 189 percentile) and average the results. Quadrature is particularly effective for low-dimensional integrals,  
 190 and therefore for computing expectations with respect to the distribution of a single or a small number of  
 191 uncertain variables. When larger numbers of variables exist, the computational load becomes

192 impractical. The third technique is Monte-Carlo sampling. This is a very popular method, because it is  
 193 very simple to implement in many situations. To evaluate the expectation of a function  $f(X)$  of an  
 194 uncertain quantity  $X$ , we randomly sample a large number, say  $N$ , of values from the probability  
 195 distribution of  $X$ . Denoting these by  $X_1, X_2, \dots, X_N$ , we then estimate  $E\{f(X)\}$  by the sample mean

196  $\hat{E}\{f(X)\} = \frac{1}{N} \sum_{n=1}^N f(X_n)$ . This estimate is unbiased and its accuracy improves with increasing  $N$ .

197 Hence, given a large enough sample we can suppose that  $\hat{E}\{f(X)\}$  is an essentially exact computation  
 198 of  $E\{f(X)\}$ . It is the Monte-Carlo sampling approach which we now focus upon.

199

200 **Two-level Monte-Carlo computation of partial EVPI**

201

202 Box 1 displays a detailed description of a Monte- Carlo sampling algorithm to evaluate the expectations  
 203 when estimating overall and partial EVPI. The process involves two nested simulation loops because  
 204 the first term in (5) involves two nested expectations. The outer loop undertakes K samples of  $\theta^i$ . In the  
 205 inner loop it is important that many (J) values of  $\theta^c$  are sampled from their conditional distribution,  
 206 conditional on the value for  $\theta^i$  that has been sampled in the outer loop. If  $\theta^i$  and  $\theta^c$  are independent we  
 207 can sample from the unconditional distribution of  $\theta^c$ . Note that, although the EVPI calculation depends  
 208 on the societal value of health benefits  $\lambda$ , the whole algorithm does not need repeating for different  $\lambda$   
 209 thresholds. If the mean cost and mean effectiveness are recorded separately for each strategy at the end  
 210 of each inner loop, then partial EVPI is quick to calculate for any  $\lambda$ . When evaluating overall EVPI, the  
 211 inner loop is redundant because there are no remaining uncertain parameters and the process is similar to  
 212 producing a cost-effectiveness plane<sup>36</sup> or a cost-effectiveness acceptability curve<sup>37</sup>.

213

214 We can use summation notation to describe these Monte-Carlo estimates. We define the following:

215  $\theta_k^i$  is the k'th random Monte-Carlo sample of the vector of parameters of interest  $\theta^i$ ,

216  $\theta_{jk}^c$  is the jth sample taken from the conditional distribution of  $\theta^c$  given that  $\theta^i = \theta_k^i$ .

217  $\theta_n$  is the vector of the n'th random Monte-Carlo samples of the full set of parameters  $\theta$ , and

218 D is the number of decision policies.

219 Estimated overall EVPI =  $\frac{1}{N} \sum_{n=1}^N \left[ \max_{d=1toD} (NB(d, \theta_n)) \right] - \max_{d=1toD} \left[ \frac{1}{L} \sum_{l=1}^L (NB(d, \theta_l)) \right]$ , (3s)

220 Estimated partial EVPI =  $\frac{1}{K} \sum_{k=1}^K \left( \max_{d=1toD} \left( \frac{1}{J} \sum_{j=1}^J [NB(d, \theta_k^i, \theta_{jk}^c)] \right) \right) - \max_{d=1toD} \left[ \frac{1}{L} \sum_{l=1}^L (NB(d, \theta_l)) \right]$ , (5s)

221 where, K is the number of different sampled values of parameters of interest  $\theta^i$ ; J, the number of  
 222 different sampled values for the other parameters  $\theta^c$  conditional upon each given  $\theta_k^i$ ; L, the number of  
 223 different sampled values of all the parameters together when calculating the expected net benefit of the  
 224 baseline adoption decision.

225

226 Felli and Hazen<sup>4,15</sup> gave a different Monte-Carlo procedure known as MC1 (see Appendix 1). When  
 227 compared with Box 1, there are two important differences. The first is that MC1 appears as a single  
 228 loop. Felli and Hazen assume that there is an algebraic expression for the expected payoff conditional  
 229 on knowing  $\theta^i$ , and thus the inner expectation in the first term of (5) can be evaluated analytically  
 230 without using an inner Monte-Carlo sampling loop. This is not always possible and the inner loop in  
 231 Box 1 provides a generalised method for any net benefit function. Note also that, although the  
 232 procedure takes a concurrent random sample of the parameters of interest ( $\theta^i$ ) and the remaining  
 233 parameters ( $\theta^c$ ), the assumption of an algebraic expression for the expected payoff is still made, and the  
 234 sampling of  $\theta^c$  is not used to evaluate the inner expectation. The second difference is that MC1 step 2ii  
 235 recommends estimating the improvement obtained given the information, immediately as each sample of  
 236 the parameters of interest is taken. Our 2 level algorithm can be amended to estimate the improvement  
 237 given by the revised decision  $d^*(\theta^i)$  over the baseline adoption decision  $d^*$  at the end of each outer loop  
 238 iteration (see Box 2).

239

240 The Box 2 algorithm is based on an alternative formula for partial EVPI, which combines the first and  
 241 second terms of (5) into a single expectation.

$$242 \text{EVPI}(\theta^i) = E_{\theta^i} \left( \max_d \left[ E_{\theta^c | \theta^i} \{ \text{NB}(d, \theta) \} \right] - E_{\theta^c | \theta^i} \{ \text{NB}(d^*, \theta) \} \right). \quad (6)$$

243 The summation notation provides a mathematical description of the Box 2 estimate:

$$244 \text{EVPI}(\theta^i) \text{ estimate} = \frac{1}{K} \sum_{k=1}^K \left( \max_{d=1 \text{ to } D} \left[ \frac{1}{J} \sum_{j=1}^J \{ \text{NB}(d, \theta_k^i, \theta_{jk}^c) \} \right] - \frac{1}{J} \sum_{j=1}^J \{ \text{NB}(d^*, \theta_k^i, \theta_{jk}^c) \} \right), \quad (6s)$$

245 With large numbers of samples the estimates provided by the general algorithm (Box 1) and that  
 246 computing improvement at each iteration (Box 2) will be equivalent. The difference between them  
 247 concerns when to estimate the improvement. In Box 1 we estimate the second term of (5s) just once for  
 248 the whole decision problem. In Box 2, we make K estimates of the improvement versus the baseline

249 adoption decision conditional on knowing the parameter of interest. If the same numbers of inner and  
 250 outer samples are taken, then there is little difference in computation time because the same total number  
 251 of samples and net benefit function evaluations are undertaken in both. The potential advantage of Box  
 252 2 is that the improvement is computed as exactly zero whenever the revised decision  $d^*(\theta^i) = d^*$ .  
 253 Because of this, with small numbers of samples the Box 2 algorithm might have some marginal  
 254 reduction in noise compared with Box 1. Furthermore, if the net benefit functions are positively  
 255 correlated, then the Box 2 algorithm is less susceptible to noise and will provide marginally more  
 256 accurate partial EVPI estimates for a given small number of samples. The number of Monte-Carlo  
 257 samples required is our next consideration.

258

### 259 **Monte-Carlo Sampling Error**

260

261 Monte-Carlo sampling estimates of any expectations including those in (5) are subject to potential error.  
 262 Consider a function  $f$  of parameters  $\theta$ , for which the true mean  $E_{\theta}[f(\theta)]$  is say  $\mu$ . The estimator

$$263 \quad \hat{\mu} = \frac{1}{N} \sum_{j=1}^N [f(\theta_j)] \quad (7)$$

264 is an unbiased estimator of the true mean  $\mu$ . The standard approach to ensuring that a Monte-Carlo  
 265 expectation is estimated with sufficient accuracy is to increase the number of samples  $N$ , until the  
 266 standard error of the estimator,  $S.E.(\hat{\mu})$ , is less than some defined acceptable level. The Monte-Carlo  
 267 sampling process provides us with an estimate of the variance of  $f(\theta)$ ,

$$268 \quad \hat{\sigma}^2 = \frac{1}{N-1} \sum_{j=1}^N \left( f(\theta_j) - \hat{\mu} \right)^2 \quad (8)$$

269 and the estimated standard error of the Monte-Carlo estimator is defined by

$$270 \quad \hat{s} = S.E.(\hat{\mu}) = \frac{\hat{\sigma}}{\sqrt{N}} \quad (9)$$

271 The standard error in the Monte-Carlo estimate of an expectation  $S.E.(\hat{\mu})$  reduces in proportion to the  
 272 square root of the number of random Monte-Carlo samples taken.

273  
 274 Applying this approach to estimating the net benefits given current information is straightforward. For  
 275 each decision option we can consider  $f(\theta)=NB(d,\theta)$  and denote the estimators of expected net benefit  
 276  $E_{\theta}[NB(d,\theta)]$  as  $\hat{\mu}_d$ , with associated variance estimators  $\hat{\sigma}_d$  and standard errors  $\hat{s}_d$ . Running a  
 277 probabilistic sensitivity analysis (as in steps 1 to 3 of Box 1), we can establish the mean and variance  
 278 estimators and choose a sample size  $N$  to achieve a chosen acceptable level of standard error.

279  
 280 However, estimating the potential Monte-Carlo error in partial EVPI computation is more complex  
 281 because we have a nested loop when we are repeatedly estimating expectations. In computing partial  
 282 EVPI, we have  $K$  outer loops, and for each sampled  $\theta_k^i$  we estimate the *conditional* expected net benefit  
 283 using  $J$  samples of  $\theta^c|\theta_k^i$  in the inner loop. We can denote the Monte-Carlo estimator of the expected net  
 284 benefit for decision option  $d$  conditional on a particular value of the parameters of interest  $\theta_k^i$ , as

$$285 \hat{\mu}_{dk} = \frac{1}{J} \sum_{j=1}^J [NB(d, \theta_k^i, \theta_{jk}^c)] \quad (10)$$

286 Denoting  $\hat{\sigma}_{dk}$  as the estimator of the variance in the net benefit conditional on the  $k$ 'th sample  $\theta_k^i$ , then  
 287 the standard error of this Carlo estimate is therefore estimated by:

$$288 \hat{s}_{dk} = S.E.(\hat{\mu}_{dk}) = \frac{\hat{\sigma}_{dk}}{\sqrt{J}} = \sqrt{\frac{1}{J} \frac{1}{(J-1)} \sum_{j=1}^J (NB(d, \theta_k^i, \theta_{jk}^c) - \hat{\mu}_{dk})^2} \quad (11)$$

289  
 290 We might expect that the standard error of the estimated conditional expected net benefit  $\hat{s}_{dk}$  will be  
 291 lower than the overall standard error  $\hat{s}_d$ , because we have learned the value of sample  $\theta_k^i$  and hence  
 292 reduced uncertainty. If it is, then the number of inner loop samples required to reach a specified

293 tolerance level could reduce. However, this will not necessarily always be the case and we give an  
 294 example in the case study section when knowing  $\theta_{k.}^i$  is at a particular value can actually increase the  
 295 variance in net benefit and the standard error. In general it is worth checking how stable these standard  
 296 errors are for different sampled values of the parameters of interest early in the process of partial EVPI  
 297 computation.

298

299 Having estimated the conditional expected net benefit for each of the D options, we take the maximum.  
 300 The partial EVPI estimate is therefore made up of K\*D Monte-Carlo expectations, each estimated with  
 301 error, within which K maximisations take place. With the maximisation taking place between the inner  
 302 and the outer expectations there is no analytic form for describing the standard error in the partial  
 303 estimate. Oakley et al. have recently developed a first suggestion for an algorithmic process for this  
 304 estimation based on small numbers of runs<sup>38</sup>. This process of taking the maximum of Monte-Carlo  
 305 estimates has one further important effect.

306

### 307 **Bias when taking maxima of Monte-Carlo expectations**

308

309 Although the Monte-Carlo estimate of an expectation is unbiased, it turns out that the estimate of the  
 310 maximum of these expectations is biased, and biased upwards. To see this, consider 2 treatments with  
 311 net benefit functions NB1( $\theta$ ) and NB2( $\theta$ ) with true but unknown expectations  $\mu_1$  and  $\mu_2$  respectively . If  
 312  $\mu_1$  and  $\mu_2$  are quite different from each other then any error in the Monte-Carlo estimators

313  $\hat{\mu}_1 = \frac{1}{N} \sum_{j=1}^N [\text{NB1}(\theta_j)]$  and  $\hat{\mu}_2 = \frac{1}{N} \sum_{j=1}^N [\text{NB2}(\theta_j)]$  is unlikely to affect which treatment is estimated to

314 have the highest expected net benefit. However, if  $\mu_1$  and  $\mu_2$  are close, then the Monte-Carlo sampling  
 315 error can cause us to mistakenly believe that the other treatment has the higher expectation, and this will  
 316 tend to cause us to over-estimate the maximum. Mathematically, we have that

$$317 \quad E[\max\{\hat{\mu}_1, \hat{\mu}_2\}] \geq \max\{E[\hat{\mu}_1], E[\hat{\mu}_2]\} = \max\{E[\text{NB1}], E[\text{NB2}]\} = \max\{\mu_1, \mu_2\} \quad (12)$$

318 Thus, the process of taking the maximum of the expectations (when they are estimated via a small  
 319 number of Monte-Carlo samples) creates a *bias* i.e. an *expected error* due to Monte-Carlo sampling.

320  
 321 The bias affects partial EVPI estimates because we evaluate maxima of expectations in both the first and  
 322 second terms of (5s). For the first term, the process of estimating the maximum of Monte-Carlo  
 323 expectations is undertaken for each different sample of the parameters of interest ( $\theta_k^i$ ). Each of the K  
 324 evaluations is biased upwards and therefore the first term in (5s) is biased upwards. The larger the  
 325 number of samples J in the inner loop, the more accurate and less biased the estimator  $\hat{\mu}_{dk}$  given each  
 326  $\theta_{ik}$ . The larger the number of samples K in the outer loop the more accurate the average of the

327 maximum expected net benefits i.e. 
$$\hat{\mu}(\theta^i) = \frac{1}{K} \sum_{k=1}^K \max_d \{ \hat{\mu}_{dk} \}$$
. If J is small and K is very large then we

328 will get a very accurate estimate of the wrong i.e. biased partial EVPI. If  $\hat{\mu}_d(\theta^i)$  is the Monte-Carlo  
 329 estimator of expected net benefit for decision option d given parameters  $\theta_i$ , and  $\mu_d(\theta^i)$  is the true  
 330 expected net benefit for decision option d given parameters  $\theta_i$ , then the size of the expected bias in the  
 331 first term of (5s) is given by the formula:

332 Expected Bias in first term of (5s) = 
$$E_{\theta^i} \left( E_{\theta^c | \theta^i} \left( \max_d \left[ \hat{\mu}_d(\theta^i) \right] \right) - \max_d \left[ \mu_d(\theta^i) \right] \right) \quad (13)$$

333 The magnitude of the bias is directly linked to the degree of separation between the true expected net  
 334 benefits. When the expected net benefits for competing treatments are close, and hence parameters have  
 335 an appreciable partial EVPI, then the bias is higher.

336  
 337 Because the second term in (5s) is also upwards biased, the overall bias in partial EVPI estimates can be  
 338 either upwards or downwards. The size and direction of the bias will depend on the net benefit  
 339 functions, the characterised uncertainty and the numbers of samples used. Increasing the sample size J

340 reduces the bias of the first term. Increasing the sample size  $L$  reduces the bias of the second term. If we  
 341 compute the baseline adoption decision's net benefit with very large  $L$ , but compute the first term with  
 342 very small number of inner loops  $J$ , then such partial EVPI computations will be upward biased. It is  
 343 important also to note that the size  $K$  of the outer sample in the 2-level calculation does not affect bias.  
 344 For overall EVPI, the first term in (3s) is unbiased but the second (negative) term is biased upwards and  
 345 hence, the Monte-Carlo estimate of overall EVPI is biased downwards. As with Monte-Carlo error in  
 346 partial EVPI estimates, the size of the expected bias cannot generally be calculated analytically. The  
 347 investigation of methods to develop an algorithm for this bias estimation is continuing.

348  
 349 There are two separate effects of using Monte-Carlo sampling to estimate the first term in (5) – the  
 350 random error if  $J$  and  $K$  are small and the bias if  $J$  is small. The bias will decrease with increasing inner  
 351 loop sample sizes, but for a chosen acceptable accuracy we typically need much larger sample sizes  
 352 when computing EVPI than when computing a single expectation. We investigate some of the stability  
 353 of partial EVPI estimates for different inner and outer sample numbers in the case studies. We also  
 354 examine a very simple 2 treatment decision problem, in which it is possible to compute the bias in  
 355 formula (13) analytically.

356

### 357 **The 'Short-Cut' 1 Level Algorithm**

358

359 In some simple models, it is possible to evaluate expectations of net benefit analytically, particularly if  
 360 parameters are independent. Suppose  $NB(\theta) = \lambda * \theta_1 - \theta_2 * \theta_3$ , and the parameters  $\theta_2$  and  $\theta_3$  are  
 361 independent, so that the expected net benefit can be calculated analytically simply by running the model  
 362 with the parameters set equal to their mean values,  $E_{\theta} \{NB(d, \theta)\} = \lambda * \bar{\theta}_1 - \bar{\theta}_2 * \bar{\theta}_3$ . Although simple,  
 363 there are economic models in practice, particularly decision tree models, which are of this form.

364

365 In such circumstances, the 2 level partial EVPI algorithm can be simplified to a 1 level process (Box 3).  
 366 This performs a one level Monte-Carlo sampling process, allowing parameters of interest to vary,  
 367 keeping remaining uncertain parameters constant at their prior means. It is much more efficient than the  
 368 two- level Monte-Carlo method, since we replace the many model runs by a single run in each of the  
 369 expectations that can be evaluated without Monte Carlo. Mathematically, we compute analytic solutions  
 370 for the inner expectations in the 1<sup>st</sup> term of (5) and all of the expectations in the 2<sup>nd</sup> term of (5). Note  
 371 that the expectations of maxima cannot be evaluated in this way. Thus, the expectation in the first term  
 372 of (3) and the outer expectation in the first term of (5) are still evaluated by Monte-Carlo in Box 3. Felli  
 373 and Hazen give a similar procedure, which they term a ‘shortcut’ (MC2) and is identical to MC1  
 374 described earlier but with those parameters not of interest set to their prior means i.e.  $\theta^c = \bar{\theta}^c$ . Note that  
 375 a misunderstanding of the Felli and Hazen ‘short cut’ method previously led some analysts to use a quite  
 376 inappropriate algorithm, which focussed on reduction in opportunity loss<sup>16,17</sup>. The level of inaccuracy in  
 377 estimating partial EVPI which resulted from this incorrect algorithm is discussed elsewhere.

378  
 379 The 1 level algorithm is correct under the following conditions. Mathematically, the outer level  
 380 expectation over the parameter set of interest  $\theta^i$  is as per equation (5), but the inner expectation is  
 381 replaced with net benefit calculated given the remaining uncertain parameters  $\theta^c$  set at their prior mean.

382 1 level partial EVPI for  $\theta^i = E_{\theta^i} \left\{ \max_d \left[ \text{NB}(d, \theta^i, \bar{\theta}^c) \right] \right\} - \max_d \{ E_{\theta} \text{NB}(d, \theta) \}$  (14)

383 Note that we now have just one expectation, and that the 1-level approach is equivalent to the 2 level  
 384 algorithm if (5)  $\equiv$  (14), i.e. if

385 
$$E_{\theta^i} \left( \max_d \left[ E_{\theta^c | \theta^i} \{ \text{NB}(d, \theta) \} \right] \right) \equiv E_{\theta^i} \left\{ \max_d \left[ \text{NB}(d, \theta^i, \bar{\theta}^c) \right] \right\}$$
 (15)

386 This is true if the left hand side inner bracket (expectation of net benefit, integrating over  $\theta^c | \theta^i$ ) is equal  
 387 to the net benefit obtained when  $\theta^c$  are fixed at their prior means (i.e.  $\theta^c = \bar{\theta}^c$ ) in the right hand side.

388

389 Felli and Hazen comment that the 1 level procedure can apply successfully “when all parameters are  
390 assumed probabilistically independent and the pay-off function is multi-linear i.e. linear in each  
391 individual parameter”, in other words condition (15) will hold if:

392 A1. For each  $d$  the function  $NB(d, \theta)$  can be expressed as a sum of products of components of  $\theta$

393 A2. All of the components of  $\theta$  are mutually probabilistically independent of each other.

394 Condition (15) will also hold in a second circumstance. It is not necessary for *all* of the parameters to be  
395 independent of each other provided that the net benefit functions are linear. In fact, the 1 level  
396 procedure can apply successfully for *any* chosen partition of the parameter vector  $\theta$  into parameters of  
397 interest  $\theta^i$ , and their complement  $\theta^c$  if the conditions below are satisfied:

398 B1. For each  $d$ , the function  $NB(d, \theta) = NB(d, \theta^i, \theta^c)$  is a linear function of the components of  $\theta^c$ ,  
399 whose coefficients may depend on  $d$  and  $\theta^i$ . If  $\theta^c$  has  $m$  components, this linear structure takes  
400 the form  $NB(d, \theta^i, \theta^c) = A1(d, \theta^i) \times \theta^c(1) + A2(d, \theta^i) \times \theta^c(2) + \dots + Am(d, \theta^i) \times \theta^c(m) + b(d, \theta^i)$ .

401 B2. The parameters  $\theta^c$  are probabilistically independent of the parameters  $\theta^i$ .

402 Thus, provided the net benefit function takes the form in sufficient condition (B1), then the one-level  
403 algorithm will be correct in the cases where there are (a) no correlations at all, (b) correlations only  
404 within  $\theta^i$ , (c) correlations only within  $\theta^c$ , or (d) correlations within  $\theta^i$  and within  $\theta^c$  but no correlations  
405 between  $\theta^i$  and  $\theta^c$ . If the net benefits are linear functions of the parameters, it is only when the  
406 correlations are between members of  $\theta^c$  and  $\theta^i$  that the 1 level algorithm will be incorrect.

407

408 The specifications of the sufficient conditions in (A1,A2) and (B1,B2) above are actually slightly  
409 stronger than the necessary condition expressed mathematically in (15) but it is unlikely in practice that  
410 the one-level algorithm would correctly compute partial EVPI in any economic model for which one or  
411 other of the two circumstances described did not hold. In the next section we consider how accurate the  
412 shortcut 1-level estimate might be as the parameters move from independent to being more highly  
413 correlated, and as the net benefit functions move from linear to greater non-linearity.

414

## 415 **CASE STUDIES**

416

### 417 **Case Study Model 1: Analytically tractable model to illustrate effects of bias**

418

419 Case study 1 has 2 treatments with a very simple pair of net benefit functions,  $NB1 = 20,000 * \theta1$ ,  
420  $NB2 = 19,500 * \theta2$ , where  $\theta1$  and  $\theta2$  are statistically independent uncertain parameters each with a  
421 normal distribution  $N(1,1)$ . Analytically, we can evaluate  $\max\{E(NB1), E(NB2)\}$  as  
422  $\max\{20000, 19500\} = 20,000$ . We compare the analytic results with repeatedly using very small  
423 numbers of Monte-Carlo samples to evaluate the expectations of  $NB1$  and  $NB2$ , and illustrate the scale  
424 of the bias due to taking maxima of two Monte-Carlo estimated expectations. In this very simple  
425 example with statistically independent, normally distributed net benefit functions, it is also possible to  
426 derive analytically, both the partial EVPI's and the expected bias due to taking maxima of Monte-Carlo  
427 estimated expectations.

428

### 429 **Case Study 1 Results - Bias**

430

431 In all of the case study results, the partial EVPI estimates are presented not in absolute financial value  
432 terms but rather relative to the overall EVPI for the decision problem. Thus, if we have an overall EVPI  
433 of say £1400, which we 'index' to 100, then a partial EVPI of £350 would be reported as 'indexed  
434 partial EVPI' = 25.

435

436 The effect of Monte-Carlo error induced bias in partial EVPI estimates depends upon the numbers of  
437 inner samples  $J$  used in the first term (5s) and the number of samples  $L$  used to estimated the expected  
438 net benefit of the baseline adoption decision in the second term of (5s). In this very simple example with

439 statistically independent, normally distributed net benefit functions, it is actually possible to derive  
440 analytically, both the partial EVPIs and the bias due taking maxima of Monte-Carlo estimated  
441 expectations (See Appendix 2). Table 3 shows the resulting bias for a range of J and L sample sizes.  
442 When L is small, the second term in (5s) is over-estimated due to the bias. In this case study the effect is  
443 strong enough, for example at L=1000, that the partial EVPI estimate is actually downwards biased for  
444 any value of J over 100. As L is increased the second term converges to its true value. When J is small  
445 and L is large, we can expect the first term in (5s) to be over-estimated and the resulting partial EVPI  
446 estimate to be upwards biased. The bias when J=100 is 0.49% of the true EVPI, and this decreases to  
447 0.1% at J=500 and 0.05% at J=1,000. Note that the actual error in a Monte-Carlo estimated EVPI can be  
448 considerably greater than this on any one run if small numbers of outer samples are used because over  
449 and above this bias we have the usual Monte-Carlo sampling error also in play.

450

#### 451 **Case Study Model 2: Accuracy of 1 level estimate in a decision tree model with correlations**

452

453 The second case study is a decision tree model comparing two drug treatments T0 and T1 (Table 1).  
454 Costs and benefits for each strategy depend upon 19 uncertain parameters characterised with  
455 multivariate normal distributions. We examine 5 different levels of correlation (0, 0.1, 0.2, 0.3, 0.6)  
456 between 6 different parameters. Zero correlation of course implies independence between all of the  
457 parameters. Correlations are anticipated between the parameters concerning the two drugs' mean  
458 response rates and the mean durations of response i.e.  $\theta_5$ ,  $\theta_7$ ,  $\theta_{14}$  and  $\theta_{16}$  all are correlated with each  
459 other. Secondly, correlations are anticipated between the two drugs' expected utility improvements,  $\theta_6$   
460 and  $\theta_{15}$ . To implement this model we randomly sample the multi-variate normal correlated values  
461 using [R] statistical software<sup>39</sup>. We also implemented an extension of Cholesky decomposition in  
462 EXCEL Visual Basic to create a new EXCEL function =MultiVariateNormalInv (see CHEBS  
463 website)<sup>40</sup>.

464

465 **Case Study 2 Results – Effects of Correlation on Accuracy of 1 Level Algorithm**

466

467 In the circumstance where correlation is zero, Figure 1 shows 1 level and 2 level partial EVPI estimates  
468 for a range of parameter(s) of interest. The estimates are almost equivalent, with the 2 level estimates  
469 just slightly higher than the 1 level estimates for each of the parameter(s) of interest examined. The  
470 largest difference is just 3% of the overall EVPI. This reflects the mathematical results that (a) the 1  
471 level and 2 level EVPI should be equivalent, because the cost-effectiveness model has net benefit  
472 functions that are sum-products of statistically independent parameters, and (b) the 2 level estimates are  
473 upwardly biased due to the maximisation of Monte-Carlo estimate in the inner loop. Note also that  
474 partial EVPI for groups of parameters is lower than the sum of the EVPIs of individual parameters e.g.  
475 utility parameters combined ( $\theta_6$  and  $\theta_{15}$ ) = 57%, compared with individual utility parameters =  
476  $46\%+24\% = 70\%$ .

477

478 If correlations are present between the parameters, then the 1 level EVPI results sometimes substantially  
479 under estimate the true EVPI. The 1 level and 2 level EVPI estimates are broadly the same when small  
480 correlations are introduced between the important parameters. For example, with correlations of 0.1, the  
481 2 level result for the utility parameters combined ( $\theta_6$  and  $\theta_{15}$ ) is 58%, 6 percentage points higher than  
482 the 1 level estimate. However, if larger correlations exist, then the 1 level EVPI ‘short-cut’ estimates  
483 can be very wrong. With correlations of 0.6, the 2 level result for the utility parameters combined ( $\theta_6$   
484 and  $\theta_{15}$ ) is 18 percentage points higher than the 1 level estimate, whilst for the response rate parameters  
485 combined ( $\theta_5$  and  $\theta_{14}$ ) shows the maximum disparity seen, at 36 percentage points. As correlation is  
486 increased the disparity between 2 level and 1 level estimates increases substantially. The results  
487 demonstrate that having linear or sum-product net benefit functions is not a sufficient condition for the 1

488 level EVPI estimates to be accurate and that the second mathematical condition, i.e. that parameters are  
489 statistically independent, is just as important as the first.

490

491 The 1 level EVPI results should be the same no matter what level of correlation is involved, because the  
492 1 level algorithm sets the remaining parameters  $\theta^c$  at their prior mean values no matter what values are  
493 sampled for the parameters of interest. The small differences shown in Fig 1 between different 1 level  
494 estimates are due to random chance of different samples of  $\theta^i$ . The 2 level algorithm correctly accounts  
495 for correlation, by sampling the remaining parameters from their *conditional* probability distributions  
496 within the inner loop. It could be sensible to put the conditional mean for  $\theta^c$  given  $\theta^i$  into the 1 level  
497 algorithm rather than the prior mean, but only in the very restricted circumstance when the elements of  
498  $\theta^c$  are conditionally independent given  $\theta^i$  and the net benefit function is multi-linear. In case study 2,  
499 such a method would not apply for any of the subgroups of parameters examined, because the elements  
500 of the vector of remaining parameters  $\theta^c$  are correlated with each other.

501

### 502 **Case Study Model 3: Accuracy of 1 level estimate in an increasingly non-linear Markov model**

503

504 Case study 3 extends the Case study 2 model incorporating a Markov model for the natural history of  
505 continued response. Table 2 shows that the parameters for mean duration of response ( $\theta_7$  and  $\theta_{16}$ ) are  
506 replaced with 2 Markov models of natural history of response to each drug with health states  
507 “responding”, “not responding” and “died” ( $\theta_{20}$  to  $\theta_{31}$ ). The mean duration of response to each drug is  
508 now a function of multiple powers of Markov transition matrices. To investigate the effects of  
509 increasingly non-linear models, we have analysed time horizons of  $P_{total} = 3, 5, 10, 15$  and 20 periods  
510 in a Dirichlet distribution. To implement the models we sampled from the Dirichlet distribution in the  
511 statistical software R<sup>41</sup>, and also extended the method of Briggs<sup>42</sup> to create a new EXCEL Visual Basic  
512 function = DirichletInv. We have characterised the level of uncertainty in these probabilities by

513 assuming that each is based on evidence from a small sample of just 10 transitions. We use a Bayesian  
 514 framework with a uniform prior of Dirichlet(1,1,1), and thus the posterior transition rates used in  
 515 sampling for those “responding” to the health states “responding”, “not responding” and “died” are  
 516 Dirichlet(7,4,2) and the equivalent transition rates for non-responders are Dirichlet (1,10,2).. We have  
 517 assumed statistical independence between the transition probabilities for those still responding and those  
 518 no longer responding and also between the transition probabilities for T1 and T0.

519

### 520 **Case Study 3 Results – Effects of Non-Linearity on Accuracy of 1 Level Algorithm**

521

522 We investigated the extent of non-linearity for each Markov model by expressing the net benefits as  
 523 functions of the individual parameters using simple linear regression and noting the resulting adjusted  $R^2$   
 524 for each. Increasing the number of periods in Markov model (e.g. 3, 5, 10, 15, 20) results in greater non-  
 525 linearity (i.e decreasing adjusted  $R^2 = 0.97, 0.95, 0.90, 0.87, 0.83$  respectively). Figure 2 shows the  
 526 effects on partial EVPI estimates. The 1 level estimates are substantially lower than the 2 level for the  
 527 trial ( $\theta_5, \theta_{14}$ ) and utility parameters ( $\theta_6, \theta_{15}$ ) and for their combination. Indeed, the 1 level partial  
 528 EVPI estimates are actually negative for the trial parameters ( $\theta_5, \theta_{14}$ ) for the 3 most non-linear case  
 529 studies. This is because the net benefit function is so non-linear that the first term in the 1 level EVPI  
 530 equation  $E_{\theta^c} \left\{ \max_d \left[ \text{NB}(d, \theta \mid \theta^c = \overline{\theta^c}) \right] \right\}$  is actually lower than the second term,  $\max_d \{ E_{\theta} \text{NB}(d, \theta) \}$ . Thus,  
 531 when we set the parameters we are not interested in ( $\theta^c$ ) to their prior means in term 1, the net benefits  
 532 obtained are lower than in term 2 when we allow all parameters to vary. Estimated partial EVPI for the  
 533 Markov transition probabilities for duration of disease ( $\theta^i = \theta_{20}$  to  $\theta_{31}$ ) show a high degree of alignment  
 534 between the 1 level and 2 level methods. This is because, after conditioning on  $\theta^i$  the net benefit  
 535 functions are now linear in the remaining statistically independent parameters. It is very important to  
 536 note that even quite high adjusted  $R^2$  does not imply that 1 level and 2 level estimates will be equal or  
 537 even of the same order of magnitude. For example for trial parameters ( $\theta_5, \theta_{14}$ ) when correlation is set

538 at 0.1, the adjusted  $R^2$  is 0.973 but the 2 level EVPI estimate is 30 compared with a 1 level of 19. This  
 539 suggests that the 2 level EVPI algorithm may be necessary, even in non-linear Markov models very well  
 540 approximated by linear regression.

541

## 542 **Results On Numbers of Inner and Outer Samples Required**

543

544 We can use the Monte-Carlo sampling process to quantify the standard errors in expected net benefits  
 545 for a given number of samples quite easily. For example, 1000 samples in case study 2 with zero  
 546 correlation provided an estimator for the mean[NB(T0)]  $\hat{\mu}_{T0} = \text{£}5,006$ , with an estimator for the sample  
 547 standard deviation [NB(T0)]  $\hat{\sigma}_{T0} = \text{£}2510$ , giving a standard error of  $\left(\frac{\hat{\sigma}_{T0}}{\sqrt{1000}}\right) = \text{£}2.51$ . The  
 548 equivalent figures for T1 are mean estimator  $\text{£}5351$ , sample standard deviation estimator  $\text{£}2864$  and  
 549 standard error  $\text{£}2.87$ . This shows clearly that the 95% confidence intervals for the expected net benefits  
 550 ( $\text{£}5006 \pm 5$  and  $\text{£}5351 \pm 6$ ) do not overlap and we can see that 1000 samples is enough to indicate that the  
 551 expected net benefit of T1 given current information is higher than that for T0.

552

553 As discussed earlier, it is likely that, conditioning on knowing the value of  $\theta_k^i$ , will give estimators of the  
 554 variance in net benefits  $\hat{\sigma}_{dk}$  which will be lower than the prior variance  $\hat{\sigma}^d$  because knowing  $\theta_k^i$  means  
 555 we are generally less uncertain about net benefits. However, this is not necessarily always the case, and  
 556 it is possible that posterior variance can be greater. When estimating  $\text{EVPI}(\theta_7)$  in case study 2 with zero  
 557 correlation, we found for example that our  $k=4$ th sampled value ( $\theta_4^i = 4.4$  years) in the outer loop  
 558 combined with  $J=1000$  inner samples provided a higher standard error  $\left(\frac{\hat{\sigma}_{T0}}{\sqrt{1000}}\right) = \text{£}3.25$  as  
 559 compared with  $\text{£}2.51$ .

560

561 We further examined the number of Monte-Carlo samples required for accurate unbiased estimates of  
562 partial EVPI using case study 2, assuming zero correlation, and focusing only on the partial EVPI for  
563 parameters ( $\theta_5$  and  $\theta_{14}$ ). Figure 3 illustrates how the estimate converges as increasing numbers of inner  
564 and outer samples are used. With very small numbers of inner and outer level samples the partial EVPI  
565 estimate can be wrong by an order of magnitude. For example, with  $J=10$  and  $K=10$ , we estimated the  
566 indexed  $EVPI(\theta_5, \theta_{14})$  at 44 compared to a converged estimate of 25 using  $J=10,000$  and  $K=1,000$ .  
567 However, even with these quite small numbers of samples the fact that the current uncertainty in  
568 variables  $\theta_5$  and  $\theta_{14}$  is important in the decision between treatments is revealed. As the numbers of  
569 inner and outer samples used are extended cumulatively in Figure 3, the partial EVPI result begins to  
570 converge. The order of magnitude of the  $EVPI(\theta_5, \theta_{14})$  estimates is stable to within 2 indexed  
571 percentage points once we have extended the sample beyond  $K=100$  outer and  $J=500$  inner samples.  
572 The number of samples needed for full convergence is not symmetrical for  $J$  and  $K$ . For example, over  
573  $K=500$  the  $EVPI(\theta_5, \theta_{14})$  estimate converges to within 1 percentage point, but for the inner level, where  
574 there is a 4 point difference between  $J=750$  and  $J=1000$  samples, and it requires samples of  $J=5,000$  to  
575 10,000 to converge to within 1 percentage point. The results suggest that fewer samples on the outer  
576 level and larger numbers of samples on the inner level could be the most efficient approach.

577

578 Of course, the acceptable level of error when calculating partial EVPI depends upon their use. If  
579 analysts want to clarify broad rankings of sensitivity or information value for model parameters then  
580 knowing whether the indexed partial EVPI is 62, 70 or 78 is probably irrelevant and a standard deviation  
581 of 4 may well be acceptable. If the exact value needs to be established within 1 indexed percentage  
582 point then higher numbers of samples will be necessary.

583

584 Having seen that  $K=100$ ,  $J=500$  produced relatively stable results for one parameter set in Case study 2,  
585 we decided to investigate the stability of partial EVPI estimates using relatively small numbers of

586 samples in four different parameter groups using the 5 models in case study 3 i.e. 20 parameter sets in  
587 total. By repeatedly estimating the partial EVPI, we were able to produce a distribution of results and  
588 hence estimate the standard deviation in the partial EVPI estimates. Figure 4 shows the standard  
589 deviations obtained for different numbers of inner and outer samples. The results show that when we  
590 increase the number of outer samples from (K=100 to K=300, with J set at 500), the standard deviations  
591 fall substantially, on average by a factor of 0.62. This is in line with a reduction in proportion to the  
592 square root of the number of outer samples i.e. reduction in standard deviation  $\propto (\sqrt{100})/(\sqrt{300})=0.58$ .  
593 In contrast, the reductions in standard deviation due to increases in the number of inner samples are not  
594 so marked. When we increase the number of inner samples from (J=100 to J=500, with K set at 100),  
595 the standard deviations fall on average by a factor of just 0.89, which is a much smaller reduction than if  
596 reductions were in proportion to the square root of the number of inner samples ( $\sqrt{100}/\sqrt{500}=0.45$ ).  
597 This demonstrates that improving the accuracy of partial EVPI estimates requires proportionately greater  
598 effort on the inner level than the outer. It is also clear that the higher the true partial EVPI, the greater  
599 the level of noise that might be expected. Figure 5 shows ‘confidence intervals’, ( $\pm 1.96 * \text{s.d.}$ ) for the  
600 partial EVPI estimates with relatively small numbers of samples. Parameters with low EVPI are  
601 estimated with low EVPI even with as small a number of samples as K=100, J=100. Parameters with  
602 much higher EVPI’s are estimated with relatively high EVPI but also have a larger confidence interval  
603 around them.

604  
605 Finally, we used case study 3 to compare the algorithm that computes improvement after each iteration  
606 (Box 2) with the general algorithm (Box 1), to assess whether estimates might exhibit less noise. We  
607 undertook 30 runs using both Box 1 and Box 2 algorithms with K=100 outer and J=100 inner samples.  
608 Figure 6a shows the results for the four different parameter sets and five different time period models.  
609 The results show that standard deviations in the indexed partial EVPI results are almost equivalent for  
610 the Box 2 algorithm compared with the Box 1 algorithm. Over all of the 20 parameters examined, the

611 average reduction in standard deviation in estimates is just 1%. This is because the net benefit functions  
612 in case study 3 are almost uncorrelated (the only linked variable is  $\theta_4$ ). We then repeated this process,  
613 but this time assumed that the natural history of response using the Markov model was the same for both  
614 treatments. That is, parameter  $\theta_{26}=\theta_{20}$ ,  $\theta_{27}=\theta_{21}$ , ...  $\theta_{31}=\theta_{25}$ . Because these parameters are now  
615 linked, the net benefit functions for the two treatments are now correlated.(correlation = 0.33, 0.44, 0.59,  
616 0.66 and 0.71 for the models with 3, 5, 10, 15 and 20 total periods respectively). Figure 6b shows that  
617 the standard deviations of the Box 2 algorithm EVPI estimates are now lower than those for Box 1, with  
618 an average reduction in standard deviation in estimates of 9%. The reduction in standard deviation  
619 observed was higher for the models with higher correlations in net benefit (estimated reduction in  
620 standard deviation in partial EVPI estimates = 1%, 6%, 15%, 11%, and 13% respectively). The standard  
621 deviation in partial EVPI estimates is reduced by approximately 2% for every 0.1 increase in the  
622 correlation between the net-benefits. Using a square root of n, rule of thumb, this suggests that using the  
623 Box 2 algorithm might require roughly 4% fewer samples for every 0.1 increase in correlation between  
624 the net-benefits to achieve the same level of accuracy in partial EVPI as the Box 1 algorithm.

625

## 626 **DISCUSSION**

627

628 This paper describes the calculation of partial EVPI, with the evaluation of two expectations, an outer  
629 expectation over the parameter set of interest and an inner expectation over the remaining parameters. A  
630 generalised algorithm of nested outer and inner loops can be used to compute Monte-Carlo estimates of  
631 the expectations and the maxima required for each outer loop. In specific circumstances, a ‘short-cut’ 1  
632 level algorithm is equivalent to the 2 level algorithm and can be recommended for use in simple models  
633 with linear and independent parameters. If net benefits are non-linear functions of parameters, or where  
634 model parameters are correlated, the 1 level algorithm can be substantially inaccurate. The scale of  
635 inaccuracy increases with non-linearity and correlation, but not always predictably so in scale. Case  
636 studies here show the 1 level algorithm under-estimating partial EVPI but elsewhere we have shown a

637 case study where over-estimates are also possible. In practice, the 1 level ‘short-cut’ algorithm could be  
638 useful to screen for parameters which do not require further analysis. If parameters do not affect the  
639 decision, our case studies show that their partial EVPI will be very close to zero using both the 2 level  
640 and the 1 level algorithm. Thus, the 1 level algorithm might be used with a relatively small number of  
641 iterations (e.g. 100) to screen for groups of parameters in very large models. The 2 level Monte-Carlo  
642 algorithm is applicable in any model, provided there is computing resource to run a large enough  
643 number of samples.

644

645 The number of inner and outer level simulations required depends upon the number of parameters, their  
646 importance to the decision, and the model’s net benefit functions. The standard error of each Monte-  
647 Carlo estimated expectation in the algorithm reduces in proportion to the square root of samples used but  
648 when this accumulates over many inner and outer loops and the maxima taken, the standard error of  
649 partial EVPI estimates is not generally able to be computed analytically. We recommend analysing the  
650 convergence of estimates to ensure a threshold accuracy of partial EVPI estimates fit for the specific  
651 purpose of the analysis. Our empirical approach, in a series of alternative models, suggests that the  
652 number of inner and outer samples should not in general be equal. In these case studies, 500 inner loops  
653 for each of the 100 outer loop iterations (i.e. 50,000 iterations in total) proved capable of estimating the  
654 order of magnitude of partial EVPI reasonably well in our examples, although it is likely that higher  
655 numbers may be needed in some situations. For very accurate calculation or in computationally  
656 intensive models, one might use adaptive processes to test for convergence in the partial EVPI results,  
657 within a pre-defined threshold.

658

659 A further consequence of Monte-Carlo sampling error is the existence of an over-estimating bias in  
660 evaluating maximum expected net benefit across decision options when using small numbers of samples.  
661 This can result in over or under-estimating the partial EVPI depending on the number of iterations used  
662 to evaluate the first and second terms. Previous authors have investigated mathematical description of

663 Monte-Carlo bias outside the EVPI context<sup>43</sup>. Again, analytical computation of this bias is generally not  
 664 possible and analysis of the convergence of estimates as the number of inner samples increases is  
 665 recommended. In our case studies the bias appeared as no more than 1 or 2 percentage points of the  
 666 overall EVPI when using 1000 inner samples. Further theoretical investigation of Monte-Carlo bias in  
 667 the context of partial EVPI would be useful and work is ongoing on a theoretical description of the  
 668 Monte-Carlo bias in partial EVPI calculation, and on using this theory to develop algorithms to quantify  
 669 the inner level sample size required for a particular threshold of accuracy<sup>38,44</sup>.

670  
 671 The differences between EVPI results using the general algorithm (Box 1) and that computing  
 672 improvement at each iteration (Box 2) were relatively small in case study 3 when net benefit functions  
 673 had low correlation. If  $EVPI(\theta^i)$  is small, then even small numbers of samples provide good estimates  
 674 using either algorithm. If  $EVPI(\theta^i)$  is large, then on a high proportion of occasions a different decision  
 675 option would be taken i.e.  $d^*(\theta_k^i) \neq d^*$ . Box 1 provides  $K$  estimates of  $E_{\theta^i}[NB(d^*(\theta_k^i), \theta) | \theta_k^i] -$   
 676  $E_{\theta}[NB(d^*, \theta)]$ . In contrast, Box 2 provides  $K$  estimates of  $E_{\theta^i}[\{NB(d^*(\theta_k^i), \theta) - NB(d^*, \theta)\} | \theta_k^i]$ . If the  
 677 net benefit functions are highly positively correlated, then the Box 2 algorithm is less susceptible to  
 678 noise and provides marginally more accurate partial EVPI estimates for a given number of samples. It is  
 679 important also to note that if the net benefit functions are negatively correlated then Box 2 estimates  
 680 would display higher variance than Box 1 estimates. From a computation time perspective, a further  
 681 refinement to the Box 2 algorithm could also be useful in the circumstance when there are very many  
 682 strategies and evaluating the net benefit functions takes appreciable computation time. This refinement  
 683 would use as small a number of inner loop iterations as possible to identify with reasonable certainty  
 684 which of the many strategies is  $d^*(\theta_k^i)$ . If  $d^*(\theta_k^i) = d^*$ , then there is zero improvement and we need no  
 685 further calculation. If  $d^*(\theta_k^i) \neq d^*$ , then we can use a larger number of inner loop samples just to  
 686 estimate the improvement in expected net benefit between the 2 relevant strategies  $d^*(\theta_k^i)$  and  $d^*$ . Such  
 687 an adaptive approach can be useful when undertaking large numbers of Monte-Carlo samples becomes  
 688 too time-consuming.

689

690 There are non-Monte-Carlo methods that can be used to compute partial EVPI. Quadrature often has  
691 limited use, because there is often a large number of uncertain parameters in economic models.  
692 However, if the number of parameters in either  $\theta^i$  or  $\theta^c$  is small, then quadrature can be used for the  
693 relevant computations in partial EVPI, and where  $\theta^i$  is a single parameter, this can cut the number of  
694 values of  $\theta^i$  required from around 1000 (which is what would typically be needed for Monte Carlo) to 10  
695 or fewer. A quite different approach is set out in by Oakley et al.<sup>45</sup>, who use a Bayesian approach based  
696 on the idea of emulating the model with a Gaussian process. Although this method is technically much  
697 more complex than Monte Carlo, it can dramatically reduce the number of model runs required and the  
698 authors recommend its application if many EVPI calculations are required in a model which has  
699 individual runs taking more than a few seconds.

700

701 There remain some areas where further methodological research would be useful. Computing  
702 population EVPI demands estimated patient numbers involved in the policy decision. Incidence and  
703 prevalence are important, as are the likely lifetime of the technology and potential changes in competitor  
704 strategies. There are arguments over the validity of analysing phased adoption of the intervention over  
705 time explicitly versus full adoption implied by the decision rule. When trading off against the costs of  
706 data collection, timing of data collection is important too. Some parameters may be collectable quickly  
707 (e.g. utility for particular health states), others take longer (e.g. long term side-effects), and still others  
708 may be inherently unknowable (e.g. the efficacy of an influenza vaccine prior to the arrival of next years  
709 strain of influenza).

710

711 EVPI is important, both in decision-making, and in planning and prioritising future data collection.  
712 Policy makers assessing interventions are keen to understand the level of uncertainty, and many  
713 guidelines recommend probabilistic sensitivity analysis<sup>20</sup>. The common representations of uncertainty,

714 the cost-effectiveness plane and the cost-effectiveness acceptability curve<sup>46</sup> show the relative importance  
715 of uncertainty in costs and effectiveness. Partial EVPI extends these by giving the breakdown by  
716 parameter, so that decision makers see clearly the source and scale of uncertainty. This paper seeks to  
717 encourage analysts to extend the approach to calculation of overall and partial EVPI. The theory and  
718 algorithms required are now in place. The case study models have shown the feasibility and performance  
719 of the method, indicating the numbers of samples needed for stable results. Wider application will bring  
720 greater understanding of decision uncertainty and research priority analysis.

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**Box 1: General 2 level Monte-Carlo Algorithm for Calculation of Partial EVPI on a Parameter Subset of Interest**

723

<p><b>Preliminary Steps</b></p> <p>0) Set up a <u>decision model</u> comparing different strategies and set up a <u>decision rule</u> e.g. Cost per QALY is <math>&lt; \lambda</math></p> <p>1) Characterise uncertain parameters with probability distributions e.g. normal(<math>\mu, \sigma^2</math>), beta(a,b), gamma (a,b), triangular(a,b,c) ... etc</p> <p>2) Simulate L (say L=10,000) sample sets of uncertain parameter values (Monte Carlo).</p> <p>3) Work out the baseline adoption decision <math>d^*</math> given current information i.e. the strategy giving (on average over L=10,000 simulations) the highest estimated expected net benefit.</p>
<p><b>Partial EVPI for a parameter subset of interest</b></p> <p>The algorithm has 2 nested loops</p> <p>4) Simulate a perfect data collection exercise for your parameter subset of interest by: sampling the parameter subset of interest once from its joint prior distribution (<b>outer level simulation</b>)</p> <p>5) estimate the net benefit of the best strategy given this new knowledge on the parameters of interest by</p> <ul style="list-style-type: none"> <li>- fixing the parameters of interest at their sampled values <math>\theta_k^i</math></li> <li>- simulating the other remaining uncertain parameters <math>\theta_{jk}^c</math> (say J=10,000 times) allowing them to vary according to their conditional probability distribution (conditional upon the parameter subset of interest at its sampled value <math>\theta_k^i</math>) (<b>inner level simulation</b>)</li> <li>- calculating the conditional expected net benefit of each strategy <math>E(\theta   \theta_k^i)[NB(d, \theta)]</math> given <math>\theta_k^i</math> by evaluating the net benefit at each <math>(\theta_{jk}^c, \theta_k^i)</math> and averaging</li> <li>- choosing the revised adoption decision <math>d^*(\theta_k^i)</math> to be the strategy which has the highest estimated expected net benefit given the sampled value for the parameters of interest</li> </ul> <p>6) Loop back to step 4 and repeat steps 4 and 5 (say K=10,000 times) and then calculate the average net benefit of the revised adoption decisions given perfect information on parameters of interest</p> <p>7) The partial EVPI for the parameter subset of interest is estimated by average net benefit of revised adoption decisions given perfect information on parameters (Step 6) minus average net benefit given current information i.e. of the baseline adoption decision (Step 3)</p>
<p><b>Overall EVPI</b></p> <p>The algorithm for overall EVPI requires only 1 loop (which can be done at the same time as steps (2,3))</p> <p>8) For each of the L=10,000 sampled sets of parameters from step (3) in turn,</p> <ul style="list-style-type: none"> <li>- compute the net benefit of each strategy given the particular sampled set of parameters,</li> <li>- work out the optimal strategy given that particular sampled set of parameters,</li> <li>- record the net benefit of the optimal strategy at each iteration</li> </ul> <p>9) With “perfect” information (i.e. no uncertainty in the values of each parameter) we would always choose the optimal strategy.</p> <p>Overall EVPI is estimated by: average net benefit of optimal adoption decisions given perfect information on all parameters (Step 8) minus average net benefit given current information i.e. of the baseline adoption decision (Step 3)</p>

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**Box 2: 2 level Monte-Carlo Algorithm for Calculation of Partial EVPI using Improvement In each Iteration**

**Partial EVPI for a parameter subset of interest**

The algorithm has 2 nested loops

- 4) Simulate a perfect data collection exercise for your parameter subset of interest by:  
sampling each parameter of interest once from its prior uncertain range (**outer level simulation**)
  - 5) estimate the net benefit of the best strategy given this new knowledge on the parameters of interest by
    - fixing the parameters of interest at their sampled values  $\theta_k^i$
    - simulating the other remaining uncertain parameters  $\theta_{j,k}^c$  (say J=10,000 times) allowing them to vary according to their conditional probability distribution (conditional upon the parameter subset of interest at its sampled value  $\theta_k^i$ ) (**inner level simulation**)
    - calculating the conditional expected net benefit of each strategy  $E_{(\theta|\theta_{ik})}[\text{NB}(d,\theta)]$  given  $\theta_k^i$  by evaluating the net benefit at each  $(\theta_{j,k}^c, \theta_k^i)$  and averaging
    - choosing the revised adoption decision  $d^*(\theta_k^i)$  to be the strategy which has the highest estimated expected net benefit given the sampled value for the parameters of interest
    - **compute improvement in conditional mean net benefit as the difference between the revised decision given  $\theta_k^i$  and the baseline adoption decision  $d^*$  given  $\theta_k^i$**   
**i.e.  $E_{(\theta|\theta_{ik})}[\text{NB}(d^*(\theta_k^i), \theta)] - E_{(\theta|\theta_{ik})}[\text{NB}(d^*, \theta)]$**
- 6) Loop back to step 4 and repeat steps 4 and 5 (say K=10,000 times)
- 7) The EVPI for the parameter of interest = **average of the improvements recorded in step 5**

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**Box 3: One level Monte-Carlo Algorithm for Calculation of Partial EVPI on a Parameter Subset of Interest**

**Preliminary Steps ....** As in Box 1

**One level Partial EVPI for a parameter subset of interest**

The algorithm has 1 loop

- 4) Simulate a perfect data collection exercise for your parameter subset of interest by:  
sampling the parameter subset of interest once from its prior distribution (**one level simulation**)
- 5) calculate the best strategy given this new knowledge on the parameter of interest by
  - fixing the parameters of interest at their sampled values
  - fixing the remaining uncertain parameters of interest at their prior mean value
  - calculating the mean net benefit of each strategy given these parameter values
  - choosing the revised adoption decision to be the strategy which has the highest net benefit given the sampled value for the parameters of interest
- 6) Loop back to step 4 and repeat steps 4 and 5 (say K=10,000 times) and then calculate the average net benefit of the revised adoption decisions given perfect information on parameters of interest
- 7) The EVPI for the parameter of interest =  
average net benefit of revised adoption decisions given perfect information on parameters (6)  
minus  
average net benefit given current information i.e. of the baseline adoption decision (3)

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773 **Table 1: Case Study 2 Model**

	Treatment T0			Treatment T1		
	Param			Param		
	No.	Prior Mean	Std Dev	No.	Prior Mean	Std Dev
Cost of drug	θ 1	£1,000	£1	θ 11	£1,500	£1
% admissions	θ 2	10%	2%	θ 12	8%	2%
Days in Hospital	θ 3	5.20	1.00	θ 13	6.10	1.00
Cost per Day	θ 4	£400	£200	θ 4	£400	£200
% Responding	θ 5	70%	10%	θ 14	80%	10%
Utility change if respond	θ 6	0.3000	0.1000	θ 15	0.3000	0.0500
Duration of response (years)	θ 7	3.0	0.5	θ 16	3.0	1.0
% Side effects	θ 8	25%	10%	θ 17	20%	5%
Change in utility if side effect	θ 9	-0.1000	0.0200	θ 18	-0.1000	0.0200
Duration of side effect (years)	θ 10	0.50	0.20	θ 19	0.50	0.20

774

775  $\lambda = \text{£}10,000$

776  $NBT0 = \lambda * (\theta5 * \theta6 * \theta7 + \theta8 * \theta9 * \theta10) - (\theta1 + \theta2 * \theta3 * \theta4)$

777  $NBT1 = \lambda * (\theta14 * \theta15 * \theta16 + \theta17 * \theta18 * \theta19) - (\theta11 + \theta12 * \theta13 * \theta4)$

778

779 **Table 2: Case Study 3 Model**

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	Treatment T0			Treatment T1		
	Param No.	Prior Mean	Std Dev	Param No.	Prior Mean	Std Dev
Cost of drug	θ 1	£1,000	£1	θ 11	£1,500	£1
% admissions	θ 2	10%	2%	θ 12	8%	2%
Days in Hospital	θ 3	5.20	1.00	θ 13	6.10	1.00
Cost per Day	θ 4	£400	£200	θ 4	£400	£200
% Achieving Initial Response	θ 5	70%	10%	θ 14	80%	10%
Utility change if respond	θ 6	0.3000	0.1000	θ 15	0.3000	0.0500
% Side effects	θ 8	25%	10%	θ 17	20%	5%
Change in utility if side effect	θ 9	-0.1000	0.0200	θ 18	-0.1000	0.0200

Natural History Model for Duration of Continued Response if Initial Response is Achieved

Markov Transition Probabilities

p(Responding --> Responding)	θ 20	60%	Dirichlet (7,4,2)	θ 26	60%	Dirichlet (7,4,2)
p(Responding --> Not Responding)	θ 21	30%		θ 27	30%	
p(Responding --> Die)	θ 22	10%		θ 28	10%	
p(Not Responding --> Responding)	θ 23	0%	Dirichlet (1,10,2)	θ 29	0%	Dirichlet (1,10,2)
p(Not Responding --> Not Responding)	θ 24	90%		θ 30	90%	
p(Not Responding --> Die)	θ 25	10%		θ 31	10%	
p(Die --> Die)		100%				

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783  $\theta_{22} = 1 - \theta_{20} - \theta_{21}$ .     $\theta_{25} = 1 - \theta_{23} - \theta_{24}$ .     $\theta_{28} = 1 - \theta_{26} - \theta_{27}$      $\theta_{31} = 1 - \theta_{29} - \theta_{30}$ .

784  $S_0 = (\theta_5, 1 - \theta_5, 0)^T$ ,     $U_0 = (\theta_6, 0, 0)^T$ ,     $S_1 = (\theta_{14}, 1 - \theta_{14}, 0)^T$ ,     $U_1 = (\theta_{15}, 0, 0)^T$ .

785  $M_0 = \begin{pmatrix} \theta_{20} & \theta_{21} & \theta_{22} \\ \theta_{23} & \theta_{24} & \theta_{25} \\ 0 & 0 & 1 \end{pmatrix}$ ,     $M_1 = \begin{pmatrix} \theta_{26} & \theta_{27} & \theta_{28} \\ \theta_{29} & \theta_{30} & \theta_{31} \\ 0 & 0 & 1 \end{pmatrix}$

786

788 Net Benefit functions depend upon the number of Markov periods used (Ptotal = 3, 5, 10, 15, 20)

789  $NBT_0 = \lambda * \left[ \left\{ \sum_{p=1}^{P_{total}} ((S_0)^T * (M_0)^p * U_0) \right\} + \theta_8 + \theta_9 + g_{10} \right] - (\theta_1 + \theta_2 * g_3 * g_4)$

790  $NBT_1 = \lambda * \left[ \left\{ \sum_{p=1}^{P_{total}} ((S_1)^T * (M_1)^p * U_1) \right\} + \theta_{17} + \theta_{18} + g_{19} \right] - (\theta_{11} + \theta_{12} * g_{13} * g_4)$

791

792 **Table 3: Bias in Monte-Carlo Estimates of EVPI Dependent on Number of Samples**

793 **(Bias in partial EVPI for parameter  $\theta^1$  in Case Study 1 as a % of its true EVPI)**

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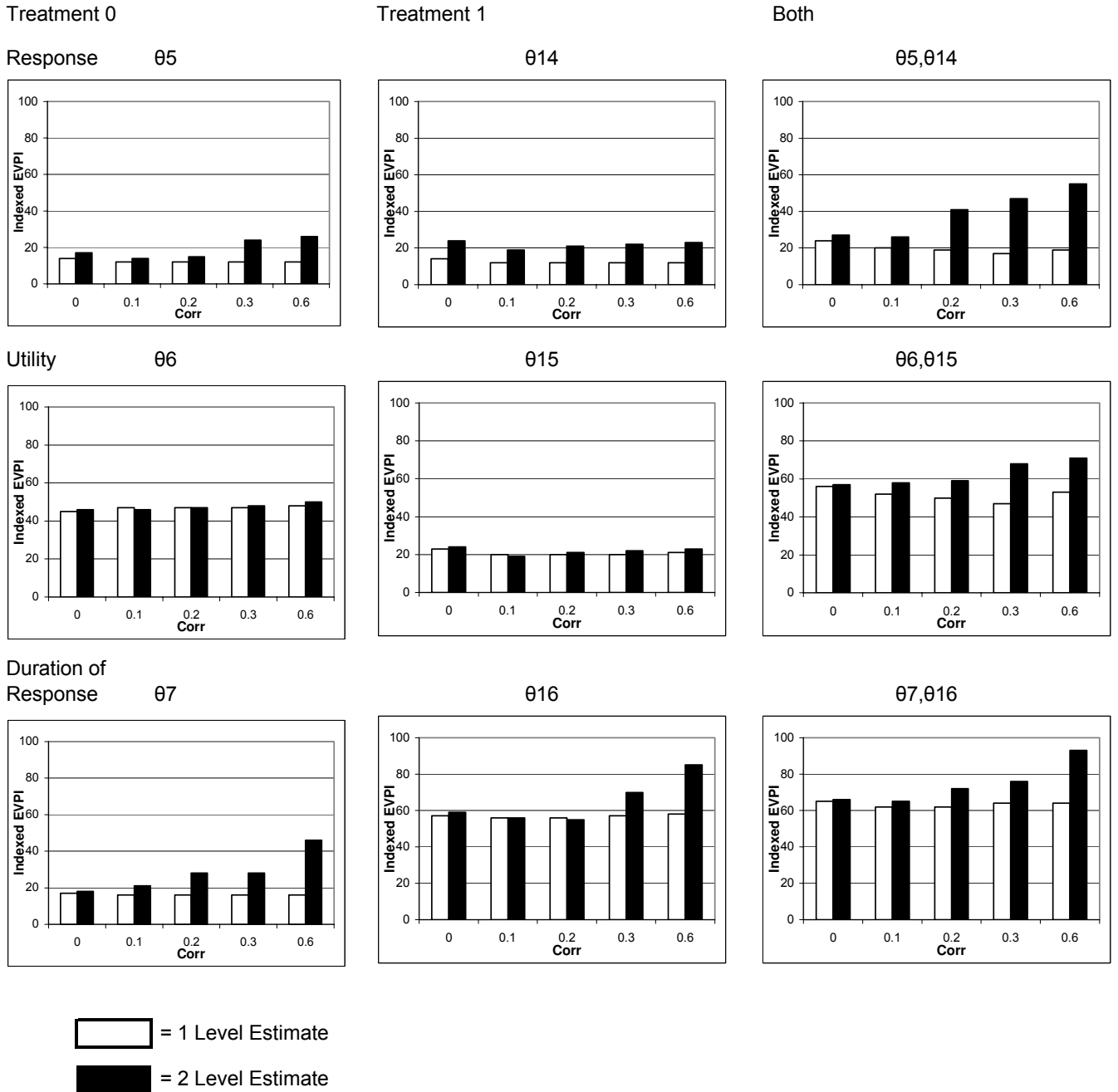
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		<b>Number of Samples in 2<sup>nd</sup> Term of (5s)</b>				
		L= 1,000	3,000	10,000	100,000	1,000,000
<b>Number of Samples in 1<sup>st</sup> Term of (5s)</b>						
J =	100	-1.55%	-0.08%	0.44%	0.49%	0.49%
	300	-1.87%	-0.41%	0.11%	0.16%	0.16%
	500	-1.94%	-0.47%	0.05%	0.10%	0.10%
	1,000	-1.99%	-0.52%	0.00%	0.05%	0.05%
	10,000	-2.03%	-0.57%	-0.05%	0.00%	0.00%
	100,000	-2.03%	-0.57%	-0.05%	0.00%	0.00%

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**Figure 1: Impact of Increasing Correlation on Inaccuracy of 1 level method to calculate partial EVPI**

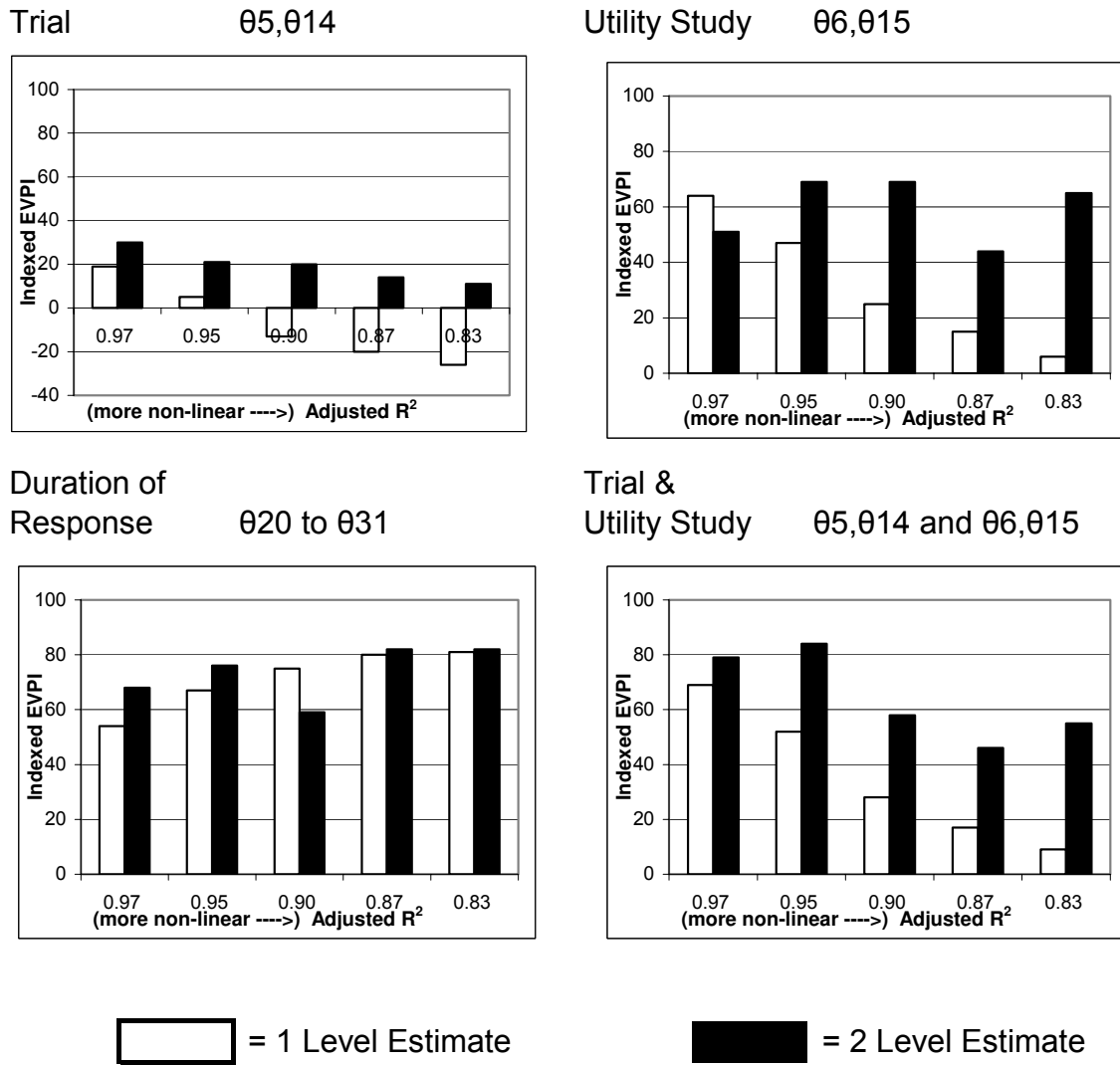


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K=1000 outer and J=1000 inner samples  
 Indexed to overall EVPI per patient = 100

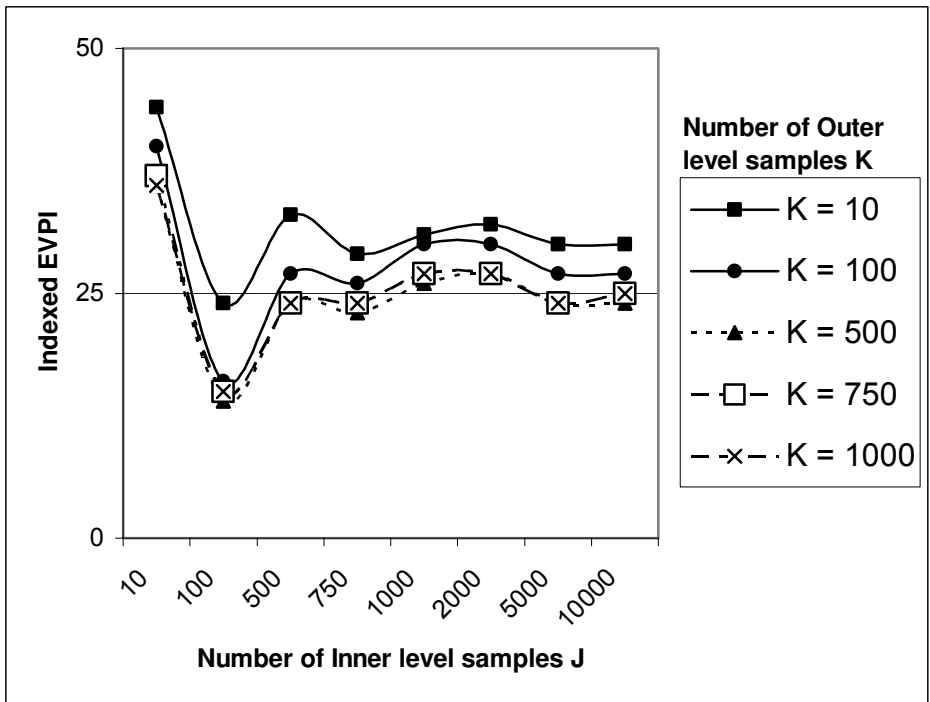
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**Figure 2: Impact of Increasing Non-Linearity on Inaccuracy of 1 level method to calculate partial EVPI**



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809 **Figure 3: Illustration of stability of Monte-Carlo EVPI Estimates as the inner and outer samples (J and K) are**  
 810 **extended (Parameters 05, 014 Case Study 2 correlation = 0)**  
 811



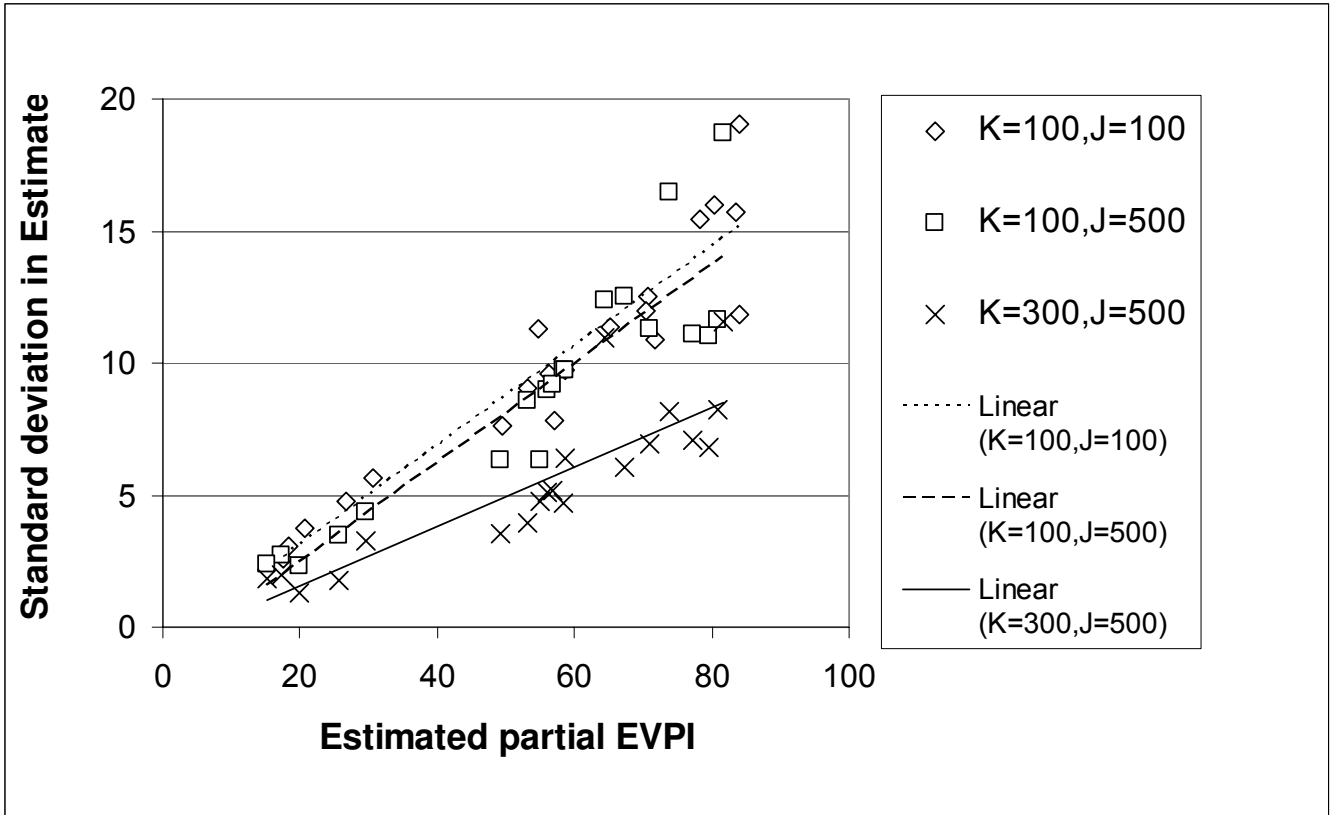
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		J (Inner Level)							
		10	100	500	750	1000	2000	5000	10000
K (Outer level)	10	44	24	33	29	31	32	30	30
	100	40	16	27	26	30	30	27	27
	500	36	14	24	23	26	27	24	24
	750	37	15	24	24	27	27	24	25
	1000	36	15	24	24	27	27	24	25

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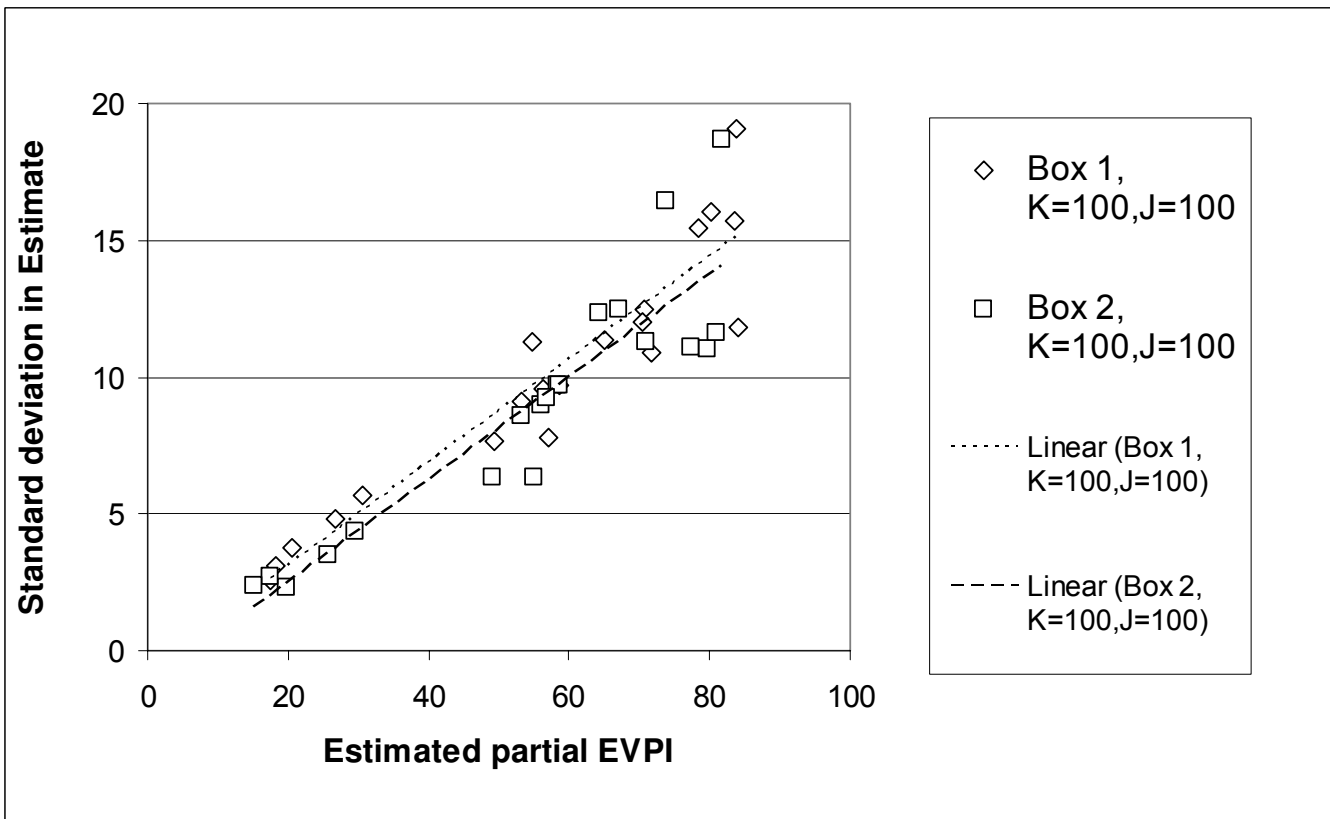
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**Figure 4:**  
**(a) Stability of partial EVPI estimates using relatively small numbers of samples (Case Study 3)**



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**(b) Stability of partial EVPI estimates using Box 1 versus Box 2 Algorithms**

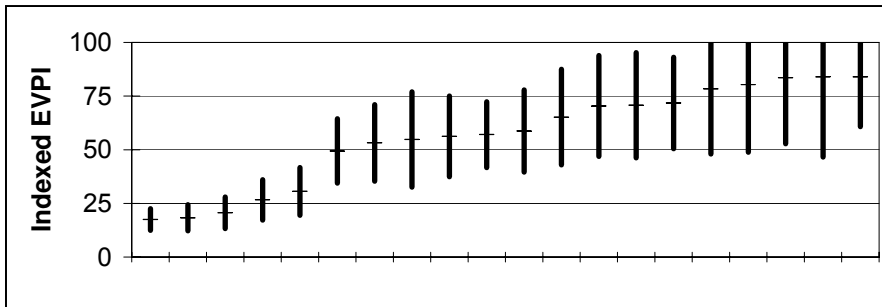


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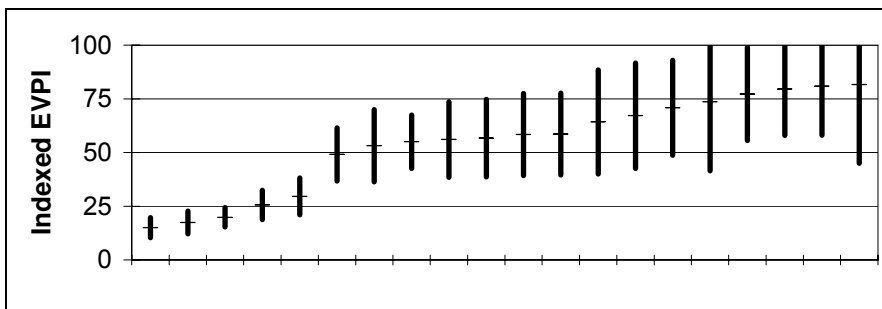
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Figure 5 'Confidence intervals' for partial EVPI estimates in Case Study 3

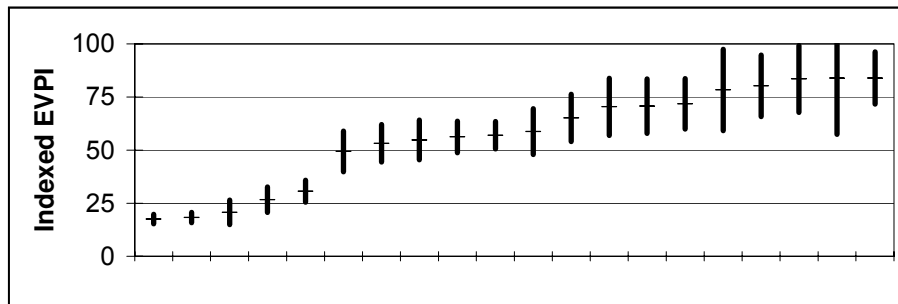
K=100, J=100



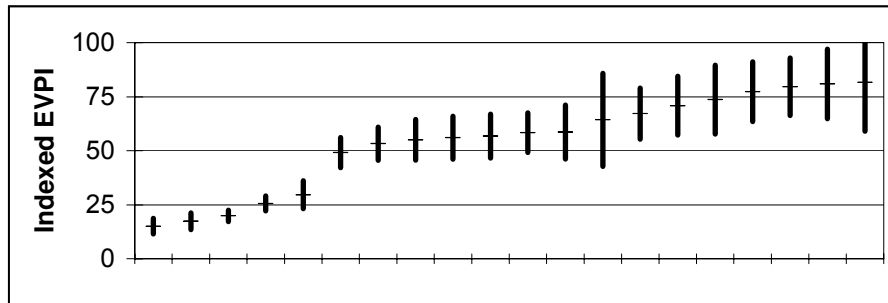
K=100, J= 500



K=300, J=100



K=300, J=500

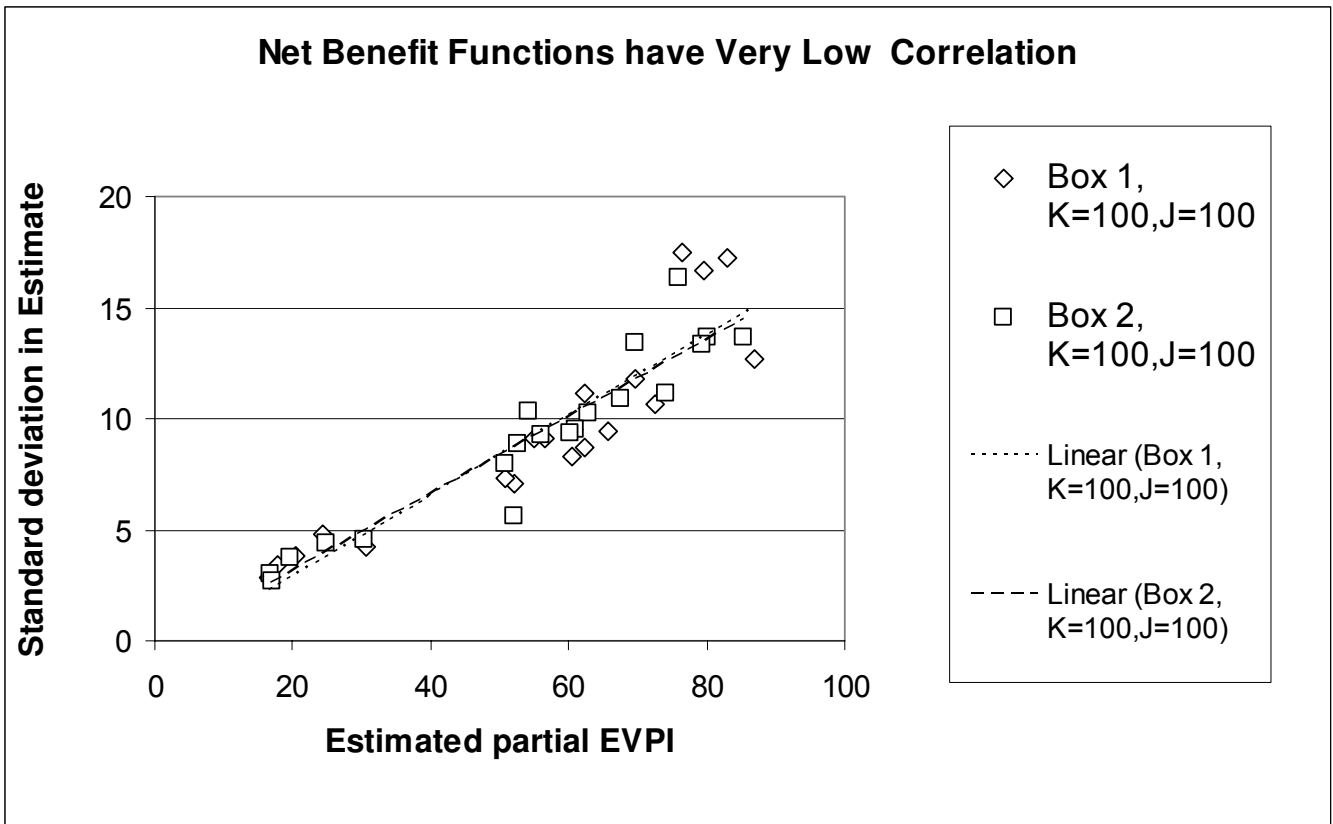


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Standard deviations based on 30 runs.

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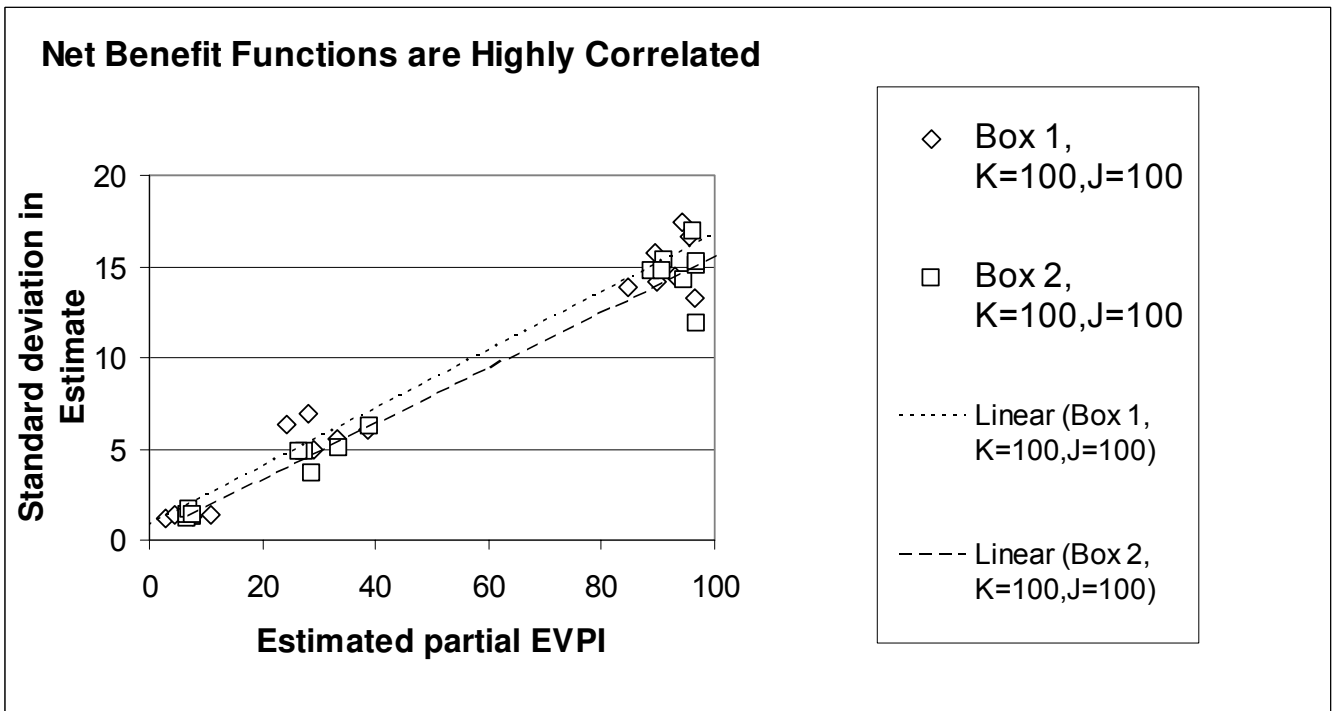
**Figure 6: Comparison of Box 1 and Box 2 Algorithm Noise**  
**(a) Stability of EVPI estimates using Box 1 versus Box 2– Net benefit Functions with Very Low Correlation**



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**(b) Stability of EVPI estimates using Box 1 versus Box 2– Net benefit Functions with High Correlation**

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833 **Appendix 1: Felli and Hazen MC1 Monte Carlo Procedure for Partial EVPI** <sup>4,15</sup>

834 Model parameters are  $\xi$ , net benefit function  $V$ , and the decision options as  $A$ . Let  $E[V | \xi, A]$  be the  
 835 decision maker's expected payoff as a function of  $\xi$  and  $A$ . The baseline adoption decision is denoted  
 836  $A^*$ .  $\xi_I$  is a collection of parameters whose EVPI we wish to calculate and let  $\xi_I^C$  be the set of remaining  
 837 parameters in the problem  $\xi = (\xi_I, \xi_I^C)$ . The decision which maximises expected value conditional upon  
 838 particular values for the parameters of interest  $\xi_I$  is denoted  $A^*(\xi_I)$ . The procedure then is:

839 MC1: General Monte Carlo Simulation Procedure .

840 1. Repeatedly generate random parameter values  $\xi = (\xi_I, \xi_I^C)$

841 2. For each generated  $\xi = (\xi_I, \xi_I^C)$ ,

842 i. Determine  $A^*(\xi_I)$  as the decision option  $A$  maximizing  $E[V | \xi_I, A]$ .

843 ii. Calculate the improvement achieved by using  $A^*(\xi_I)$

$$844 \text{Improvement} = E[V | \xi_I, \xi_I^C, A^*(\xi_I)] - E[V | \xi_I, \xi_I^C, A^*]$$

845 End For

846 3. Estimate EVPI ( $\xi_I$ ) as the average of the calculated improvement values.

847 Here it is assumed in Step 2i of the procedure that there is an algebraic expression for the quantity

$$848 E[V | \xi_I, A] = E_{\xi_I^C} [E[V | \xi_I, \xi_I^C, A | \xi_I]].$$

849 **Appendix 2: Means of maxima of two independent normally distributed variables**

850

851 Suppose  $X_1, X_2$  are independent normal random variables with parameters  $\mu_1, \sigma_1$  and  $\mu_2, \sigma_2$ , respectively.

852 Suppose  $\mu_1 > \mu_2$ . Then

853 
$$E[\max\{X_1, X_2\}] = E[X_1 + \max\{0, X_2 - X_1\}] = \mu_1 + E[\max\{0, X_2 - X_1\}] = \mu_1 + E[\max\{0, Y\}]$$

854 where  $Y = X_2 - X_1 \sim \text{normal}(\mu_Y, \sigma)$ , with  $\mu_Y = \mu_2 - \mu_1$ ,  $\sigma^2 = \sigma_1^2 + \sigma_2^2$ . We have

855 
$$E[\max\{0, Y\}] = E[\max\{0, \mu + \sigma Z\}] = \sigma E[\max\{0, Z - c\}]$$

856 where  $Z$  is a standard normal variable and  $c = -\mu_Y/\sigma$ . Then with  $\phi(z)$  the standard normal density and

857  $\Phi(c) = \int_{-\infty}^c \phi(z) dz$ , the cumulative standard normal distribution function, we have

858 
$$E[\max\{0, Z - c\}] = \int_{-\infty}^{\infty} \max\{0, z - c\} \phi(z) dz = \int_{-\infty}^c 0 \cdot \phi(z) dz + \int_c^{\infty} (z - c) \phi(z) dz$$

859 
$$= \int_c^{\infty} z \phi(z) dz - c \int_c^{\infty} \phi(z) dz$$

860 
$$= \int_c^{\infty} z \phi(z) dz - c[1 - \Phi(c)] = \int_c^{\infty} z \phi(z) dz - c[1 - \Phi(c)]$$

861 
$$= \int_c^{\infty} z \frac{1}{\sqrt{2\pi}} e^{-z^2/2} dz - c[1 - \Phi(c)]$$

862 
$$= \frac{1}{\sqrt{2\pi}} e^{-c^2/2} - c[1 - \Phi(c)]$$

863 Hence,  $E[\max\{X_1, X_2\}] = \mu_1 + \sigma \left( \frac{1}{\sqrt{2\pi}} e^{-c^2/2} - c[1 - \Phi(c)] \right)$

864 **Application to Case Study 1**

865 When NB1, NB2 are independent normally distributed with parameters  $(\mu_1, \sigma_1)$  and  $(\mu_2, \sigma_2)$ , then

866 
$$E[\max\{\text{NB1}, \text{NB2}\}] = \text{EMAX}(\mu_1, \sigma_1, \mu_2, \sigma_2) = \mu + \sigma \left( \frac{1}{\sqrt{2\pi}} e^{-c^2/2} - c[1 - \Phi(c)] \right) \quad (10)$$

867 where  $\Phi(\cdot)$  is the standard normal distribution function, and

868 
$$\mu = \max\{\mu_1, \mu_2\} \quad \sigma = (\sigma_1^2 + \sigma_2^2)^{1/2} \quad c = |\mu_2 - \mu_1|/\sigma$$

869 Because  $\theta_1$  and  $\theta_2$  are independent normal(1,1) random variables, the Monte-Carlo estimate of EVPI( $\theta^i$ )  
 870 when using K outer, J inner and L samples for each component is given by

$$\begin{aligned}
 \text{MCEVPI}_{J,K,L}(\theta^1) &= \frac{1}{K} \sum_k \left[ \max_d \frac{1}{J} \sum_j NB(d, \theta_{1k}, \theta_{2j}) \right] - \max_d \frac{1}{L} \sum_l NB(d, \theta_l) \\
 &= \frac{1}{K} \sum_k \left[ \max \left\{ \frac{1}{J} \sum_j 20\theta_{1k}, \frac{1}{J} \sum_j 19.5\theta_{2j} \right\} \right] - \max \left\{ \frac{1}{L} \sum_l 20\theta_{1l}, \frac{1}{L} \sum_l 19.5\theta_{2l} \right\} \\
 &= \frac{1}{K} \sum_k \left[ \max \{20\theta_{1k}, 19.5\bar{\theta}_{2j}\} \right] - \max \{20\bar{\theta}_{1L}, 19.5\bar{\theta}_{2L}\}
 \end{aligned}$$

874 where,  $\bar{\theta}_{2j} = \frac{1}{J} \sum_j \theta_{2j} \sim \text{normal}(1, 1/\sqrt{J})$ .

875 Therefore, we can calculate the expected value of a Monte-Carlo estimate as,

$$\begin{aligned}
 E[\text{MCEVPI}_{J,K,L} \text{EVPI}(\theta^1)] &= E \left[ \max \{20\theta_{1k}, 19.5\bar{\theta}_{2j}\} \right] - E \left[ \max \{20\bar{\theta}_{1L}, 19.5\bar{\theta}_{2L}\} \right] \\
 &= \text{EMAX}(20, 20, 19.5, 19.5/\sqrt{J}) - \text{EMAX}(20, 20/\sqrt{L}, 19.5, 19.5/\sqrt{L})
 \end{aligned}$$

878 The true expected value of perfect information on  $\theta^1$  is given by

$$\begin{aligned}
 \text{EVPI}(\theta^1) &= E_{\theta_1} \left[ \max_d E \left[ NB(d, \theta) | \theta_1 \right] \right] - \max_d E[NB(d, \theta)] \\
 &= E_{\theta_1} \left[ \max \{20\theta_1, 19.5\} \right] - \max \{20, 19.5\} \\
 &= \text{EMAX}(20, 20, 19.5, 0) - 20.
 \end{aligned}$$

882 Then Bias(J,L) = E[MCEVPI<sub>J,K,L</sub>( $\theta^1$ )] – EVPI( $\theta^1$ )

$$\begin{aligned}
 &= \{ \text{EMAX}(20, 20, 19.5, 19.5/\sqrt{J}) \\
 &\quad - \text{EMAX}(20, 20/\sqrt{L}, 19.5, 19.5/\sqrt{L}) \} \\
 &\quad - \{ \text{EMAX}(20, 20, 19.5, 0) - 20 \}.
 \end{aligned}$$

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