AN ILLUSTRATED FRAMEWORK FOR REPRESENTING UNCERTAINTY AND ITS CONSEQUENCES IN HEALTH TECHNOLOGY APPRAISALS

Marta Soares; Susan Griffin; Eldon Spackman; Laura Bojke; Claire McKenna; Karl Claxton; Stephen Palmer;

SUMMARY

In generating cost effectiveness evidence, the net benefits of the technology of interest and those of relevant comparators cannot be known with certainty as these are commonly informed by sampled data and other judgements. By characterising uncertainty in the evidence base, uncertainty in the adoption decision can be evaluated. Methods to quantify decision uncertainty and its consequences are well established, and graphical displays of decision uncertainty such as cost effectiveness acceptability curves are often made available to decisions makers. However, decisions often fail to consider such displays as decision makers struggle to make use of the information on uncertainty.

Within this work we developed a structured framework to explore uncertainties in health technology assessment. We illustrate the framework using a case study, to show how information on decision uncertainty, its determinants and consequences, can aid decision makers in practice to examine the significance of decision uncertainty, and to identify key sources of uncertainty (and needs for further research).

1. INTRODUCTION

Evaluations of cost effectiveness are often used to inform decisions on the reimbursement (or coverage) of health care technologies; for such, assessments of the net benefits associated with their use (considering both resource and health outcomes implications) and that of relevant alternatives are required. Net benefits cannot be known with certainty as these are almost always informed by sampled data and other judgements. Also, the evidence base is increasingly expected to be less mature, as decisions are increasingly being made closer and closer to licence – for example, the UK aims to decide on the use of 'new' treatments 6 months after licensing (single technology appraisal process conducted by National Institute for Clinical Excellence, NICE).

By characterising uncertainty in the evidence base, uncertainty in the adoption decision can be evaluated. Despite reimbursement decisions being based on expected net benefits, decision uncertainty is important as there is often some consideration of whether current evidence is sufficient to support these mean based estimates. Adoption decisions may also be linked to evidence development, where policies such as 'only in research' or 'approval with evidence development' become alternatives to adoption and rejection. In this case, quantifications of decision uncertainty and its consequences are key to determine guidance. [Claxton et al, Health technology assessment report, forthcoming]

Methods to quantify decision uncertainty and its consequences are well established (Claxton et al., 2005, Griffin et al., 2011), and graphical displays of decision uncertainty such as cost effectiveness acceptability curves (CEACs) are often made available to decisions makers. However, these displays are of limited use. NICE, for example, suggests appraisal committees to consider more favourably technologies for which decision uncertainty is lower – it is, however, unclear how current displays of uncertainty are useful in informing the judgements needed to put this in practice. For this reason, decisions often fail to consider decision uncertainty in practice. Within this work we developed a novel approach to explore uncertainties in the context of HTA, using a structured framework here illustrated using a case study.

2. UNCERTAINTY IN DECISION MAKING

2.1 Sources and implications of decision uncertainty

The use of uncertain evidence or judgements in an appraisal generates decision uncertainty. An important source of uncertainty is structural uncertainty, i.e. uncertainty over the way the evaluation is structured (decision models are often used to do so). Structural uncertainty can be defined as uncertainty generated by the use of scientific judgments made when constructing a model of any sort, such as a decision model, statistical model or even standard meta-analysis.(Bojke et al., 2009) Another source of uncertainty is parameter uncertainty. It occurs when the evidence used to describe well defined parameters of interest to the appraisal is itself uncertain, for example, due to the use of sampled data or expert judgements (the latter reflects epistemic uncertainty or uncertainty in knowledge). Other uncertainties can concern choices over sources of evidence (when multiple are available); or additional uncertainty due to poor representativeness of the evidence. Whilst many jurisdictions require that parameter uncertainty is considered, other types of 'uncertainties' are seldom made explicit in HTA.

When the available information is uncertain, the confidence in a decision made (based on such evidence) may be reduced, i.e. the decision itself may be uncertain. Alongside every adoption decision, it is thus key to describe decision uncertainty (the level of it and consequences) where all uncertainties relevant to an appraisal are included. To do so usefully it is important to consider the following:

i) How uncertain might a decision based on mean cost effectiveness be

As suggested previously, by making explicit the multiple uncertainties in an appraisal, uncertainty in the expected costs and effects associated with the technologies of interest can be quantified, which in turn allows quantifying uncertainty over cost effectiveness and decision uncertainty. A high level of decision uncertainty means the likelihood of the preferred treatment not being cost effective (likelihood of error, or likelihood of making the wrong decision) is high. However, the significance of uncertainty is not easy to determine based solely on its level: for example, a high level of uncertainty may not be relevant if treatments are very similar. An estimate of the consequences of uncertainty is thus needed.

ii) What are the consequences, in terms of population health (or equivalent NHS resources), if an incorrect decision is made

Expected consequences of decision uncertainty depend not only on its level but also on the effects of an incorrect decision. Under uncertainty, a decision made may be wrong in which case a different treatment would have been the best use of NHS resources. Population health (or equivalent NHS resources) may thus be lost. If likely losses are significant, decision uncertainty can be considered significant. The consequences of uncertainty can also inform whether new research is worthwhile –new evidence can, at most, eliminate decision uncertainty and avert its consequences; hence, investments in research should not exceed the expected consequences of uncertainty.

iii) What are the causes of decision uncertainty and is it worthwhile conducting new research to resolve such uncertainties?

Not every source of uncertainty will affect the decision made. As an example, consider an uncertain parameter: the value of this parameter is not known for sure, but is expected to be within a certain range of values. If the same decision is attained for all values within this range (when considered in turn), uncertainty over this parameter does not generate decision uncertainty. The reverse may also happen, where small variations in the value of a parameter will switch the adoption decision. It is thus important to assess the impact of each source of uncertainty and, in this way, identify key uncertainties in an appraisal (and start identifying future research aims).

2.2 Current methods for presenting and exploring decision uncertainty

This section details current methods used to characterise uncertainty in HTA and summarises their limitations.

Decision models can be designed to evaluate decision uncertainty due to parameters, by propagating uncertainties jointly from the input information through the model structure. This procedure is identified as probabilistic sensitivity analysis (PSA), and requires that uncertainty over parameters is firstly described using distributions, and secondly that Monte Carlo simulation is used to propagate this uncertainty through the model onto the cost and effect measures. The simulation procedure returns a set of simulated costs and effects that can be interpreted as alternative realisations under uncertainty: sets of values in plausible ranges will be more common in this sample. Such direct interpretation of uncertainty is inherently Bayesian.

In presenting results from PSA, scatter plots of the simulated pairs of incremental costs and incremental effects (cost effectiveness planes) can be used; these are however difficult to interpret as they rely on visual inspection.(Claxton, 2008a) Alternatively, one can evaluate the proportion of simulations that suggest the treatment to be cost effective, and express this as the likelihood of our treatment being cost effective, that is the degree of confidence we have in a particular decision. The CEAC plots these probabilities for a range of threshold values. (Fenwick et al., 2004) These probabilities are of limited interest as they do not inform the decision maker of the consequences of the existing uncertainty.

To identify key parameters to the model, univariate sensitivity analyses (and best/worst-case scenarios) are frequently used. Such analyses rely on changing the values of individual parameters and assessing the impact over cost effectiveness, and are limited for several reasons. Firstly, the likelihood of observing specific values of the parameter is not considered; thus, extreme values for the parameter can lead to changes in the adoption decision but there is no consideration on how plausible are such values and on the consequences in terms of overall decision uncertainty. Secondly, results do not consider the combined effect of multiple sources of uncertainty (as PSA does), which may either annul or enlarge the significance of the parameter. Available methods are thus limited in describing the impact of parameter uncertainty.

Other ‘uncertainties’, such as structural, can be parameterised and dealt with as input parameters(Claxton, 2008a, Jackson et al., 2011), but this is seldom done. Instead, alternative assumptions or judgements are commonly represented using scenarios. Much of the deliberation by the appraisal committees in the UK often focus on the credibility of the alternative assumptions represented by the scenarios. Whereas it is possible to explore parameter uncertainty within each scenario, there is as yet no clear way of analysing the impact of between scenario uncertainty.

In summary, methods available to describe decision uncertainty fail to consider its expected consequences, and fail to describe the contribution of individual sources of uncertainty.

3. THE FRAMEWORK ILLUSTRATED BY THE CLOPIDOGREL CASE STUDY

This work presents a structured framework for the analysis and presentation of decision uncertainty, its sources and significance, based on existing methodologies that quantify the level and consequences of uncertainty. To illustrate how uncertainty can be presented in a way that more directly informs the decision making process, we here present a re-analysis of an appraisal presented to NICE based on the proposed framework.

3.1 Framework of analyses

The case study was firstly introduced using a description of the decision problem, followed by a summary of the model structure and sources of evidence used to inform the appraisal. Cost-effectiveness results were presented initially to show which treatment (out of the set of mutually exclusive interventions) was expected to offer the

greatest net benefits (NB).(Laska et al., 1999) Per patient expected net *health* benefits (NHB) for each intervention, *i,* were expressed in health units, using the quality adjusted life year. NHBs represent the difference between the expected health with the intervention (h_i) and the health likely to be forgone elsewhere are a consequence of the costs of the intervention (c_i/k), which requires an estimate of the cost-effectiveness threshold (k):

$$NHB_i = h_i - c_i/k \quad (1)$$

Net benefits were also expressed in terms of the NHS resources required to generate the NHB_i (these are expressed in monetary units and referred to as net monetary benefits, or NMB):

$$NMB_i = h_i\, k - c_i\ . \quad (2)$$

Net benefits use the same information required to present the more familiar incremental cost effectiveness ratios (ICERs), i.e. estimates of expected costs and QALYs. The intervention expected to be cost-effective is the one with the highest expected NMB or NHB, which is equivalent to drawing conclusions about cost-effectiveness based on ICERs. Per patient NBs can be expressed for the population of current and future patients to reflect the absolute value of the technology to the NHS. Prevalent (P_0) and future incident (I_t) populations, and a judgement about the time horizon over which the technology will be used (technology time horizon, TH) are required to estimate total population: $P_0 + \sum_{t=1}^{TH} I_t \Big/ (1+r)^{t-1}$, where future cohorts of patients are discounted at a rate *r*.

Population net benefits ($popNHB_i$ or $popNMB_i$) are calculated by multiplying the per patient estimates by the total population.

In the case study, parameter uncertainty was explored using PSA.(Briggs, 2005) The probability of treatments being cost effective was used to illustrate the level of decision uncertainty, but we further explored the consequences of such uncertainty using EVI analyses. This analysis extends PSA in that it measures not only the likelihood of a wrong decision but also the expected losses incurred due to uncertainty – i.e. it quantifies the losses to the NHS associated with the possibility of the decision being incorrect. For such, the difference in net health of the new treatment and the ones that might be, in fact, cost effective is quantified for a range of possible realisations of all uncertain quantities. Overall, if uncertainty is resolved, better decisions can be made and the NHS stands to gain – the consequences of uncertainty, once resolved, will thus translate into gains in health. Specifically, the overall consequences of uncertainty (the EVPI measure) can be calculated using the following:

$$EVPI_\theta = E_\theta[\max(NB_i)] - \max(E_\theta[NB_i]), \quad (3)$$

where θ represents the set of uncertain parameters in the evaluation. The EVPI value can be scaled up to population values and interpreted as an estimate of the population NBs that could be gained, over the time horizon of this technology, if the uncertainty about treatments could be immediately resolved(Claxton, 2008b, Claxton and Sculpher, 2006). Decision uncertainty can be deemed significant when more research seems worthwhile, i.e. when the popEVPI exceed the likely costs of conducting such research.

EVI analysis was also used to evaluate the impact of resolving uncertainty in one (or a subset) of parameters. Such analyses consider the likelihood of observing specific values of the parameter(s) of interest and assume that parameters other than those of interest remain uncertain, and thus overcome the limitations of univariate analyses. By quantifying the effect of parameter uncertainty not only on the likelihood of the wrong decision but also on its consequences, this analysis reveals the key determinants of decision uncertainty.

The current work also explores the consequences of uncertainty in the presence of scenarios. When a particular scenario (e.g. s=1) is assumed to be true, the notation regarding the consequences of parameter uncertainty (within scenario) should be expressed as in Equation 4 [equivalent to Equation 1]. To consider

between scenario uncertainty, it is inappropriate to take a weighted average of expected costs and QALY across scenarios [see Appendix 1 and Price et al (2011)]. We here argue that marginal and joint expectations should be considered within an EVI approach, as follows:

within scenario uncertainty: $EVPI_{\theta|s=1} = E_{\theta}[\max(NB_{i,\ s=1})] - \max(E_{\theta}[NB_{i,\ s=1}])$ (4)

between scenario uncertainty: $EVPI_{s} = E_{S}[\max(E_{\theta}NB_{i})] - \max(E_{S}E_{\theta}[NB_{i}])$ (5)

parameter uncertainty: $EVPI_{\theta} = E_{\theta}[\max(E_{S}NB_{i})] - \max(E_{S}E_{\theta}[NB_{i}])$, (6)

within and between scenario uncertainty: $EVPI_{\theta,s} = E_{S}E_{\theta}[\max(NB_{i})] - \max(E_{S}E_{\theta}[NB_{i}])$, (7)

where *s* represents the scenarios of interest. Note that $EVPI_{s}$ does not ignore the existence of parameter uncertainty, but it uses its marginal distribution to consider it in calculation. See Appendix 1 for more detail.

In expressing scenario uncertainty in this way, pre-specified judgements over the likelihood of each scenario is required. For example, if three scenarios exist (1, 2 and 3) with an associated likelihood of 0.5, 0.4 and 0.1, respectively, Equation 7 becomes: $EVPI_{\theta,s} = 0.5{\cdot}E_{\theta}[\max(NB_{i,s=1})]+0.4{\cdot}E_{\theta}[\max(NB_{i,s=2})] +0.1{\cdot}E_{\theta}[\max(NB_{i,s=3})]-\max(0.5{\cdot}E_{\theta}[NB_{i,\ s=1}]+0.4{\cdot}E_{\theta}[NB_{i,s=2}]+ 0.1{\cdot}E_{\theta}[NB_{i,\ s=3}])$. If fully uncertain about which scenario is more plausible, an equal chance can be assigned to each scenario (e.g. 33% if three scenarios exist).

3.2 Case study

This case study evaluates alternative clopidogrel treatment durations alongside lifetime treatment with standard therapy alone, for the management of patients with non-ST-segment elevation acute coronary syndromes presenting with a moderate to high risk of ischemic events. Given treatment with antiplatelet agents should start immediately after the acute event, only incident cases are assumed eligible for treatment (in the UK, there are 60,000 incident patients annually).

The use of clopidogrel in this indication was appraised by NICE (TA80 in 2004) which decided on the use of clopidogrel as an adjunct to standard therapy, but recommended research to inform optimal treatment duration. Subsequent re-analysis (2009) evaluated the following treatment strategies: adjunct treatment with clopidogrel for 12 months [clop12], 6 months [clop6], 3 months [clop3] and 1 month [clop1], and lifetime treatment with standard therapy alone (including aspirin) [NHS]. Results were used in NICE's clinical guidelines (CG94), published in 2010. For the purpose of this analysis, lifetime treatment with standard therapy was considered the treatment established in the NHS. A possible decision to use clopidogrel represents thus a change in guidance. This study used the NHS perspective and a discount rate of 3.5% for future costs and QALYs.[NICE methods guide 2008] The technology time horizon was assumed to be 10 years.

3.3 Description of the decision model and input information

The model used by Rogowski et al (2009) combines a short term decision tree and a Markov model representing the longer term. The short-term tree characterises the period of up to 12 months following an acute event, tracking for possible myocardial infarctions (MI) or death. The Markov model was defined to have four states (well, death, MI, post-MI) and was run for a period 40 years using yearly cycles. A summary of the parameters used to define the decision model is shown in Table I. A more detailed characterisation of this model is elsewhere.(Rogowski et al., 2009)

The probabilities of death and non-fatal MI applied in the first year were derived from the Prospective Registry of Acute Ischaemic Syndrome in the UK (PRAIS-UK).(Taneja et al., 2004) Treatment with clopidogrel was assumed to prevent death and non-fatal MIs, and this was parameterised using relative treatment effects (identified as RE in Table I). The CURE trial established the effectiveness of clopidogrel in patients with NSTE-ACS.(Gerschutz and Bhatt, 2002) Results show clopidogrel was significantly more effective than placebo at reducing the risk of the composite outcome of cardiovascular death, nonfatal MI or stroke. Relative treatment

effects were applied throughout the duration of the clopidogrel treatment period (in the short term model), within which these were assumed constant. Hence, any benefits of treatment with clopidogrel were assumed to stop at the time of withdrawal, and patients were modelled to rebound to the same prognosis as an equivalent patient on aspirin alone. However, results of the CURE trial suggested that benefits of clopidogrel may be most apparent within the first 3 months of treatment. This possibility was explored by Rogowski et al (2009) in scenario analyses, as was in the current work.

Table I Parameters of the decision model

	Parameter		Description	Source	Distribution
Natural history	1	P_die_0.1	Short term: probability of death, 0-1 months	PRAIS-UK data [11]	Dirichlet
	2	P_NFMI_0.1	Short term: probability of a non-fatal MI, 0-1 months		
	3	P_die_1.3	Short term: probability of death, 1-3 months		Dirichlet
	4	P_NFMI_1.3	Short term: probability of a non-fatal MI, 1-3 months		
	5	P_die_3.6	Short term: probability of death, 3-6 months		Dirichlet
	6	P_NFMI_3.6	Short term: probability of a non-fatal MI, 3-6		
	7	P_die_6.12	Short term: probability of death, 6-12 months		Dirichlet
	8	P_NFMI_6.12	Short term: probability of a non-fatal MI, 6-12 months		
	9	TP_AC	Long term: annual transition probability (TP) – Well(A) to MI(C)	Main et al 2004 [1]	Normal (log hazard)
	10	TP_AD	Long term: annual TP – MI(C) to Dead(D)		Normal (log hazard)
	11	TP_CD	Long term: annual TP – MI(C) to Dead(D)		Normal (log hazard)
	12	TP_BD	Long term: annual TP – Post-MI(B) to Dead(D)		Normal (log hazard)
RR	17	RR_death	Treatment effects (relative risks, RR) – All-Cause Mortality	CURE trial [4-9]	Normal (Log RR)
	18	RR_NFMI	Treatment effects (RR) – Non fatal MI		Normal (Log RR)
Utilities	13	U_Well	Utility weights per health state: IHD Year 1	Karnon et al. 2006 [12]	Beta
	14	U_Well1	Utility weights per health state: Post IHD		Beta
	15	U_NFMI	Utility weights per health state: MI Year 1		Beta
	16	U_POSTMI	Utility weights per health state: Post MI		Beta
Costs	19	C_Well	Cost per health state: IHD Year 1	*	*
	20	C_MI_LT	Cost per health state: MI Year 1	*	*
	21	C_PostMI	Cost per health state: Post MI	*	*
	22	TC_Well_Dead	Cost per health state: transitions to death	*	*
	23 to 27	C_clop12, …, C_NHS	Cost per treatment strategy	*	*
	28	Clop_cost	Cost per mg of Clopidogrel (2100 mg, 2007)	BNF (2007)	constant

*to reduce the number of model parameters and allow tractability in the further analysis, resource use and cost parameters in the original model[2] were here used to derive costs per health state and costs per treatment. Uncertainty over these parameters was described by the empiric distribution from the original Monte Carlo simulations.

The long-term model was used to quantify the remaining QALYs and costs of patients once they exited the short-term model. The speed at which transitions between states happen was parameterised using transition probabilities (Table I). These were estimated using the Nottingham Heart Attack Register (NHAR) data (n = 1279), and were assumed independent of treatment. Utility parameters were derived using published evidence from Karnon et al (2006). Costs and resource use were informed using multiple sources.(Rogowski et al., 2009)

Inputs in the model were assumed uncertain, and the model was run probabilistically using Monte Carlo simulation (PSA, 5000 simulations). Expected cost-effectiveness used these probabilistic results.(National Institute for Health and Clinical Excellence, 2008) EVI analyses did not assume linearity, i.e. two nested simulation procedures were used (each with 5000 simulations). Results consider a threshold value of £20 000 per QALY (a threshold of £30 000 per QALY is also considered in tables, but not in the text).

4. RE-ANALYSIS OF THE CLOPIDOGREL APPRAISAL

4.1 Cost effectiveness

Expected per patient net benefits (Table II) show that clopidogrel regimens offer benefits in relation to standard NHS care. Twelve months treatment duration was the regimen expected to be cost-effective in the incremental analysis. Results show that the NHS stands to gain a minimum of 7,502 QALYs (or £150 million) by changing its guidance to consider clopidogrel instead of NHS standard care. This represents the value of clop1 (in relation to

NHS standard care) for the potential population of users over the technology time horizon. The value of moving from NHS standard care to clop12 is 14,786 QALYs.

Table II Expected cost-effectiveness per patient treated and for the population

				Per patient		Population level	
				Cost-effectiveness threshold at:		Cost-effectiveness threshold at:	
				£20,000 per QALY	£30,000 per QALY	£20,000 per QALY	£30,000 per QALY
Treatment	**Costs**	**QALYs**	**ICER,** £/QALY	**NB,** QALY (£)	**NB,** QALY (£)	**Incr NB*,** QALYs (£m)	**Incr NB*,** QALYs (£m)
clop12	£20,127	8.122	18,663	7.115 (142,307)	7.451 (223,525)	495 (9.9)	2,798 (56.0m)
clop6	£19,860	8.107	10,477	7.114 (142,288)	7.445 (223,362)	3,465 (69.3)	4,736 (94.7m)
clop3	£19,712	8.093	9,396	7.108 (142,154)	7.436 (223,087)	3,324 (66.5)	4,305 (86.1m)
clop1	£19,598	8.081	4,961	7.101 (142,025)	7.428 (222,837)	7,502 (150)	8,327 (166.5m)
NHS	£19,502	8.062	-	7.087 (141,734)	7.412 (222,353)	-	-

NBs are presented in both health (NHB) and monetary units (NMB)
* The mean additional population NB of moving from the least to most effective alternative, i.e., the incremental NB of clop12 compared to NHS is the sum of these increments (14,786 QALY or £296m at £20,000 per QALY)

4.2 Decision uncertainty

Estimates of expected cost and QALYs in clopidogrel's appraisal are uncertain so there is a chance that a decision to approve this treatment based on existing evidence will be incorrect, i.e., standard care might offer greater NBs. A judgement is required about the chance that 12 months of treatment is incorrect and if so which of the other four alternatives are likely to offer higher NB, and how much higher. Such judgment can be informed by PSA, already used to estimate mean costs and QALY. The probabilities that each of the five alternatives in the case study is cost-effective using PSA are reported in Table III. These indicate that it is likely that 12 months treatment is not cost effective – with a probability of 0.476. However, much of this probability of error is allocated to 6 months treatment with clopidogrel (0.18 probability) where the difference in NBs is expected to be relatively modest.

Table III Decision uncertainty and its expected consequences

	Cost-effectiveness threshold at:					
	£20,000 per QALY			**£30,000 per QALY**		
Treatment	**Incr NB** QALY (£m)	**Probability cost-effective**	**Expected consequences** QALY (£m)	**Incr NB** QALY (£m)	**Probability cost-effective**	**Expected consequences** QALY (£m)
1: clop12	495 (9.9m)	0.524	5,194 (103.9)	2,798 (56.0m)	0.677	3,657 (109.7)
2: clop6	3,465 (69.3m)	0.180		4,736 (94.7m)	0.092	
3: clop3	3,324 (66.5m)	0.018		4,305 (86.1m)	0.009	
4: clop1	7,502 (150.0m)	0.075		8,327 (166.5m)	0.052	
5: NHS	-	0.202		-	0.170	

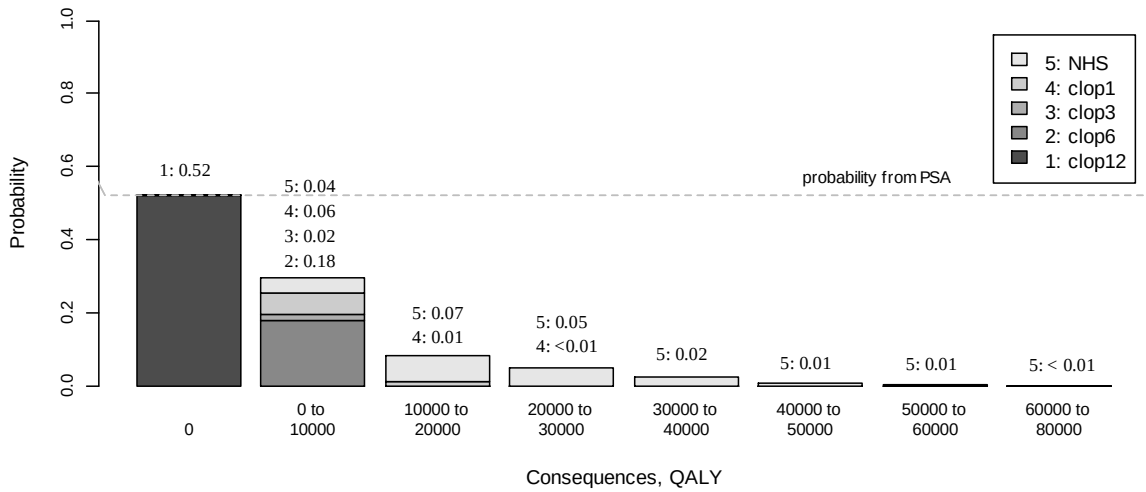
4.3 Assessing the consequences of uncertainty

The consequences of uncertainty are due to the fact that adopting clop12 may be the wrong decision, in which case the NHS is incurring in losses given the 'best' treatment is not being used. Given we do not know QALYs and costs of each treatment with certainty there is also uncertainty over the magnitude of such losses, or consequences. To evaluate the consequences of uncertainty, the expected or average difference between NBs

for the different technologies should *not* be taken, as biased results will be obtained. Alternatively, the distribution of potential consequences from decision uncertainty should be obtained through PSA.

The distribution of consequences of uncertainty is illustrated in Figure 1 for the case study, using a histogram of estimates for the population (bins assume values of 0, 0 to 10 000, 10 000 to 20 000, and so on). The consequences plotted were obtained by recording the cost effective treatment and it's NB for each possible realisation of the uncertain inputs. When, for a specific realisation, the cost effective treatment was clop12, no consequences from uncertainty were assumed as clop12 was the treatment recommended for adoption under current information. Figure 1 shows this situation to have been most common (52%). For realizations of the inputs where the decision would not have been to adopt clop12, then the consequences were valued as the difference between the NB of the cost effective treatment and that of clop12. Figure 1 lists for each bin the treatments that generate the plotted consequences and with which likelihood. For the case study, there was a greater chance of relatively small consequences (30% less than 10,000 QALYs, as shown by the sum of probabilities in the second bin 18%+2%+6%+4%) which occur predominantly when 6 months treatment duration offers the highest NHBs (probability of 0.18). But there is a small chance of larger consequences (less than 5% chance that they are greater than 30,000 QALYs) when standard NHS treatment offers the highest NBs. This means there remains important uncertainty about the cost-effectiveness of clopidogrel itself, and not just its duration.

Figure 1 Distribution of the consequences of uncertainty



The expected consequence of uncertainty is simply the average over this distribution, being valued at 5,194 QALYs (Table III) or £103.9m in equivalent NHS resources. The potential benefits may exceed the likely costs of conducting such research, and therefore a judgement at this point that more research might be worthwhile seems reasonable. Decision uncertainty can thus be considered significant.

Estimates presented assume 10 years technology time horizon. It is worth noting that the expected consequences of uncertainty increase with the technology time horizon (as the size of the patient population that can benefit increases). If 15 years were assumed the consequences of uncertainty would have been valued at 7,193 QALY [instead of 5,194 QALYs].

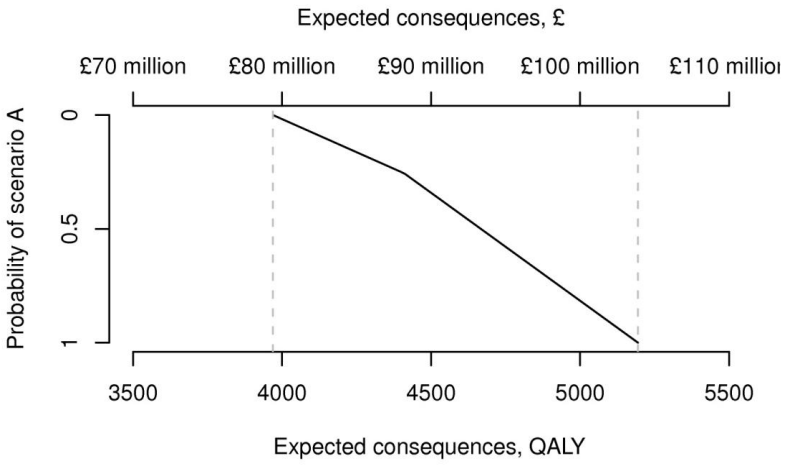
Alternative scenarios

In the case study, a constant relative treatment effect for different durations of treatment has been assumed in the analyses above (scenario A). Decision uncertainty characterisations presented in previous sections reflect parameter uncertainty within that one scenario. An alternative assumption (scenario B) was that the relative

treatment effect also differed by duration. This alternative assumption made longer durations less cost-effective and reduced the expected consequences of parameter uncertainty from 5,195 to 3,969 QALYs (see Appendix 2).

When more than one scenario is credible and carry some 'weight', there will be uncertainty *between* as well as *within* scenarios. The 'weighting' of scenarios can be made explicit by assigning probabilities to represent how credible each is believed to be. Although scenario A was regarded as more credible by the Appraisal Committee, scenario B might nevertheless carry some weight or have some probability associated to it. Figure 2 shows the joint consequences of within and between scenario uncertainty (Equation 7), for a range of probabilities that scenario A is true (y-axis). Note that consequences are valued in QALYs (NHBs) in the x-axis, but that equivalent NMBs are also shown in an additional x-axis at the top of the plot.

Figure 2 Expected consequences of uncertainty with alternative scenarios



4.4 Assessing the significance of sources of uncertainty

An assessment of the significance of sources of uncertainty requires judgements on the importance of particular (types of) parameters and on the consequences of existing uncertainty over these parameters.

i) How important are particular types of parameters to estimates of NBs

A simple summary of the direction and strength of the relationships between the model inputs (the parameters) and outputs (NBs) can be provided by calculating elasticities for each, i.e., the proportionate change in the NB of each alternative, and differences in NB, due to a one percent change in the value of the parameter, e.g., those parameters with high elasticities (especially with respect to differences in NB) might be regarded as more 'important'. These elasticities are presented for the case study in Table IV. They give some indication of the relative importance for certain comparisons of the parameter: e.g., RR_death seems particularly important for all comparisons. Also, results allow identifying those parameters that are of no or very limited importance: e.g., parameters 1-6 in the comparison of 12 and 6 months treatment duration. Finally, such analyses aid identifying the direction of the relationship: e.g., the elasticity for C_Well is negative, indicating that if the costs of NHS care in the 'well state' are higher, then 12 month treatment will be less cost-effective compared to 6 months or current NHS care.

Although measures of importance based on elasticities are more instructive than a series of arbitrary one way sensitivity analysis, they do not directly help the assessment of what values parameters must take to change decisions and how likely such values might be.

Table IV Elasticities associated with parameters

	Parameter		Elasticity over the NHE (QALY) of clop12	clop6	clop3	clop1	NHS	Elasticity over the INHE (QALY) of clop12 vs. NHS	clop12 vs. clop6	clop12 vs. all
Natural history	1	P_die_0.1	-0.208	-0.207	-0.207	-0.207	-0.222	0.014	-	0.003
	2	P_NFMI_0.1	-0.012	-0.012	-0.011	-0.011	-0.015	0.004	-	-
	3	P_die_1.3	-0.137	-0.137	-0.137	-0.147	-0.145	0.008	-	0.004
	4	P_NFMI_1.3	-0.002	-0.002	-0.002	-0.002	-0.002	0.001	-	-
	5	P_die_3.6	-0.146	-0.146	-0.157	-0.157	-0.154	0.008	-	0.007
	6	P_NFMI_3.6	-0.005	-0.005	-0.007	-0.007	-0.007	0.002	-	0.001
	7	P_die_6.12	-0.148	-0.159	-0.158	-0.157	-0.155	0.007	0.011	0.01
	8	P_NFMI_6.12	-0.005	-0.007	-0.007	-0.007	-0.007	0.002	0.002	0.002
	9	TP_AC	-0.121	-0.12	-0.12	-0.12	-0.118	-0.003	-0.001	-0.002
	10	TP_AD	-3.637	-3.622	-3.604	-3.594	-3.541	-0.096	-0.016	-0.047
	11	TP_CD	-0.233	-0.235	-0.239	-0.24	-0.253	0.02	0.002	0.009
	12	TP_BD	-0.586	-0.593	-0.602	-0.605	-0.641	0.055	0.007	0.024
Utilities	13	U_Well	0.746	0.745	0.743	0.742	0.737	0.009	0.001	0.004
	14	U_Well1	6.09	6.064	6.034	6.017	5.929	0.16	0.026	0.079
	15	U_NFMI	0.133	0.134	0.136	0.136	0.144	-0.011	-0.001	-0.005
	16	U_POSTMI	1.138	1.15	1.165	1.171	1.236	-0.099	-0.012	-0.043
RE	17	RR_death	-0.639	-0.491	-0.344	-0.207		-0.641	-0.15	-0.38
	18	RR_NFMI	-0.024	-0.018	-0.013	-0.011		-0.025	-0.006	-0.014
Costs	19	C_Well	-0.74	-0.737	-0.733	-0.731	-0.72	-0.019	-0.003	-0.009
	20	C_MI_LT	-0.051	-0.052	-0.053	-0.053	-0.056	0.004	0.001	0.002
	21	C_PostMI	-0.142	-0.143	-0.145	-0.146	-0.154	0.012	0.002	0.005
	22	TC_Well_Dead	-0.027	-0.027	-0.027	-0.027	-0.027	-	-	-
	23	C_t1	-0.045	-	-	-	-	-0.045	-0.045	-0.045
	24	C_t2	-	-0.033	-	-	-	-	0.033	0.008
	25	C_t3	-	-	-0.026	-	-	-	-	0.007
	26	C_t4	-	-	-	-0.022	-	-	-	0.005
	27	C_t5	-	-	-	-	-0.016	0.016	-	0.004

ii) What values these parameters would have to take to change a decision based on expected cost-effectiveness

A simple summary of the values particular parameters must take to make each of the alternatives cost-effective can also be provided. These 'threshold values' for parameters are presented for the case study in Table V. This provides additional information to the elasticities in Table IV, e.g., there are only 6 parameters which could possibly take values that would lead to current NHS care generating higher NBs than 12 months of treatment with clopidogrel. However, although instructive, such 'threshold values' do not indicate how likely it is that threshold will be crossed or the combined effect of groups of related parameters.

Table V Thresholds associated with parameter values

	Parameter	Mean value	Clop12	Clop6	Clop3	Clop1	NHS
Natural history	1_die_0.1	0.032	0 to 0.10	0.11 to 0.54	0.54 to 0.63	0.63 to 1	-
	2_NFMI_0.1	0.04	0 to 0.14	0.14 to 0.71	0.71 to 0.82	0.82 to 1	-
	3_die_1.3	0.022	0 to 0.10	0.10 to 0.55	0.55 to 1	-	-
	4_NFMI_1.3	0.004	0 to 0.10	0.10 to 0.7	0.7 to 1	-	-
	5_die_3.6	0.023	0.01 to 0.10	0.10 to 1	0 to 0.01	-	-
	6_NFMI_3.6	0.011	0 to 0.11	0.11 to 1	-	-	-
	7_die_6.12	0.024	0.02 to 1	0 to 0.02	-	-	-
	8_NFMI_6.12	0.009	0.005 to 1	0 to 0.005	-	-	-
	9TP_AC	0.018	0 to 0.06	0.06 to 1	-	-	-
	10TP_AD	0.072	0 to 0.08	0.08 to 0.10	-	-	0.10 to 1
	11TP_CD	0.188	0.12 to 1	0 to 0.12	-	-	-
	12TP_BD	0.07	0.06 to 1	0.04 to 0.06	-	-	0 to 0.04
Utilities	13U_Well	0.798	0.29 to 1	0 to 0.29	-	-	-
	14U_Well1	0.93	0.90 to 1	0.74 to 0.90	-	-	0 to 0.74
	15U_NFMI	0.801	0 to 1	-	-	-	-
	16U_POSTMI	0.931	0 to 1	-	-	-	-
RE	17RR_death	0.931	0 to 0.93	0.94 to 0.97	0.97 to 0.98	0.98 to 0.99	1.00 to max*
	18RR_NFMI	0.71	0 to 0.82	0.83 to 1.55	1.56 to 1.83	-	1.84 to max*
Costs	19C_Well	2061.5	0 to 2690	2690 to 5611	-	-	5611 to max*
	20C_MI_LT	6050	0 to max*	-	-	-	-
	21C_PostMI	2309.7	870 to max*	0 to 870	-	-	-
	22TC_Well_Dead	871.5	0 to 20474	20474 to max*	-	-	-
	23C_t1	895.1	0 to 910	910 to max*	-	-	-
	24C_t2	651.6	630 to max*	0 to 630	-	-	-
	25C_t3	524.2	370 to max*	-	0 to 370	-	-
	26C_t4	434.8	150 to max*	-	-	0 to 150	-
	27C_t5	329.8	0 to max	-	-	-	-

iii) How likely it is that parameters might take values which will change a decision based on expected cost-effectiveness

The judgement about how likely it is that parameters might take values which will change the technology expected to be cost effective, can be informed by results of probabilistic analysis. This is because the distributions assigned to parameters in PSA describe how uncertain parameter estimates are, and reflect the amount and quality of exiting evidence. The probability that each parameter might take values which would lead to each of the alternatives being cost-effective are reported for the case study in Table VI. This, essentially, decomposes the overall probabilities reported in Table V into the contribution that each parameter makes. Interestingly, it indicates that it is uncertainty in the estimates of relative effect (RR_Death) that contributes most to the probability of error associated with 12 months of treatment. It is the only parameter which (alone) might take values that could make any of the other alternatives cost-effective. It is also worth noting that there is a very small chance that cost in the 'well state' (C_Well) might be sufficiently high that standard NHS care would be cost-effective, i.e., if NHS costs associated with the 'well state' are higher than any cost savings associated with moving more patients more quickly to the well state will tend to be lower.

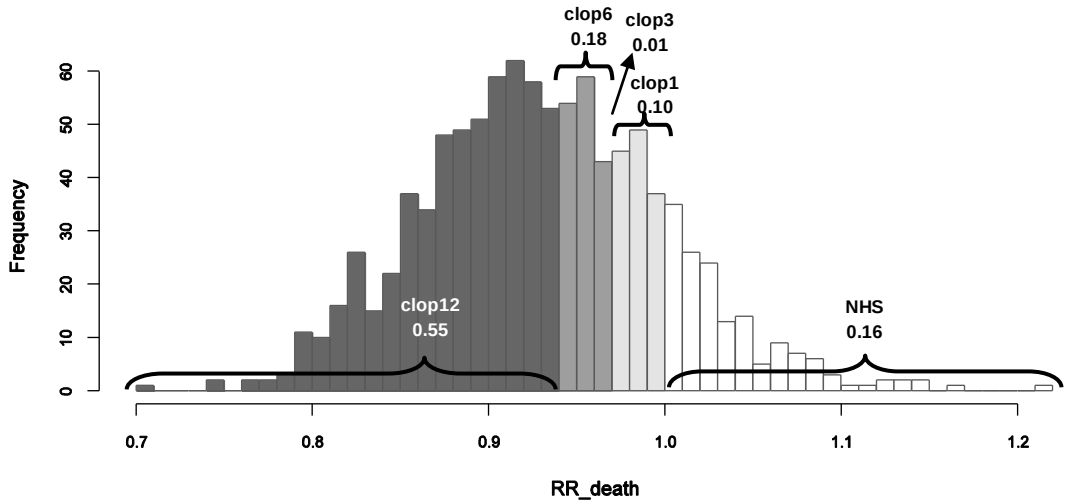
Table VI Probabilities associated with parameter values

	Parameter	Clop12	Clop6	Clop3	Clop1	NHS
Natural history	1 P_die_0.1	1	-	-	-	-
	2 P_NFMI_0.1	1	-	-	-	-
	3 P_die_1.3	1	-	-	-	-
	4 P_NFMI_1.3	1	-	-	-	-
	5 P_die_3.6	1	-	-	-	-
	6 P_NFMI_3.6	1	-	-	-	-
	7 P_die_6.12	0.65	0.35	-	-	-
	8 P_NFMI_6.12	0.91	0.09	-	-	-
	9 TP_AC	1	-	-	-	-
	10 TP_AD	0.83	0.17	-	-	-
	11 TP_CD	1	-	-	-	-
	12 TP_BD	0.85	0.15	-	-	-
Utilities	13 U_Well	1	-	-	-	-
	14 U_Well1	0.94	0.06	-	-	-
	15 U_NFMI	1	-	-	-	-
	16 U_POSTMI	1	-	-	-	-
RE	17 RR_death	0.55	0.18	0.01	0.10	0.16
	18 RR_NFMI	0.97	0.03	-	-	-
Costs	19 C_Well	0.78	0.19	-	-	0.03
	20 C_MI_LT	1	-	-	-	-
	21 C_PostMI	0.89	0.11	-	-	-
	22 TC_Well_Dead	1	-	-	-	-
	23 C_t1	0.95	0.05	-	-	-
	24 C_t2	0.99	0.01	-	-	-
	25 C_t3	1	-	-	-	-
	26 C_t4	1	-	-	-	-
	27 C_t5	1	-	-	-	-

The probability of error associated with 12 month of treatment reported in Table III will, in general, not equal the sum of probabilities of error across the parameters, because the overall probability from PSA takes account of the joint effect of uncertainty in all parameters simultaneously. Even if parameters are independent they will be related to differences in NBs in different ways (indicated by the sign and magnitude of the elasticities – see Table IV), so sometimes the effect of uncertainty in one may, to some extent, 'substitute' or 'complement' the effect of uncertainty in others.

The link between the parameter value thresholds and the probability of observing such values is illustrated in Figure 3 for RR_death. This histogram (showing the distribution of values this parameter may take) is shaded to highlight the ranges of values that lead to different adoption decisions. The likelihood of observing such ranges is given by the labels in the Figure. It is clear that the parameter RR_Death contributes to decision uncertainty; however, we are still unclear on what are the consequences from these shifts in the adoption decision.

Figure 3 Histogram of the values of parameter RR_death



iv) what are the consequences of uncertainty in the values of parameters?

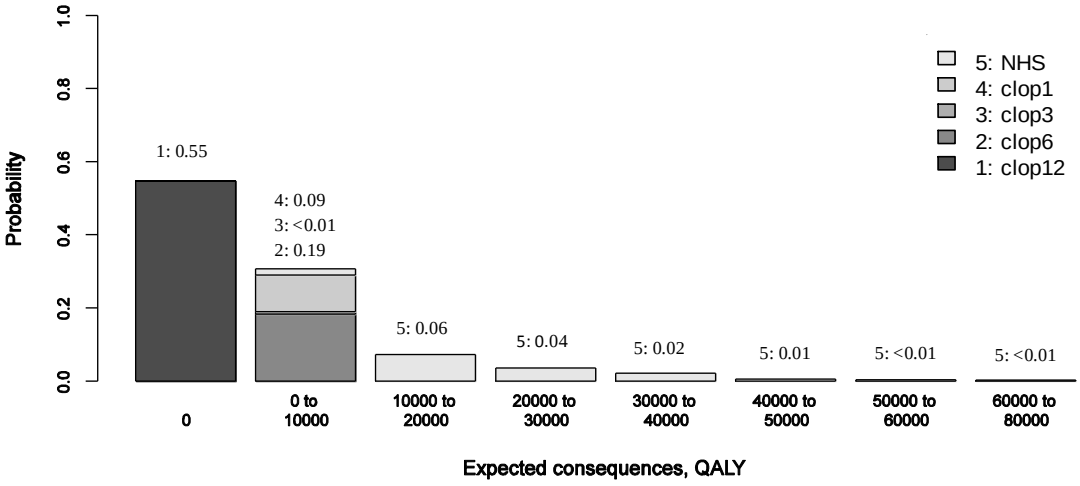
To explore the importance of parameters to decision uncertainty, an assessment of the likely consequences of uncertainty over these is helpful. This assessment can also directly inform the judgement of what evidence is needed and whether the type of research required to generate it will be possible with approval. In a similar way to Section 4.3, the results of PSA can inform this judgement since estimates of the expected consequences of uncertainty associated with each parameter combines both uncertainty in its potential values and their importance in terms of changing decisions and differences in NBs. The expected consequences of uncertainty associated with each parameter in the case study are reported in Table VII (each parameter has been evaluated separately from the remaining). This decomposes the overall expected consequences reported in Table III into the contribution that each parameter makes and which other alternatives might offer higher NBs than 12 month treatment. Note that the overall expected consequences of uncertainty reported in Table III (5,194 QALYs) will not, in general, equal the sum of the expected consequences for each of the parameters separately. Table VII confirms that it is uncertainty in the estimates of relative effect (RR_Death) that contributes the most to overall decision uncertainty and where there is potentially the most to be gained by resolving this uncertainty through additional research (4,433 QALYs or £88.7m).

Table VII Consequences of uncertainty associated with parameter values

		Expected consequences (QALYs)					
		Decomposed by treatment choice					
	Parameter	clop12	clop6	clop3	clop1	NHS	Overall
Natural history*	1 P_die_0.1	0	-	-	-	-	0
	2 P_NFMI_0.1	0	-	-	-	-	0
	3 P_die_1.3	0	-	-	-	-	0
	4 P_NFMI_1.3	0	-	-	-	-	0
	5 P_die_3.6	0	-	-	-	-	0
	6 P_NFMI_3.6	0	-	-	-	-	0
	7 P_die_6.12	0	250	-	-	-	250
	8 P_NFMI_6.12	0	9	-	-	-	9
	9 TP_AC	0	-	-	-	-	0
	10 TP_AD	0	47	-	-	-	47
	11 TP_CD	0	-	-	-	-	0
	12 TP_BD	0	35	-	-	-	35
Utilities*	13 U_Well	0	-	-	-	-	0
	14 U_Well1	0	10	-	-	-	10
	15 U_NFMI	0	-	-	-	-	0
	16 U_POSTMI	0	-	-	-	-	0
RE	17 RR_death	0	284	16	518	3614	4433
	18 RR_NFMI	0	3	-	-	-	3
Costs*	19 C_Well	0	153	-	-	321	474
	20 C_MI_LT	0	-	-	-	-	0
	21 C_PostMI	0	8	-	-	-	8
	22 TC_Well_Dead	0	-	-	-	-	0
	23 C_t1	0	8	-	-	-	8
	24 C_t2	0	0	-	-	-	0
	25 C_t3	0	-	-	-	-	0
	26 C_t4	0	-	-	-	-	0
	27 C_t5	0	-	-	-	-	0

The distribution of the consequences of uncertainty associated with the parameter RR_death is shown in Figure 4 (analogous to Figure 1). There is a 55% likelihood that values assumed by RR_death lead to the decision to adopt clop12, in which case there are no consequences of uncertainty.

Figure 4 Distribution of the consequences of uncertainty on RR_death



Given the significant uncertainty over RR_death (valued at 4 433 QALY or £89m, Table VII), more precise estimates of relative effects are of value. An RCT is likely to be required. However, the potential benefits of resolving the uncertainty associated with other groups of parameters, e.g., costs and natural history (Table VIII), might mean that other types of cheaper, non experimental research, could be worthwhile as well.

Table VIII Consequences of uncertainty associated with groups of parameters

Group of parameters	**Expected consequences**, QALY (£m)
Natural history	369 (7.4)
Relative treatment effects	4504 (90.1)
Utilities	15 (0.3)
Costs	547 (10.9)

* These are not equal to the sum of expected consequences for component parameters.

It may not be possible to implement such an RCT if clop12 is approved. This is because implementing a trial with a control arm of standard NHS could be considered unethical, given we know that clop12 is effective and cost-effective. In such case the value of resolving uncertainty is lost. Where the opportunity to conduct further research is foregone at the moment of a binary approve/reject decision, the decision maker should consider recommending research. [Claxton et al, Health technology assessment report, forthcoming]

Implications of scenario uncertainty

In Section 4.3 the contribution alternative scenarios might make to the overall expected consequences of uncertainty, and therefore the potential gains from further evidence, was considered and discussed. Table IX decomposes the assessment of the consequences of uncertainty in the presence of scenarios to evaluate the expected consequences of between scenario uncertainty, parameter uncertainty in the presence of scenarios. The consequences of between scenario uncertainty represent what might be gained if evidence could immediately distinguish which scenario was 'true'. This can help to inform the assessment of what type of evidence might be needed and whether the research required to generate it is likely to be possible once a technology is approved for widespread NHS use. For the purpose of these analyses, scenarios A and B were assumed equally likely.

The overall expected consequences of uncertainty (within and between scenario uncertainty jointly considered) were valued at 4,667 QALYs. However, the expected consequences of between scenario uncertainty is relatively modest at 85 QALYs, i.e., it might not be worth resolving the uncertainty over which scenario best represents the decision problem. Most of what might be gained from further evidence is associated with the parameters rather than the alternative scenarios. This suggests that more evidence about overall relative effect on mortality is more important than resolving uncertainty about whether such an effect differs by treatment duration.

Table IX Expected consequences of uncertainty when scenarios are equally likely

Consequences of uncertainty on	**Value,** QALY (£m)
parameters, within scenario A (base case)	5 194 (103.9)
parameters, within scenario B	3 969 (79.4)
parameters, considering between scenario uncertainty	2 356 (47.1)
between scenario uncertainty, considering uncertainty within scenarios	85 (1.7)
parameters and scenario uncertainty	4 667 (13.3)

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Appendix 1: *Accounting for between scenario uncertainty*

One source of uncertainty in estimating the true value of the expected costs and health outcomes associated with alternative interventions has been described variously as modelling, structural or scenario uncertainty. Scenario uncertainty arises when alternative plausible modelling assumptions can be made. Potential sources of scenario uncertainty include alternative assumptions about which sources of evidence are relevant to the decision problem, the choice of mathematical model to estimate model parameters and the type and structure of the decision model that is used to generate estimates of costs and health outcomes. Unless the scenario uncertainty can be characterised by a parameter within the decision model, its impact on decision uncertainty will not be reflected in routine probabilistic sensitivity analysis based on Monte Carlo simulation and further analytical processes are required. This technical note describes in more detail how to estimate appropriately the value of further research in the presence of both parameter and scenario uncertainty. This is relevant when providing information for the assessments required at points 3 and 4 of the checklist described in [ref to main report].

1. How to estimate cost effectiveness in the presence of scenario uncertainty

The estimation of expected costs, c, and health outcomes, h, will be informed by the available evidence, $\boldsymbol{\theta}$, and the set of assumptions, S, that characterise a particular scenario. The results of a cost-effectiveness analysis for each alternative intervention j can be expressed in terms of net health effects,

$NHE\ \ j,\boldsymbol{\theta},s\ = h\ \ j,\boldsymbol{\theta},s\ - \dfrac{c\ \ j,\boldsymbol{\theta},s}{k}$. Where k is the cost-effectiveness threshold.

The assessment of cost-effectiveness is made by taking the expectation of net health effects across the parameter uncertainty and the range and likelihood of the alternative scenarios, $E_{\boldsymbol{\theta}}E_s NHE\ \ j,\boldsymbol{\theta},s$.

Parameter uncertainty (uncertainty as to the true value of $\boldsymbol{\theta}$) can be characterised by assigning probability distributions to the model parameters. This allows the results of the model to be evaluated by probabilistic sensitivity analysis; a Monte Carlo simulation procedure can be used to repeatedly sample from those distributions a set of model inputs, and for each set calculate the corresponding model outputs. The expectation of the model outputs is found by averaging across the results of the Monte Carlo simulation. If scenario uncertainty has not been characterised by a probability distribution and sampled simultaneously alongside the parameter values, that Monte Carlo simulation procedure will estimate the expectation of net health effects across parameter uncertainty within a single scenario, e.g. $E_{\boldsymbol{\theta}}NHE\ \ j,\boldsymbol{\theta},s=1$. The Monte Carlo simulation procedure must then be repeated for each possible scenario. The expected net health effects across parameter uncertainty from each scenario can then be combined utilising the likelihood of each possible scenario in order to describe the expected net health effects across both parameter and scenario uncertainty.

2. How to estimate the value of research in the presence of scenario uncertainty

The best a decision maker could do would be to select the intervention that maximised health gains for a particular realisation of $\boldsymbol{\theta}$ and S. The expected net health effects associated with this error free choice is $E_{\boldsymbol{\theta}}E_s \max_j NHE\ \ j,\boldsymbol{\theta},s$. The maximum value of further research that would eliminate all uncertainty, including scenario uncertainty, is $EVPI_{\boldsymbol{\theta},s} = E_{\boldsymbol{\theta}}E_s \max_j NHE\ \ j,\boldsymbol{\theta},s\ - \max_j E_{\boldsymbol{\theta}}E_s NHE\ \ j,\boldsymbol{\theta},s$.

Given we believe a certain scenario to be true, for example scenario 1, the maximum value of further research to eliminate parameter ($\boldsymbol{\theta}$) uncertainty, is $EVPI_{\boldsymbol{\theta}|s=1} = E_{\boldsymbol{\theta}} \max_j NHE \quad j, \boldsymbol{\theta}, s=1 \; - \max_j E_{\boldsymbol{\theta}} NHE \quad j, \boldsymbol{\theta}, s=1$.

Combining the expected value of further research within each possible scenario using the likelihood of each scenario would not describe the value of research that would eliminate both scenario and parameter uncertainty. When alternative scenarios would suggest that different interventions would be expected to be cost-effective the net health effects of choosing the best intervention when integrating both parameter and modelling uncertainty cannot be found by averaging the net health effects of choosing the best intervention within each scenario. This is because: $\max_j E_s E_\theta NHE \quad j, \theta, s \; \neq E_s \left[\max_j E_\theta NHE \quad j, \theta, s \right]$. Averaging across the scenarios in this way ignores scenario uncertainty as it assumes the decision maker can select alternative treatments based on knowing how the scenario uncertainty is resolved. It is only when scenario uncertainty is not associated with decision uncertainty, i.e. when the same intervention would be identified as cost-effective in all scenarios, would this produce an unbiased estimate of the value of further research.

An appropriate method by which to evaluate the value of further research that would eliminate both parameter and scenario uncertainty would be to stack the Monte Carlo simulations, ensuring that the proportion of Monte Carlo simulations selected from the probabilistic sensitivity analysis within each scenario corresponds to the likelihood of that scenario being correct. In order to produce representative results this may require a larger number of simulations than would be selected based on consideration of parameter uncertainty alone, particularly if the likelihood of any particular scenario is low.

Measures quantifying the maximum value of eliminating uncertainty in either parameters or scenarios can also be of importance. The maximum value of further research to eliminate parameter ($\boldsymbol{\theta}$) uncertainty when scenario uncertainty is present is $EVPI_{\boldsymbol{\theta}} = E_{\boldsymbol{\theta}} \max_j E_s NHE \quad j, \boldsymbol{\theta}, s \; - \max_j E_{\boldsymbol{\theta}} E_s NHE \quad j, \boldsymbol{\theta}, s$. The maximum value of further research to eliminate scenario uncertainty, in the presence of parameter uncertainty, is

$$EVPI_s = E_s \max_j E_{\boldsymbol{\theta}} NHE \quad j, \boldsymbol{\theta}, s \; - \max_j E_{\boldsymbol{\theta}} E_s NHE \quad j, \boldsymbol{\theta}, s$$

__ *Example* _____

Table A.8 presents the net health effects for each intervention based on competing plausible forms of the function $NHE \quad j, \theta, s$; $s = 1, 2$. It is assumed that each value of $\boldsymbol{\theta}$ is equally likely, and each scenario is equally plausible. Therefore the expectation across parameter or scenario uncertainty can be found by averaging across the relevant set of results.

Table A.8 Population net health effects for alternative scenario

	Scenario 1 (Base case) Overall population		
θ	NHE(1,θ)	NHE(2,θ)	Max
1	4125	3250	4125
2	750	5250	5250
3	6000	2250	6000
4	10250	6000	10250
E_θ	5281	4188	6406

	Scenario 2 Overall population		
θ	NHE(1,θ)	NHE(2,θ)	Max
1	4125	4750	4750
2	750	6750	6750
3	6000	3750	6000

4	10250	7500	10250
E_θ	5281	5688	6938

	Average across scenarios Overall population		
θ	NHE(1,θ)	NHE(2,θ)	Max
1	4125	4000	4125
2	750	6000	6000
3	6000	3000	6000
4	10250	6750	10250
E_θ	5281	4938	6594

Based on scenario 1 it would appear that intervention 1 were cost-effective as it offers the greatest expected net health effects, $\max_j E_{\boldsymbol{\theta}} NHE \quad j, \boldsymbol{\theta}, s = 1 \quad = 5281$. However, in the alternative scenario 2 the net health effects of intervention 2 are estimated to be larger than those associated with intervention 1, and so it no longer appears cost-effective, $\max_j E_{\boldsymbol{\theta}} NHE \quad j, \boldsymbol{\theta}, s = 2 \quad = 5688$. In the presence of both scenario and parameter uncertainty it would appear that intervention 1 were cost-effective, $\max_j E_{\boldsymbol{\theta}} E_s NHE \quad j, \boldsymbol{\theta}, s \quad = 5281$.

Averaging across the expected net health effects from within each scenario result would be equivalent to assuming that the decision maker could select a different intervention based on how the scenario uncertainty resolved, giving expected net health effects of $E_s \max_j E_{\boldsymbol{\theta}} NHE \quad j, \boldsymbol{\theta}, s \quad = 5485$.

Table A.9 presents the value of further research for a range of possible research questions.

Table A.9 Population net health effects with equally likely alternative modelling assumptions

	Value	Calculation
$EVPI_{\boldsymbol{\theta}\mid s=1}$	1125	6406 - max(5281, 4188)
$EVPI_{\boldsymbol{\theta}\mid s=2}$	1250	6938 - max(5281, 5688)
$EVPI_{\boldsymbol{\theta}}$	1313	6594 - max(5281, 4938)
$EVPI_s$	203	mean(max(5281,4188), max(5281,5688)) - max(5281, 4938)
$EVPI_{\boldsymbol{\theta},s}$	1391	mean(6406,6938) - max(5281, 4938)

The value of resolving parameter uncertainty in scenario 1 is 1125. In scenario 2 this value is 1250. Note that in this example the value of research to resolve parameter uncertainty is estimated to be greater when it takes account of scenario uncertainty (1313), even though the research would not resolve the scenario uncertainty. The value of resolving only scenario uncertainty is 203. The value of resolving both parameter and scenario uncertainty is in this example equal to 1391.

Appendix 2: *Cost effectiveness of CLOP within each scenario*

Table 4.4 Expected cost-effectiveness with alternative scenarios

Scenario A (base case)				**Cost-effectiveness threshold at:**	
				£20,000 per QALY	**£30,000 per QALY**
Treatment	**Costs,**	**Health effects,** QALY	**ICER,** £/QALY	**NHE,** QALY (£m)	**NHE,** QALY (£m)
clop12	£10,394,830,647	4 194 554	£18,663	3 674 813 (73,496)	3 848 060 (115,442)
clop6	£10,256,672,674	4 187 151	£10,477	3 674 318 (73,486)	3 845 262 (115,358)
clop3	£10,180,425,730	4 179 874	£9,396	3 670 853 (73,417)	3 840 526 (115,216)
clop1	£10,121,529,942	4 173 605	£4,961	3 667 529 (73,351)	3 836 221 (115,087)
NHS	£10,072,035,344	4 163 629	-	3 660 027 (73,201)	3 827 894 (114,837)

Scenario B				**Cost-effectiveness threshold at:**	
				£20,000 per QALY	**£30,000 per QALY**
Treatment	**Costs,**	**Health effects,** QALY	**ICER,** £/QALY	**NHE,** QALY (£m)	**NHE,** QALY (£m)
clop12	£10,377,895,363	4 236 359	£20,494	3 717 464 (74,349)	3 890 429 (116,713)
clop6	£10,236,295,027	4 229 449	£11,963	3 717 635 (74,353)	3 888 240 (116,647)
clop3	£10,154,505,201	4 222 613	£4,087	3 714 887 (74,298)	3 884 129 (116,524)
clop1	£10,044,958,670	4 195 806	£3,601	3 693 558 (73,871)	3 860 974 (115,829)
NHS	£9,941,658,953	4 167 119	-	3 670 036 (73,401)	3 835 730 (115,072)

Table 4.5 Expected consequences of uncertainty with alternative scenarios

Scenario A, base case		**Cost-effectiveness threshold at:**					
		£20,000 per QALY			**£30,000 per QALY**		
Treatment	**ICER,** £/QALY	**Incr NHE *,** QALY (£m)	**Probability cost-effective**	**Expected consequences,** QALY (£m)	**Incr NHE *,** QALY (£m)	**Probability cost-effective**	**Expected consequences,** QALY (£m)
1: clop12	18,663	495 (9.9)	0.524	5 194 (103.9)	2,798 (56.0)	0.677	3 657 (109.7)
2: clop6	10,477	3,465 (69.3)	0.180		4,736 (94.7)	0.092	
3: clop3	9,396	3,324 (66.5)	0.018		4,305 (86.1)	0.009	
4: clop1	4,961	7,502 (150.0)	0.075		8,327 (166.5)	0.052	
5: NHS	-	-	0.202		-	0.170	

Scenario B		**Cost-effectiveness threshold at:**					
		£20,000 per QALY			**£30,000 per QALY**		
Treatment	**ICER** £/QALY	**Incr NHE *,** QALY (£m)	**Probability cost-effective**	**Expected consequences,** QALY (£m)	**Incr NHE *,** QALY (£m)	**Probability cost-effective**	**Expected consequences,** QALY (£m)
1: clop12	20,494	-171 (-3.4)	0.435	3 969 (79.4)	2,189 (43.8)	0.564	2 871 (86.1)
2: clop6	11,963	2,747 (54.9)	0.327		4,110 (82.2)	0.268	
3: clop3	4,087	21,329 (426.6)	0.237		23,155 (463.1)	0.168	
4: clop1	3,601	23,522 (470.4)	0.001		25,244 (504.9)	0.000	
5: NHS	-	-	0.000		-	0.000	

* For scenario A, the incremental NHE (Incr NHE) represents the mean additional population NHE of moving from the least to most effective alternative. For simplicity, in scenario B the order of treatments was maintained from that of scenario A.