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Improving the efficiency and relevance of health technology assessment: The role of iterative decision analytic modelling

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DISCUSSION PAPER 179

IMPROVING THE EFFICIENCY AND RELEVANCE OF HEALTH TECHNOLOGY ASSESSMENT: THE ROLE OF ITERATIVE DECISION ANALYTIC MODELLING

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Abstract

Decision making in health care involves two sets of related decisions: those concerning appropriate service provision on the basis of existing information; and those concerned with whether to fund additional research to reduce the uncertainty relating to the decision. Information acquisition is not costless, and the allocation of funds to the enhancement of the decision makers' information set, in a budget-constrained health service, reduces the 'pot' of resources available for health service provision. Hence, a framework is necessary to unify these decisions and ensure that HTA is subject to the same evaluation of efficiency as service provision.

A framework is presented which addresses these two sets of decisions through the employment of decision analytic models and Bayesian value of information analysis, early and regularly within the health technology assessment process. The model becomes the vehicle of health technology assessment, managing and directing future research effort on an iterative basis over the lifetime of the technology. This ensures consistency in decision making between service provision, research and development priorities and research methods. Fulfilling the aim of the National Health Service HTA programme, that research is "produced in the most economical way" using "cost effective research protocols".

The proposed framework is applied to the decision concerning the appropriate management of female patients with symptoms of urinary tract infection, which was the subject of a recent NHS HTA call for proposals. A probabilistic model is employed to fully characterise and assess the uncertainty surrounding the decision. The expected value of perfect information (EVPI) is then calculated for the full model, for each individual management strategy and for particular model parameters. Research effort can then be focused on those areas where the cost of uncertainty is high and where additional research is potentially cost-effective. The analysis can be used to identify the most appropriate research protocol and to concentrate research upon particular parameters where more precise estimates would be of most value.

1. INTRODUCTION

Decision making in health care is inevitably undertaken in a context of uncertainty concerning the effectiveness and resource costs of health care interventions and programmes. Therefore, two related sets of decisions need to be taken: those concerning appropriate service provision on the basis of existing information; and those concerned with whether to fund additional research to reduce the uncertainty relating to the decision. Decision analytic models have been suggested as a systematic means of guiding both types of decision making under conditions of uncertainty [1,2] and recently Claxton et al [3] have illustrated the benefits of employing stochastic models incorporating Bayesian Value of Information (VOI) analysis to address these decisions.

This paper builds on earlier work relating to iterative frameworks for HTA [4,5], the use of models to prioritise research [6,7] and methods for estimating the VOI from research [3,8,9], by suggesting that such models should be instigated with the emergence of a new health technology and updated regularly as more information emerges. In this framework, each subsequent modelling stage is informed by the preceding model, updated to incorporate information acquired to date. Thus the model assumes a predominant role in the management of the HTA process, providing a vehicle to unify iterative decisions concerning efficient services to patients, the potential cost of uncertainty, the value of additional information and the most efficient means of acquiring that information throughout the life-cycle of the technology. Integrating this framework within the HTA process would improve the efficiency of a health technology assessment programme, ensuring that HTA is subject to the same efficiency criteria as service provision.

The benefits and practicality of the proposed approach are demonstrated through application to the decision concerning the management of non-pregnant women with symptoms of urinary tract infection (Section 3). Prior to the example application, the methods employed within the framework are introduced in Section 2.

2. METHODOLOGICAL BACKGROUND

Recently a Bayesian decision theoretic framework has been suggested for the evaluation of health technologies [3,8,9]. This approach distinguishes the decision concerning efficient service provision, given the existing level of information available, from the decision concerning whether to fund the generation of new information through further research to inform this decision in the future.

The decision concerning efficient service provision given existing information involves identifying the strategy associated with the best decision payoff given no additional information (the *a priori* act [10]). Within the evaluation of health technologies, decision payoffs are expressed in terms of the net benefit[1] associated with strategy (t) expressed in either health outcome (η) or monetary terms (μ) [8,9,11,12]:

$$\eta_t = QALY_t - (Cost_t * \lambda^{-1}) \qquad \text{[equation 1a]}$$

$$\mu_t = (\lambda * QALY_t) - Cost_t \qquad \text{[equation 1b]}$$

where: λ = monetary valuation of health outcome

[1] When only two technologies are being assessed the decision payoff can be expressed in terms of incremental net benefit (see Claxton [3 ,8 ,9])

The monetary valuation of health outcome (λ) represents the value that society places upon the health outcome in monetary terms.[2] This can be considered exogenous to the model and the analysis presented for a range of values of λ.

Given an objective to maximise health for a given budget the *a priori* act is identified as the technology/strategy that generates the maximum expected net benefit.[3] Hence, only the mean of the distribution of net benefit is relevant for this decision [8]. The choice of a strategy other than that which maximises expected net benefit - for example in order to satisfy the requirements of traditional statistical significance - imposes costs upon society in terms of net benefits forgone (see Section 3.2.3) and contradicts the objective of maximising health gain subject to resource constraints [8].

However, the uncertainty surrounding the net benefits attainable from the strategy, represented by the distribution of net benefits, is critical for the decision concerning whether to fund the collection of further information to inform the service provision decision in the future [8]. Basic measures of uncertainty have previously been suggested [13,14] and employed to provide an indication of the worth of further information collection. However, the widespread application of these techniques to the HTA process is limited by their qualitative nature. The framework suggested in this paper takes a more formal approach to both measuring uncertainty and determining the worth of further data collection, employing stochastic modelling and Bayesian VOI analysis [8,9]. Here the decision concerning the worth of further data collection is based upon the expected cost of uncertainty, which in turn is determined by the extent of the uncertainty surrounding the *a priori* decision and the consequences of this uncertainty. The

[2] Although when valuing information, which is a public good, it is appropriate that λ represents the societal willingness to pay for health outcome, a health service decision makers view of λ may be influenced by the shadow price of the budget constraint.

[3] The maximum expected net benefit decision rule is equivalent to choosing the strategy with the largest ICER below

extent of the uncertainty associated with the *a priori* decision is measured by the error probability, expressed as the proportion of iterations in which uncertainty results in a decision other than that which maximises expected net benefit being undertaken. The associated consequences are measured in terms of the health benefits forgone as a result of this uncertainty. When these health benefits are valued according to society's willingness-to-pay for health outcome (λ), the approach gives a monetary value for the amount that society is willing to pay to reduce the uncertainty surrounding the service provision decision. This valuation can then be compared to the cost of gathering further information to determine whether research is worthwhile [9].

3. APPLICATION

The benefits and the practicality of the proposed approach are illustrated through an application to the decision concerning the appropriate management of non-pregnant women presenting to general practice with the symptoms of uncomplicated urinary tract infection.[4] This provides a suitable example to demonstrate the value of the framework, as it is an area where existing information is limited and there is considerable variation amongst physicians concerning the most appropriate method of patient management [15,16]. In addition, the recent introduction of new methods of diagnosis (dipsticks) should prompt a reassessment regarding optimum service provision and the need for further research. Recently, the NHS health technology assessment programme identified the "Use of dipsticks and diagnostic algorithms in the diagnosis of urinary tract infection" as a research priority and called for proposals for primary research (97/14).

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the cut-off level when all dominated strategies are excluded [43]

[4] Pregnant women; men; children and women presenting with symptoms suggesting upper urinary tract infection (fever; chills; nausea and loin pain) are excluded from the study due to their increased risk of underlying structural abnormalities and complications.

The aims of the analysis are: (i) to identify the appropriate patient management strategy given the current level of information (the *a priori* act); (ii) to determine whether the call for primary research in the area of UTI diagnosis was justified; and (iii) to provide additional information regarding priorities for the research process.

A deterministic model is presented initially to provide a conventional decision analysis (Section 3.1). Probabilistic analysis is then employed to illustrate the extent of the uncertainty surrounding the decision based upon existing information (Section 3.2). Finally, a VOI analysis indicates the elements of the decision where further information is potentially of value to society (section 3.3).

3.1 A deterministic model of the management of UTI

3.1.1. Introduction

The symptoms associated with urinary tract infection (UTI) are common in general practice: dysuria and frequency have been reported in 27% and 34% of women [17]. These symptoms are a major cause of consultation in general practice and account for 1%-3% of all GP consultations [18] and 2% of all prescriptions [19]. Although the majority of cases in women are short-term and self-limiting, this condition does represent a considerable resource burden for the NHS.

Early discussions with practitioners identified two main approaches for managing UTI in general practice. The first is empiric antibiotic treatment on presentation of symptoms and the second involves the use of diagnostic tests to exclude or confirm the presence of UTI prior to antibiotic treatment. Two test procedures were identified for consideration within the model: the dipstick test, a near-patient test generating immediate results; and the laboratory test, involving an

Table 1: Strategies employed within the model of UTI management

Strategy name	Strategy description
No treatment	GPs provide general advice on relieving symptoms and inform patients that symptoms will resolve within seven days.
Empiric treatment	All individuals presenting with symptoms of UTI receive a three-day course of general antibiotics.
Empiric treatment plus laboratory test	The laboratory test is used to supplement empiric treatment. Whilst all patients provide a urine sample for testing, during the initial consultation, the results only affect the management of those patients with persistent symptoms. For these patients antibiotic sensitivity will be available at the second GP visit for those who tested positive, which will enable the GP to prescribe a course of specific antibiotics. This gives the patients with UTI who test positive a second chance for antibiotics to clear the infection. Antibiotics will not be altered on the basis of the sensitivity results until the second consultation.
Dipstick and treatment	The dipstick test is employed within the initial consultation to provide an indication of presence of disease and to restrict the use of antibiotics to those considered most likely to have UTI, as denoted by the result of the dipstick test.
Dipstick and treatment plus laboratory test	The laboratory test is used to supplement the dipstick test. Whilst all patients with a positive dipstick result provide an urine sample for further testing, during the initial consultation, the results only affect those patients with persistent symptoms. For these patients antibiotic sensitivity will be available at the second GP visit for those who tested positive, which will enable the GP to prescribe a course of specific antibiotics. This gives the patients with UTI who test positive a second chance for antibiotics to clear the infection. Antibiotics will not be altered on the basis of the sensitivity results until the second consultation.
Laboratory test and wait for preliminary results	All patients at the initial consultation provide a urine sample and treatment is determined by the initial result of this test. Hence treatment is delayed until the initial positive/negative result is available.
Laboratory test and wait for sensitivities	All patients at the initial consultation provide a urine sample and treatment is determined by the sensitivity result of this test. Hence treatment is delayed until the results of the sensitivity analysis are available. As a result, specific antibiotics are given to every confirmed case of UTI as a first treatment, leaving no secondary course of treatment for those with persistent symptoms.

overnight urine culture. In consultation with practitioners, seven simple management strategies were generated from these two main approaches to the primary management of UTI. These seven strategies form the basis of the model (detailed in Table 1). A simplified version of the decision tree is illustrated in Figure 1. The assumptions that underlie the structure of the model are detailed within Appendix 1.

3.1.2. Data

The readily available published literature[16,20-22], including previous modelling studies [23,24], were reviewed to provide parameter estimates with which to populate the model. However, generally there was a lack of available published information, necessitating the use of expert opinion to estimate some parameter values.

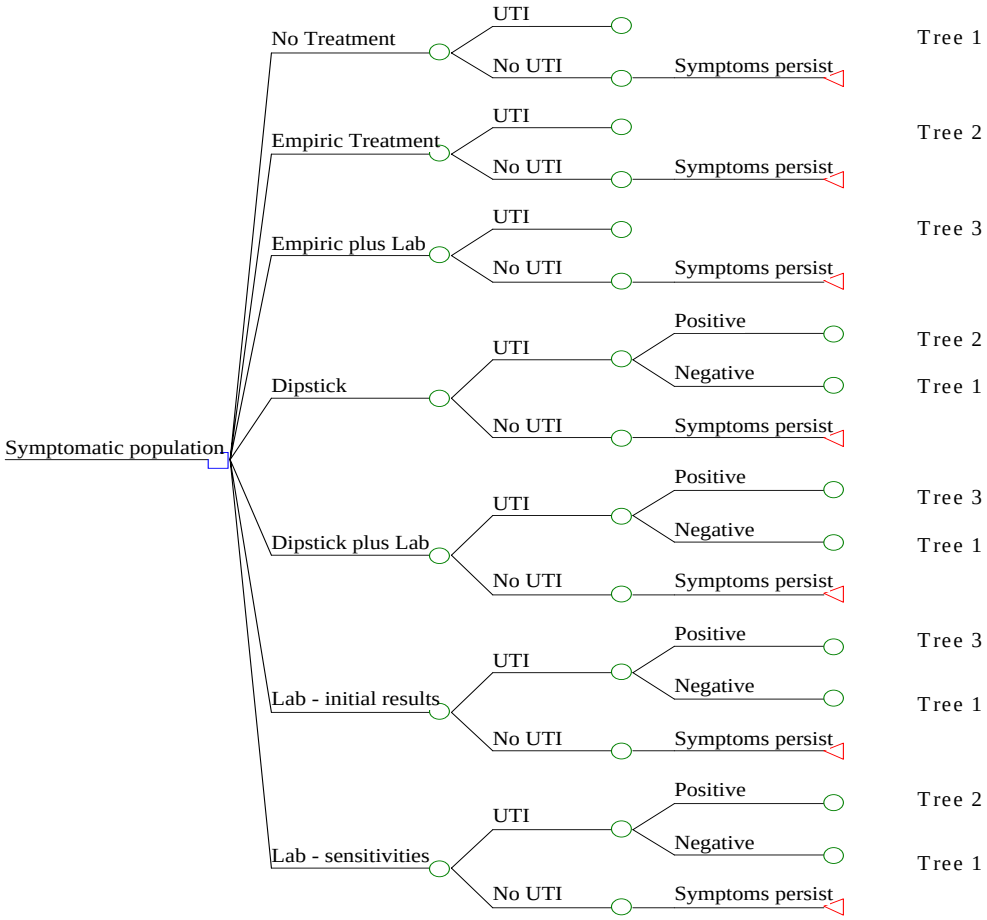
Table 2 details the base case values, range and source of information for each of the parameters used within the model.

3.1.3. Methods

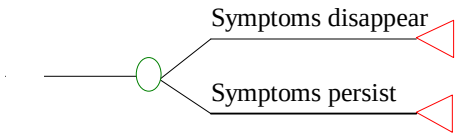
Costs

The model concentrates upon the differences in variable costs between strategies, because each option involves an identical environmental setting. The resources involved with each strategy, in terms of test usage, drugs prescribed and the number of GP visits, are recorded for each stage of the model for both the UTI and non-UTI branches. The management strategies are then costed by applying unit costs (Table 2) to the expected resource volumes associated with each strategy.

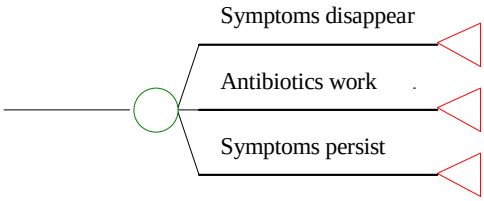
Figure 1: The patient management decision



Tree 1



Tree 2



Tree 3

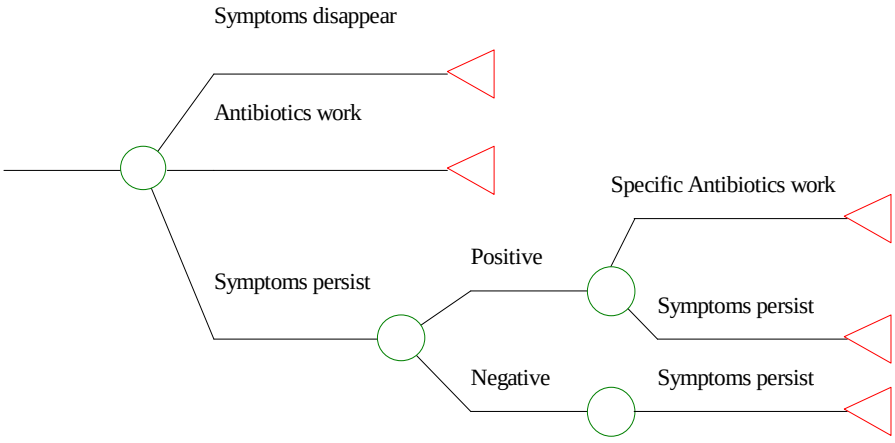


Table 2: Parameters of the Model

	Base value	Source	Range
Pathway Probabilities			
Prevalence of symptoms in target group	5%	Brumfit et al, 1987 [20]	5% - 20%
Probability of UTI given symptoms	50%	Madden et al, 1996 [16]	43% - 90%
Sensitivity of Dipstick	89%	Expert opinion	88% - 99.5%
Specificity of Dipstick	68%	Expert opinion	53.3% - 82.5%
Sensitivity of Lab culture	100%	Expert opinion	90% - 100%
Specificity of Lab culture	100%	Pfaller et al, 1987 [21]	90% - 100%
Probability symptoms resolve naturally given UTI	50%	Brumfitt et al,1987 [20]	20% - 65%
Probability antibiotics resolve symptoms given UTI	90%	Brumfitt et al,1987 [20]	81% - 95%
Probability specific antibiotics resolve symptoms given UTI	90%	Madden et al, 1996 [16]	81% - 95%
Probability of side effects due to antibiotic treatment	10%	Norrby, 1990 [22]	5% - 30%
Resource cost			
Dipstick	£ 0.20	Madden et al, 1996 [16]	£ 0.05 - £ 0.50
Antibiotics - 3 day course, general	£ 0.21	BNF, March 1998 [41]	£ 0.05 - £ 0.50
Specific antibiotics - 3 day course *	£ 2.82	BNF, March 1998 [41]	£ 1.00 - £ 4.50
Lab culture + sensitivity	£ 5.42	Expert opinion	£ 2.50 - £ 8.50
Lab culture	£ 2.60	Expert opinion	£ 1.00 - £ 4.00
GP visit	£ 9.00	Unit costs of Health and Social Care, 1997 [42]	£ 4.00 - £13.00
Procedure/Event times			
Symptom days for non-responsive UTI	7 days	Expert opinion	5 - 15 days
Period before antibiotics resolve symptoms	2 days	Brumfitt et al, 1987 [20]	1 - 3 days
Period before infection resolves naturally	3 days	Brumfitt et al, 1987 [20]	1 - 4 days
Period before basic laboratory results known	2 days	Expert opinion	1 - 3 days
Period before laboratory sensitivity results known	3 days	Expert opinion	1 - 4 days
Duration of side effects	2 days	Carlson et al, 1985 [23]	2 - 4 days
Utilities			
Persistent Dysuria	0.2894	Barry et al, 1997 [24]	0.01 - 0.3
Other side effects	0.2894	Barry et al, 1997 [24]	0.01 - 0.3

* The unit cost of specific antibiotics is an average of the costs of the individual drugs which could be prescribed

Costs are estimated from an NHS perspective. The costs of over-the-counter treatments for side effects are excluded from the analysis as we assume they are purchased by patients privately.

Health outcomes

The expected number of symptom days suffered by patients is estimated for each strategy with reference to the average times taken for symptoms to resolve naturally or through antibiotics; the average length of time for laboratory results to be available and the additional days of symptoms caused by side effects to antibiotics (Table 2). QALYs associated with an episode of UTI are calculated for each management strategy by applying utility weights (Table 2) to symptom days (either due to the original cause or due to side effects of treatment)[24].

Cost-effectiveness

The expected costs and health outcomes per episode of UTI associated with each patient management strategy are used to determine the net benefits in monetary terms for each strategy for a variety of values of λ.

3.1.4. Results

Base case scenario

The results of the basic deterministic model suggest that the appropriate *a priori* act given values of λ lower than £271,000 per QALY, involves empiric treatment of symptoms. Above this valuation of a unit of health gain (λ) the basic deterministic model suggests that the empiric plus laboratory culture strategy is the appropriate decision. The deterministic model suggests that the use of diagnostic tests (dipstick or laboratory) as a primary element of the management strategy generates fewer net benefits than empiric treatment, regardless of λ.

Table 3: Results of sensitivity analysis *

Parameter	Range	Empiric + Lab £'000		Dipstick £'000		Dipstick + Lab £'000	
Parameter value (either lowest or highest in range)		**Low**	**High**	**Low**	**High**	**Low**	**High**
Pathway probabilities							
Probability of UTI given symptoms	43% - 90%	£ 363	£ 109	-	-	-	-
Sensitivity of Dipstick	88% - 99.5%	£ 271	-	-	£ 2	-	£ 147
Specificity of Dipstick	53.3% - 82.5%	£ 271	£ 271	-	-	-	-
Sensitivity of Lab culture	90% - 100%	£ 297	£ 271	-	-	-	-
Specificity of Lab culture	90% - 100%	£ 374	£ 271	-	-	-	-
Probability symptoms resolve naturally given UTI	20% - 65%	£ 171	£ 386	-	-	-	-
Probability antibiotics resolve symptoms given UTI	81% - 95%	£ 78	£ 540	-	-	£ 365	-
Probability specific antibiotics resolve symptoms given UTI	81% - 95%	£ 306	£ 255	-	-	-	-
Probability of side effects due to antibiotic treatment	5% - 30%	£ 255	-	-	£ 5	-	£ 206
Unit costs							
Dipstick	£ 0.05 - £ 0.50	£ 271	£ 271	-	-	-	-
Antibiotics - 3 day course, general	£ 0.05 - £ 0.50	£ 271	£ 271	-	-	-	-
Specific antibiotics - 3 day course	£ 1.00 - £ 4.50	£ 270	£ 273	-	-	-	-
Lab culture + sensitivity	£ 2.50 - £ 8.50	£ 225	£ 320	-	-	-	-
Lab culture	£ 1.00 - £ 4.00	£ 246	£ 293	-	-	-	-
GP visit	£ 4.00 - £ 13.00	£ 192	£ 335	-	-	-	-
Event times							
Symptom days for non-responsive UTI	5 - 15 days	-	£ 49	-	-	-	-
Period before antibiotics resolve symptoms	1 - 3 days	£ 174	£ 620	-	-	-	-
Period before infection resolves naturally	1 - 4 days	£ 271	£ 620	-	-	-	-
Period before basic laboratory results known	1 - 3 days	£ 271	£ 271	-	-	-	-
Period before laboratory sensitivity results known	1 - 4 days	£ 271	£ 620	-	-	-	-
Duration of side effects	2 - 4 days	£ 271	-	-	£ 57	-	£ 177

* The numbers contained within the table give the level of λ at which each strategy becomes optimal assuming the lowest and highest value in the range for each parameter individually. For example: if the probability of side effects takes the highest value in the range then at a λ of £5,001 the dipstick strategy generates the maximum expected net benefits and is optimal.

Sensitivity analysis

An initial estimate of the impact of parameter uncertainty upon the results of the model is attained through one-way sensitivity analysis over a plausible range of values (Table 2).

The results of this analysis suggest that the 'empiric' strategy is always the lowest cost strategy and that the 'no treatment' strategy and the strategies employing laboratory tests as the initial element of patient management constantly generate fewer net benefits than the empiric strategy.[5] The results, in terms of the value of a unit of health gain (λ) at which each of the remaining alternative strategies becomes optimal, are provided in Table 3 for the lowest and highest values in the range for each parameter. These results suggest that both the simple dipstick strategy and that complemented by the laboratory culture are sensitive to variation in the parameter values for the sensitivity of the dipstick, and both the duration and probability of side effects due to antibiotics.

The deterministic model suggests that the cost-effectiveness of the 'empiric' strategy is fairly robust to parameter uncertainty although further research concerning diagnosis and management of UTI may be required. Basing further research upon the results of this sensitivity analysis would lead to a focus upon the sensitivity of the dipstick; the probability and duration of side effects; the probability of antibiotic resolution; and the event times, in particular the average length of an episode of unresolved UTI. In addition, the results suggest that the laboratory strategies can be excluded from any further research protocols as irrelevant alternatives, on the basis of that they are dominated throughout the deterministic analysis.

[5] Hence the empiric; no treatment and both laboratory strategies are excluded from Table 3.

3.2 A probabilistic model of management of UTI

3.2.1 Introduction

The techniques of deterministic sensitivity analysis are not well suited to handling interactions between parameters[6] [25] and, therefore, can only give an indication of the impact of uncertainty upon the decision.

In order to fully characterise uncertainty surrounding a decision and to value research aimed at reducing this uncertainty a more formal examination of the uncertainty is required. This involves the identification, characterisation and incorporation of existing available (prior) information within the model (Section 3.2.2). Monte Carlo simulation [26] is then used to generate a distribution of net benefits for each strategy within the model. The expected values of these distributions are calculated and compared to identify the *a priori* act. The extent of the spread in each distribution illustrates the extent of the uncertainty concerning the net benefits that accrue from that strategy. A quantitative measure of the uncertainty surrounding each strategy is provided by the associated error probability.[7]

The uncertainty associated with specific parameters or groups of parameters within the model can be ascertained through the use of conditional probabilistic sensitivity analysis [26] which involves repeating the Monte Carlo simulation with distributions attached only to the variables of interest.

[6] Joint interactions are ignored within one-way sensitivity analysis, over-estimated by analysis of extremes and difficult to interpret through multi-way sensitivity analysis [25].

[7] The error probability is the probability that the strategy does not have the maximum expected net benefit. Where there are more than 2 alternative technologies under consideration the error probability associated with each strategy is determined as the proportion of iterations within the simulation where that strategy is not optimal. See Claxton [3] for details on applying the approach when there are only 2 technologies under consideration.

3.2.2 Characterising existing information for the UTI model

The existing information and hence uncertainty surrounding individual parameters is embodied within the model through the specification of (prior) probability distributions for each model input. These distributions represent both the range of values that each parameter can take and the likelihood that the parameter assumes any specific value.

Probability distributions characterising existing information were assigned to every parameter within the UTI model, details are given in Table 4. The unit costs, utility and event time parameters were characterised as lognormal distributions[8] with the mean given by the base case value and the standard deviation derived from the assumption that the range represented a 95% confidence interval. The probability parameters were characterised as triangular distributions with the mode given by the base-case value and the extremes of the distribution given by the range.[9]

Table 4: Prior Information

Parameter	Distribution	Specification
Probabilities	Triangular	Base case value = mode Range = extremes of distribution
Resource costs	Lognormal	Base case value = mean Range = 95% CI to give sd
Event times	Lognormal	Base case value = mean Range = 95% CI to give sd
Utilities	Lognormal	Base case value = mean Range = 95% CI to give sd

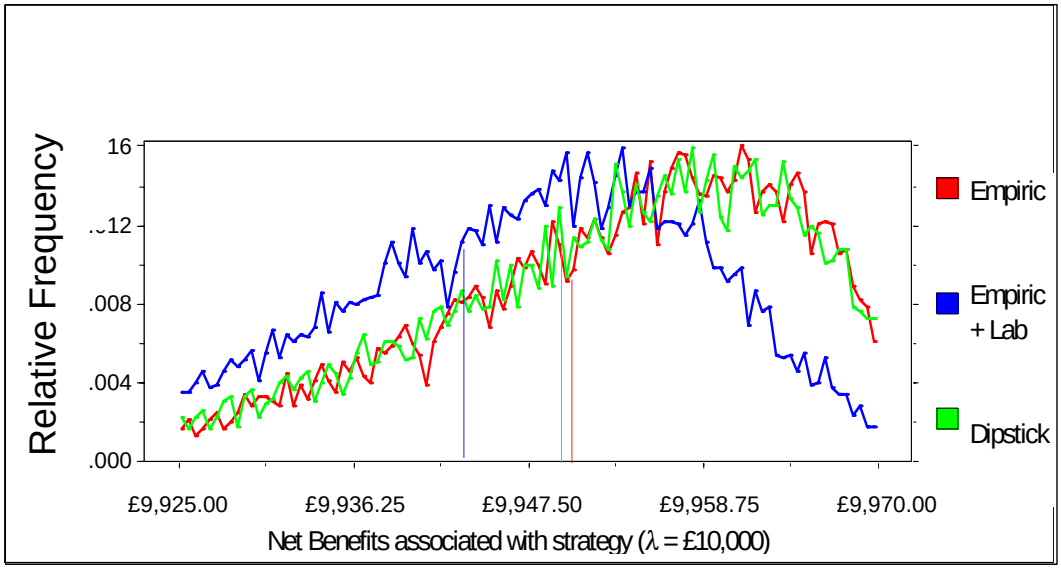
[8] Lognormal distributions seemed appropriate for these parameters because they are positively skewed distributions which are bounded by zero [26].
[9] The distributions chosen for the probabilistic model were deliberately simplistic due to the lack of available published information and a desire not to overcomplicate the analysis.

3.2.3 Results of the probabilistic analysis

Net benefits

Monte Carlo simulation employing 10,000 iterations (using the Excel [27] add-on Crystal Ball [28]) was used to propagate these distributions through the model and generate a distribution of net benefits for each of the seven patient management strategies for a range of values of λ. For each value of λ the means of the distributions are compared to identify the *a priori* act. Figure 2 illustrates the distribution of net benefits (in monetary terms) for the empiric; the empiric plus laboratory; and the dipstick strategies for a λ value of £10,000 per QALY. At this value of λ the Empiric strategy is identified as the *a priori* act. The results of the probabilistic model indicate that 'empiric' treatment is the appropriate *a priori* act for values of λ up to £300,000 per QALY. Beyond this level of λ the appropriate *a priori* act is the empiric plus laboratory strategy.

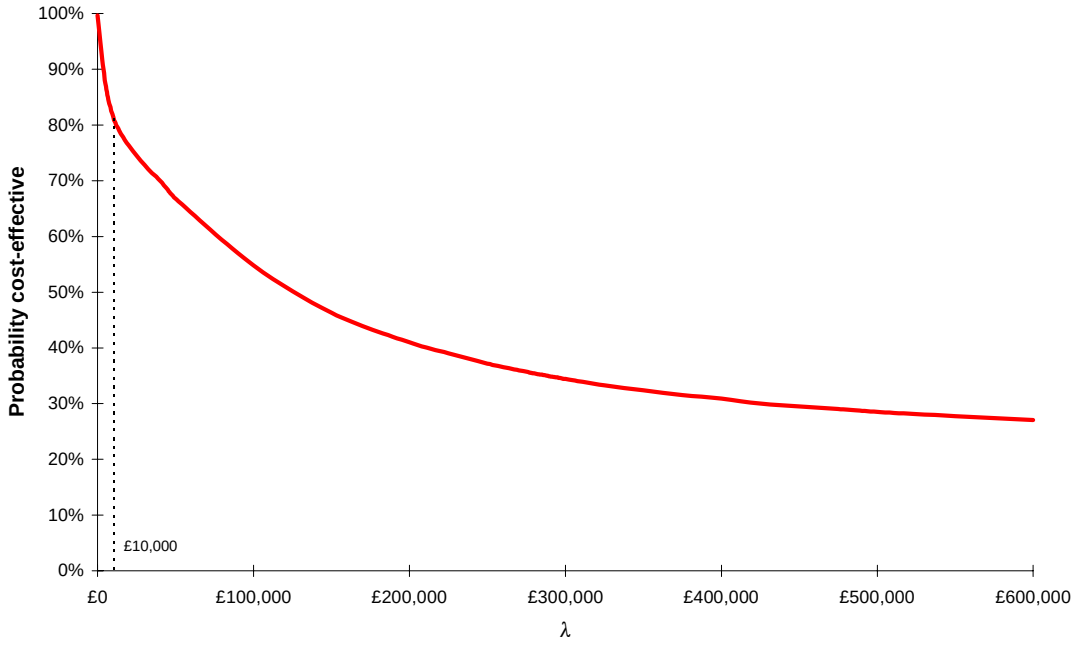
Figure 2: Net benefit distributions λ = £ 10,000 per QALY



The vertical lines illustrate the mean of each distribution:
Mean (Empiric strategy) = £ 9,952
Mean (Empiric + Lab strategy) = £ 9,944
Mean (Dipstick) = £ 9,951

The error probability associated with empiric treatment (the optimal *a priori* act) at a λ value of £10,000 is 0.186, whilst the error probability for the remaining strategies varies between 0.18 (dipstick strategy) and 1 (dipstick plus lab; basic lab; and lab and wait strategies). Failure to implement 'empiric' treatment, in favour of the no treatment strategy, on the grounds that it is not 'statistically significant' (the error probability is greater than the conventional benchmarks of 0.05 or 0.025) imposes costs upon society, in terms of the net benefits foregone, of £14 per episode, or £ 93 million for the population of the UK.[10]

Figure 3: Cost-effectiveness acceptability curve for Empiric strategy



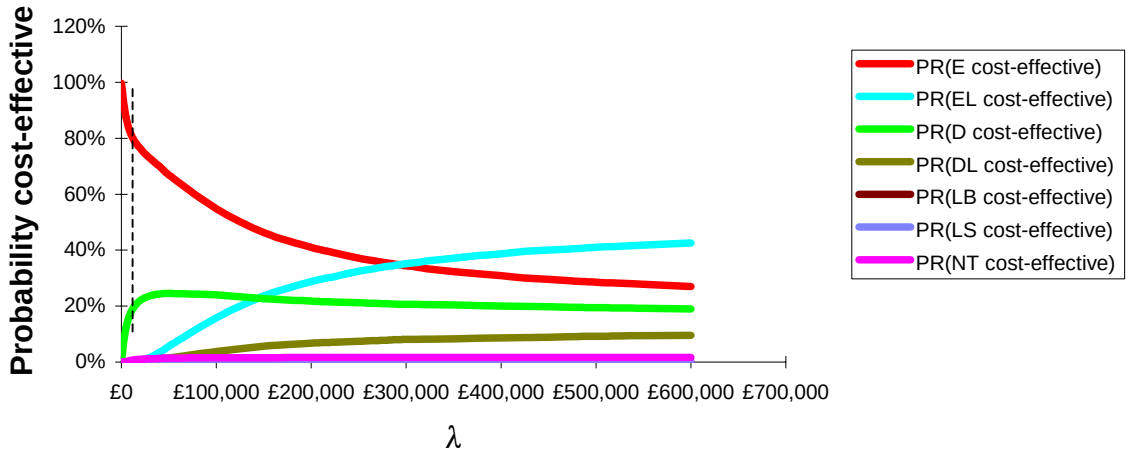
Cost-effectiveness acceptability curves

Figure 3 illustrates the uncertainty associated with the decision to adopt the empiric strategy for a range of λ values, presented in the form of a cost-effectiveness acceptability curve (CEAC). This curve shows the probability that the empiric strategy is the optimal choice for service

[10] An estimate of prevalence is obtained from published literature [20], estimates of the female population are obtained from national statistics [44], the life of the information is assumed to be 5 years and a discount rate of 6% is

provision (1 - error probability) over a range of values of λ [29-31]. A CEAC can be generated for each strategy through calculation of the error probability associated with the strategy for a range of values of λ. Figure 4 illustrates the CEAC associated with each strategy within the UTI decision problem. Each curve has been graphed simultaneously to produce a family of cost-effectiveness acceptability curves.[11]

Figure 4: A family of Cost-effectiveness Acceptability Curves



*These lie along the x axis as they have a probability of being cost-effective of zero

Decision rules

Since the underlying objective of maximising health outcomes from limited resources implies a decision rule for identifying the *a priori* act upon the basis of maximum expected net benefit, rather than on the basis of maximum likelihood of being optimal,[12] the outer limit of the family of CEACs cannot be used to identify the optimal decision for every level of λ. Instead, a cost-effectiveness acceptability frontier (CEAF) illustrating the uncertainty associated with the *a priori*

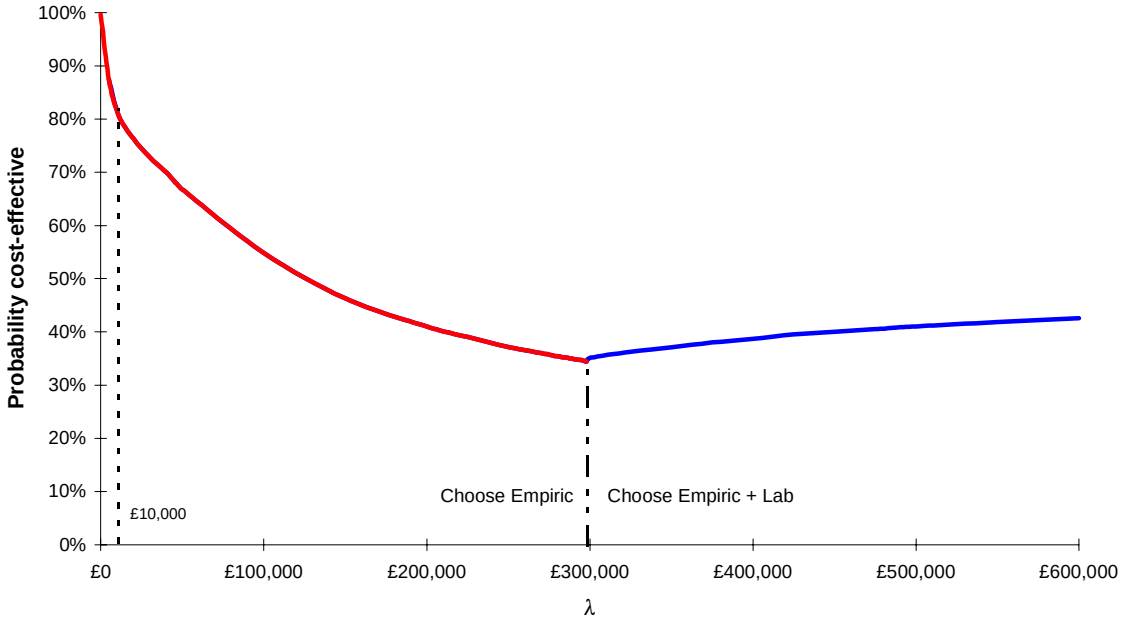
used.

[11] Note that the vertical summation of the curves for all strategies is 100% for every value of λ.

[12] Note that these two decision rules will be equivalent only when the distribution of net benefits is symmetric *(personal communication with A. Stinnett)*.

act over a range of values of λ can be generated by graphing the error probability associated with the optimal strategy at each level of λ (Figure 5). This frontier does not follow the outer limit of the family of CEAC in this example due to skewness in the distributions of net benefit (see Appendix 2 for a simple example to explain this phenomenon).

Figure 5: Cost-effectiveness acceptability frontier



3.3 The value of information

3.3.1 Introduction

Information from additional research is valuable to the decision-maker because it reduces the uncertainty surrounding the decision concerning efficient service provision. Bayesian VOI analysis provides a method to measure the expected costs of decision uncertainty and, therefore value research aimed at reducing this uncertainty. The analysis, which follows from probabilistic sensitivity analysis, involves formal consideration and valuation of the

consequences associated with the uncertainty to provide an explicit measure of the cost associated with the uncertainty surrounding a decision [32-34]. In HTA, the consequences associated with uncertainty are the net benefits forgone when the service provision decision made upon the basis of existing information is incorrect. Expressing net benefits in monetary terms (μ) gives an explicit monetary valuation of the costs of uncertainty that can be compared to the cost of collecting further information to determine the worth of research [9]. As the monetary valuation of health outcomes may not be known with certainty, the analysis can be presented to the decision-maker for a range of values of λ. When the valuation of health outcome (λ) employed within the analysis is equivalent to that employed in service provision decisions, the valuation of information approach ensures consistency between research prioritisation and service provision [9].

3.3.2. Methods

The expected value of perfect information (EVPI) is equivalent to the expected costs of uncertainty surrounding the service provision decision made upon the basis of existing information, because perfect information eliminates all uncertainty and associated costs [8,9,32-34]. Hence, establishing the expected costs of uncertainty surrounding a decision provides a measure of the maximum possible payoff from research. When λ represents a societal willingness to pay for health outcome, the EVPI represents the amount society is willing-to-pay to eliminate uncertainty associated with the decision, providing an explicit upper limit on the VOI obtained from further data acquisition. When compared with the cost of research, the EVPI provides an initial hurdle for determining whether further research is potentially cost-effective [9].

Several authors [8,9,32-34] detail a parametric approach to establishing the expected value of perfect information. Within this paper a non-parametric approach to determining EVPI employing Monte Carlo simulation is employed [10,35-37]:

$EVPI_{episode}$ = $E[NB_{t**}] - E[NB_{t*}]$ (equation 2a)

= improvement in expected net benefit associated with perfect information

where: NB_t = net benefit associated with technology t

t* = the technology chosen by the decision-maker given no additional information (*a priori* act)

t** = the technology chosen by the decision-maker with perfect information (posterior act)

Each iteration in the simulation represents a realisation of current uncertainty and a position of perfect information, for which the posterior act can be determined. The improvement in net benefits associated with this realisation can then be calculated. Taking the expectation of the improvement values over all iterations gives the expected value of perfect information for an individual episode of UTI [36] (see Appendix 3 for a simple example of the calculation of EVPI)[37].

The overall value of perfect information for a population is then determined by applying this opportunity loss to the overall number of episodes that will be affected by the information [3,8,9].

$$EVPI_{population} = EVPI_{episode} * \Sigma^{P}_{p=1} [I_p / (1+r)^p] \quad \text{(equation 2b)}$$

where: I = incidence in period

p = period

P = total number of periods for which information from research would inform the decision

r = discount rate

In addition to determining the EVPI for the entire decision, the techniques can be applied to particular elements of the decision to direct and focus research in the same way as suggested for the methods employing basic uncertainty measures [13,14]. Calculating the EVPI for particular elements of the model involves estimating the EVPI for the full model and the EVPI for the remaining elements of the model, excluding those of interest (calculated as below). The EVPI for the elements of interest is then isolated as the difference between these two measures of EVPI.[13]

To determine the EVPI for a particular strategy involves calculating the EVPI for the model when this strategy is excluded as an alternative. This in turn involves recalculating the improvement values associated with perfect information such that the strategy of interest is excluded as a potential posterior act (equation 2c):[14]

$$EVPI_{episode\backslash strategy\ 1} = E [NB_{t^{**}\backslash t1} - NB_{t^{*}\backslash t1}] \quad \text{(equation 2c)}$$

where: $NB_{t^{**}\backslash t1}$ = net benefit associated with technology t, excluding strategy 1

[13] The EVPI for elements of interest is estimated in this manner rather than by excluding those elements which are not of interest because this would restrict interactions between those elements.

[14] It is obvious that an EVPI can not be calculated for a strategy over the range of values of λ for which it is the *a priori* choice.

To determine the EVPI for a particular parameter or group of parameters the EVPI excluding this (these) parameter(s) is estimated. This is achieved by repeating the Monte Carlo simulation assuming no uncertainty surrounding the parameter(s) of interest,[15] a procedure equivalent to conditional probabilistic sensitivity analysis [26,38].

Table 5: Expected value of perfect information for UK population +

	£ 5,000	£ 10,000	£ 15,000
Full model	£312,378	£914,626	£1,609,410
Parameter groups			
Antibiotic	£18,468	£57,786	£123,900
Cost	£31,293	£41,134	£44,169
Dipstick Accuracy	£137,319	£327,504	£530,302
Lab Accuracy	£31,842	£59,464	£79,893
Lab Time	£31,842	£59,464	£79,893
Infection limit	£14,040	£76,279	£180,320
Natural resolution	£4,780	£12,347	£31,684
Side effects	£250,513	£686,604	£1,156,102
Utility	£250,513	£686,604	£1,156,102
Strategies			
No Treatment strategy	£9,704	£58,344	£127,485
Empiric + Lab strategy	£0	£2,237	£21,271
Dipstick strategy	£265,907	£716,614	£1,181,945
Dipstick + Lab strategy	£0	£0	£1,568
Lab + wait basic strategy	£0	£0	£0
Lab + wait sensitivities strategy	£0	£0	£0

These figures are based on the current UK population and gender split. The useful lifetime of the information is taken as 5 years. The future benefits from the information are discounted at 6% per annum.

3.3.3. Results

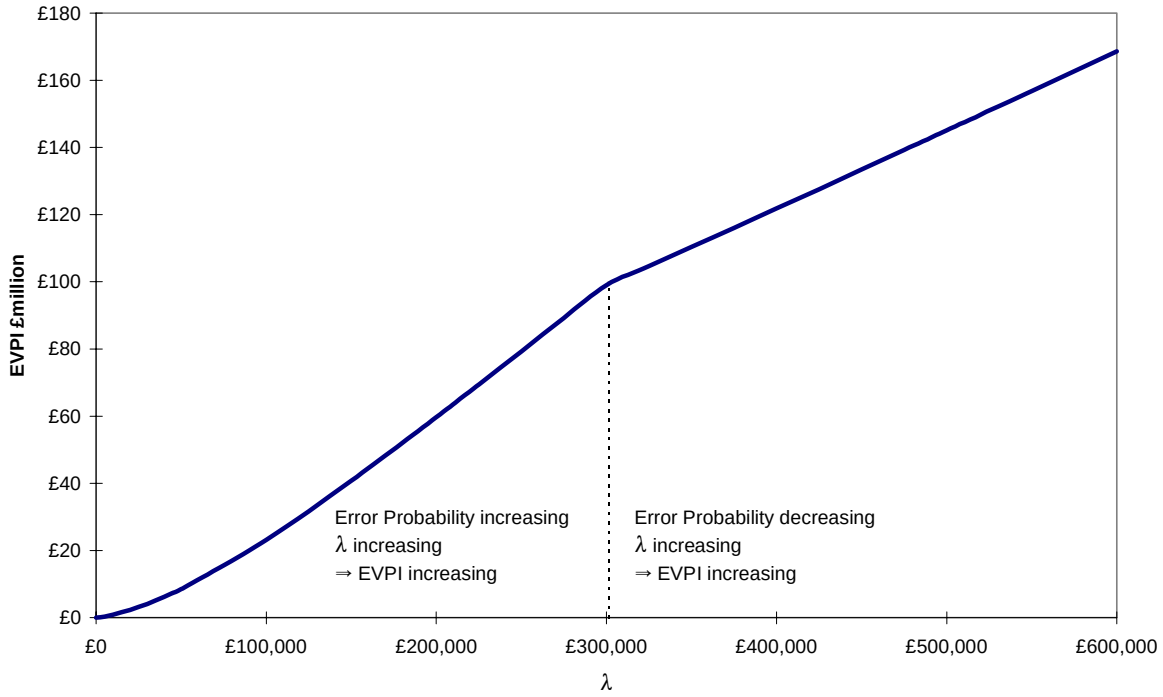
The results of the VOI analysis suggest that there is considerable value associated with further data acquisition concerning model parameters as a whole (see Table 5). At a λ value of £10,000 per QALY the EVPI is calculated to be £0.14 per episode of UTI, and £ 900,000 for the population as a whole.[16] Figure 6 illustrates the population EVPI for the full model for a range of

[15] The prior distributions for the parameter(s) of interest are collapsed to their expected values which is reasonable where the relationship is not markedly non-linear [3].

[16] An estimate of prevalence is obtained from published literature [20], estimates of the female population are obtained from national statistics [44], the life of the information is assumed to be 5 years and a discount rate of 6% is

values of λ. These results suggest that further data acquisition may be potentially cost-effective.

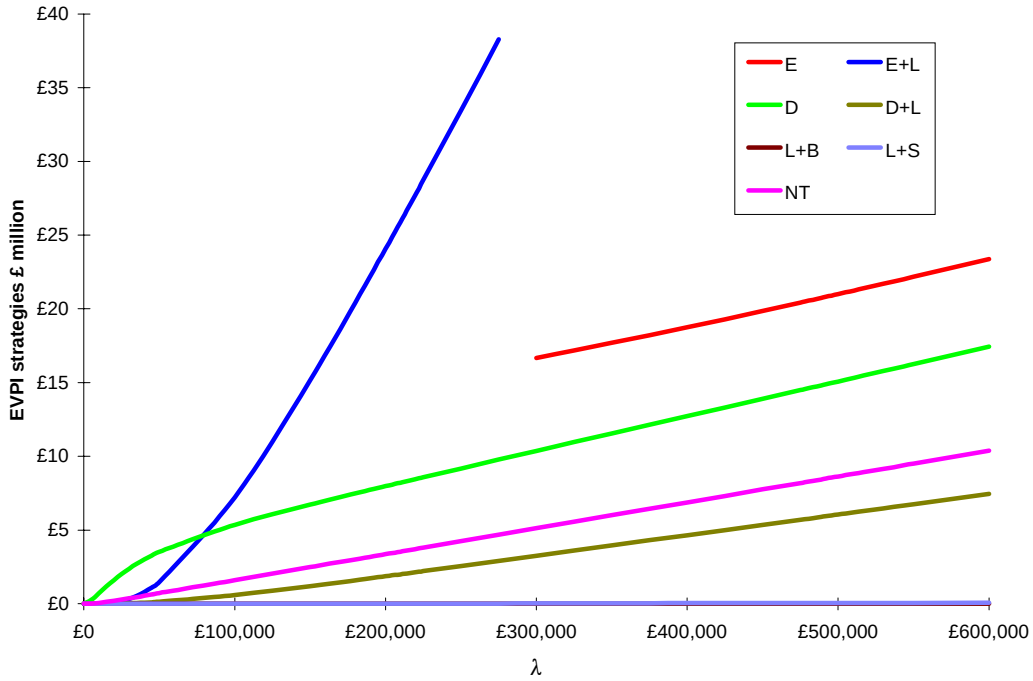
Figure 6: EVPI - full model



The EVPI for the Dipstick strategy is £0.11 per episode of UTI at a λ value of £10,000 per QALY (£700,000 for the population). At a λ value of £50,000 per QALY , this increases to £0.53 per episode of UTI (£3.5 million for the population). For the empiric plus laboratory strategy, the EVPI is £0.0003 per episode of UTI at a λ value of £10,000 per QALY (£2,000 for the population), and £0.22 per episode of UTI at a λ value of £50,000 per QALY (£1.5 million for the population). Figure 7 illustrates the EVPI associated with each strategy over a range of values of λ.

Figure 7: EVPI for strategies

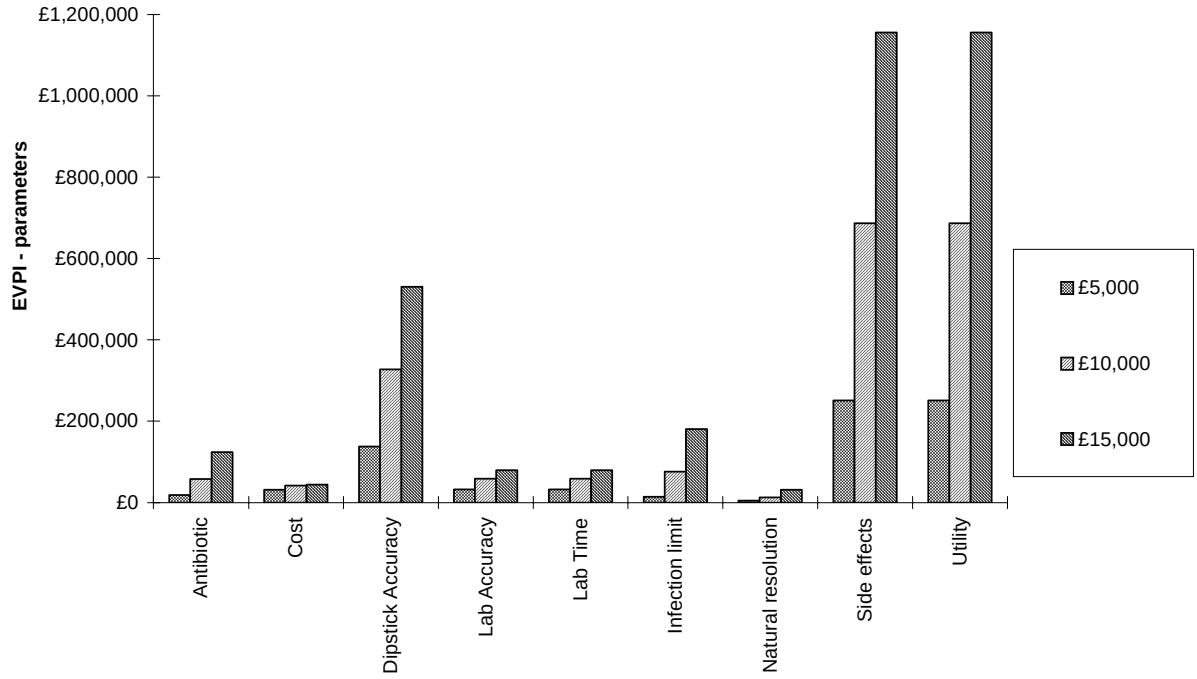
used.



*These lie along the x axis as they have EVPI of zero.
Note: there is no EVPI associated with a strategy over the range of λ values for which the strategy is identified as the *a priori* act.

The analysis for groups of parameters illustrates that, at a λ value of £10,000 per QALY, the EVPI for side effects is £0.10 per episode of UTI as is the EVPI for utilities (£700,000 for the population), whilst that for unit costs is £0.006 per episode (£41,000 for the population) and for the probability of natural resolution the EVPI is only £0.002 per episode (£12,000 for the population). Figure 8 illustrates the EVPI for various groups of parameters associated with λ values of £5k; £10k and £15k per QALY.

Figure 8: EVPI for parameter groups



4. DISCUSSION

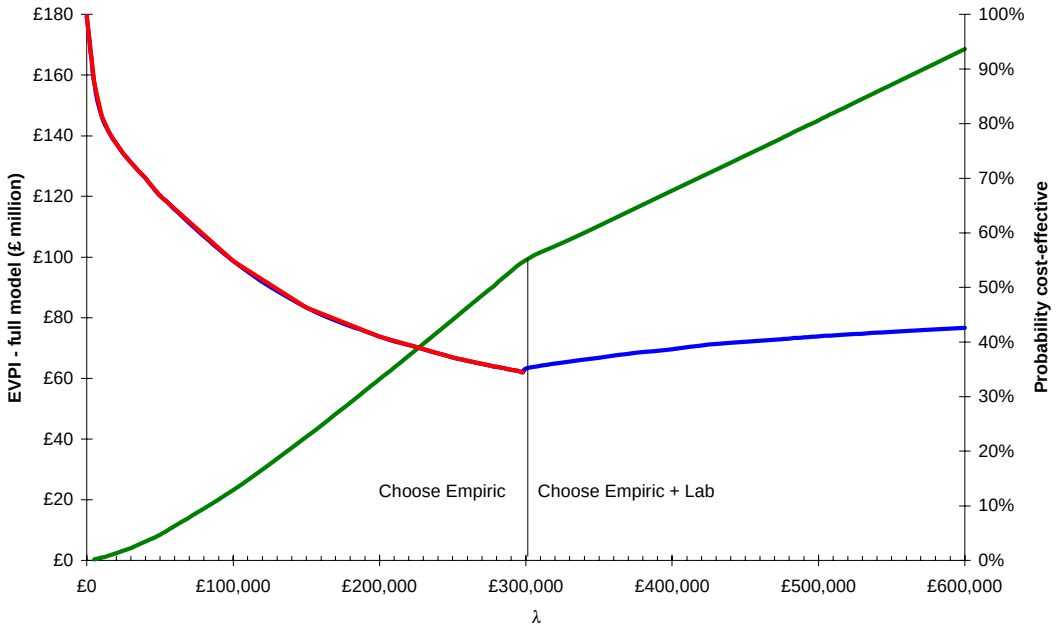
4.1 Unifying decisions about service provision and about research

It is clear that resources expended for providing health services cannot be used for research to generate additional information, and *vice versa*. It is essential, therefore, that a framework is developed and adopted in which the economic appraisal of service provision is coupled with assessment of the cost-effectiveness of future research. This paper argues that iterative decision modelling provides such a framework. The value of this framework has been illustrated using a contemporary decision problem – the management of non-pregnant women presenting to general practice with the symptoms of uncomplicated UTI.

As regards the optimal treatment *based on current information,* the results of the stochastic model identify the 'empiric' strategy as the optimal decision for valuation of health benefits (λ) below £ 300,000 per QALY, and the empiric plus laboratory strategy for values of λ above £

300,000 per QALY.[17]

Figure 9: EVPI vs. Cost-effectiveness Acceptability Frontier



The secondary decision problem is whether research to provide further information to inform the service provision decision in the future is worthwhile. The stochastic model measures the uncertainty associated with choosing the 'empiric' strategy as varying between 1% - 66% as the valuation of health benefit increases to £ 300,000. The uncertainty associated with the empiric plus laboratory strategy falls from 65% as the value of health benefit increases from £ 300,000 (Figure 5). The VOI analysis generates explicit valuations that can be compared to the cost of further investigation to determine whether additional research is potentially worthwhile. Figure 9 illustrates the relationship between the level of uncertainty (as represented by the cost-effectiveness frontier) and the expected value of perfect information.

[17] The deterministic model suggests that the empiric strategy is optimal up to a λ value of £271,256. The difference is due to some of the parameters having non-symmetric probability distributions so that the mean in the stochastic model is not equal to the base case value within the deterministic model.

The decision over which strategies/technologies to include within proposals for further research can be guided by the expected value of perfect information about individual strategies. The EVPI for each strategy is linked with the probability that the strategy is optimal and therefore is related to the cost-effectiveness acceptability curve (Figure 4). The fact that the dipstick strategy is associated with the second highest probability of being optimal for a considerable range of values of λ indicates that there will be a large EVPI associated with this strategy. This illustrates that whilst the dipstick strategy is never optimal within the analysis it may be worth collecting further information about the strategy. Therefore it does not necessarily follow that there will be no value associated with acquiring more information about a dominated strategy. Indeed this example demonstrates that the concept of dominance in a deterministic analysis can not be used to exclude an alternative from further research. In fact, it is possible that the value of information surrounding a non dominated but non optimal strategy will be lower than a dominated alternative. In these circumstances using the concept of dominance to identify 'relevant' alternatives for further evaluation will be very misleading [39].

Research can be focused upon the particular areas of the decision for which a reduction in uncertainty via further information is of most value by calculating the expected value of perfect information for individual parameters and groups of parameters. The EVPI analysis for particular parameters suggests that further information concerning utilities and side effects provide most value, whilst information about prevalence of UTI given symptoms, probability of natural resolution of symptoms and unit costs provide the least value.

It is of interest that the value of information associated with the accuracy of the laboratory test is higher than that for the unit costs. This result contradicts the one-way sensitivity analysis that found no impact for these parameters, due mainly to the domination of the strategies involving

laboratory tests. Hence a standard approach to handling uncertainty would have missed the importance of these parameters. This discrepancy within the results is due to the fact that one-way sensitivity analysis investigates the impact of parameter uncertainty on strategies individually, whilst the VOI analysis investigates the cost of uncertainty within the model. The laboratory test is included within four of the seven patient management strategies and hence uncertainty surrounding the accuracy of this test will have a large associated cost.

The value of perfect information provides a necessary, but not sufficient, condition for the worth of further information. To determine the value of specific research, it is necessary to value the reduction in uncertainty that is actually achievable from the research, in terms of the reduction in the expected costs of uncertainty. When measured in monetary terms this gives society's willingness-to-pay for the specific research proposal, which is considered worthwhile where the valuation exceeds the cost. The techniques can also be employed to design technically efficient research proposals in terms of optimal sample size and allocation [3,8] thus improving the efficiency in HTA.

4.2 Using iterative decision analysis in research commissioning

Where early stage modelling is not undertaken, implicit judgements must be made about which parameters are important for the purposes of HTA, and the extent of evidence required. As a result, proposals for further data acquisition may either lack focus, leading to an unnecessarily large information requirement, or fail to provide information about key parameters for estimation. This can result in inefficient and potentially uninformative programmes of data acquisition.

As an illustration, the results of the UTI model presented here can be used to assess whether the call for primary research in the area of UTI diagnosis from the NHS HTA programme was justified. It is not clear whether a formal systematic review was undertaken prior to the call for

primary research - apparently none was formally commissioned. The early stage model, presented here, used available clinical evidence and clinical opinion to estimate parameters. A systematic review of published literature may reduce the uncertainty in the model in general, and of specific parameters, markedly. If such a review were commissioned, this model would provide an indication of the parameters on which it should focus, with the parameters relating to utilities and side effects most highly valued. Indeed, the model could provide a valuable insight into the most efficient search strategy for each parameter. An economic rationale can only be established for devoting additional resources to searching less accessible literature (e.g. grey and foreign language literature) with reference to the VOI associated with a given parameter and the probability that a study is going to be identified which significantly alters parameter estimates based on prior information.

If we assume that a systematic review had been undertaken and no additional information identified, further primary research would seem justified on the basis of the model's results. Although the NHS HTA call does not presume that a randomised trial would be the preferred design, this may be the preferred form of data acquisition for some parameters, in particular the effectiveness of antibiotics. The EVPI about antibiotics is £ 58,000, given a λ value of £10,000 per QALY, and since a trial is likely to cost in excess of this it is unlikely that it will be worthwhile. Although we have not presented data on the optimal sample size of these trials, the model and VOI analysis could have been employed for that purpose [8 ,9 ,40], providing crucial information to potential trialists.

However, the parameters for which the value of additional information is greatest (utilities and side effects) would not require measurement in expensive trials, given that the problem of selection bias is not expected to be significant in the estimation of these parameters. Split

sample designs would be appropriate to provide further data on dipstick and laboratory test accuracy and non-experimental designs would be appropriate for the probability of resolution of UTI without intervention. Given a limited budget for the NHS HTA programme, early stage modelling would have indicated that a trial was not the most urgent research design in this area and that further information on the most important parameters may have been generated more efficiently using non-experimental designs.

5. Conclusions

Information acquisition is not costless, and the allocation of funds to the enhancement of the decision makers' information set, in a budget-constrained health service, reduces the 'pot' of resources available for health service provision. Hence, it is necessary to ensure that the process of HTA is subject to the same evaluation of efficiency as is service provision. This paper argues that employing decision analytic models, early and on an iterative basis in HTA, to evaluate the efficiency of health care technologies, will assist in the management of health services R&D and help to ensure that both service provision and R&D provide good value for money. The approach has been illustrated using an application to the decision problem of the management of UTI, which shows that these methods are practical and generate valuable information that is unlikely otherwise to be available.

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Appendix 1: Simplifying assumptions used within the UTI model

- A proportion of the women who present with symptoms of UTI in general practice will have other disorders. A lack of quantitative information of other possible causes of symptoms in this group [1] led us to treat all non-UTI cases identically in the model.
- We make the assumption that those with non-UTI will not benefit from any of the strategies considered, and the only possible health outcome for these patients is that symptoms will persist, as illustrated in Figure 1. However, as these patients are not immediately identifiable the resources used in the management of their symptoms are included within the analysis of each strategy.
- Uncomplicated UTI tends to be a self-limiting condition, with 50% of cases resolving naturally after 3 days [20] and the remainder get better after a week on average (base case).
- Where no treatment is given to patients with UTI, either as a deliberate strategy or as the result of an incorrect test result, symptoms are assumed to either disappear after 3 days or to persist for 7 days (sub-tree 1).
- Where UTI is the cause of symptoms, antibiotics may resolve symptoms after 2 days from the start of the course [20], otherwise the patient experiences the same outcomes as apply where antibiotics are not used.
- It is assumed that patients given antibiotics fully comply with the course of treatment.
- When used, test results dictate the subsequent management of the patient. Antibiotics (and possibly a confirmatory laboratory culture) follow a positive result and no further treatment follows a negative one. When laboratory tests are undertaken an initial positive/negative result can confirm the presence/absence of UTI and further analysis of positive results provides details of bacterial sensitivities that can direct prescribing. Where available, this information is employed to manage patients whose symptoms persist (sub-tree 3).
- 10% of those receiving antibiotics are expected to experience side effects as a result [22], which prolong the period of symptoms by an extra 2 days [23].
- We assume that there is no worsening of symptoms or progression to pyelonephritis due to withholding or delaying antibiotic treatment within this patient population.
- Patients are assumed to return to the GP where symptoms persist, and the resources associated with these visits are included within the model. However, as the model deals with the primary management of uncomplicated UTI in women any subsequent

[1] The data that is available relates to a specific group of patients consulting via a university health centre and is not considered representative of the population under study here [45].

investigations in those whose symptoms persist following the completion of the management strategy are considered to be outside the scope of the model and are excluded from the analysis.

Appendix 2: Expected net benefits, error probabilities and skewed distributions

The following table gives 3 iterations from a Monte Carlo simulation involving 2 treatments (A and B).

Net benefits in monetary terms

	Treatment A	Treatment B
Iteration 1	15	9
Iteration 2	11	12
Iteration 3	13	15
Expected NB	**13**	**12**

Given the objective to maximise health subject to a budget constraint the *a priori* decision is identified as the treatment with the maximum expected net benefit. Therefore the *a priori* decision is to undertake Treatment A.

However, the distributions of net benefits are skewed. This results in a situation where the error probability associated with the choice of Treatment A is 66%.

This simple example illustrates that when there are skewed distributions of net benefit the treatment/strategy/technology with the maximum expected net benefit will not necessarily have the minimum error probability (maximum probability of being optimal). When using cost-effectiveness acceptability curves this translates to a position where the uppermost curve does not necessarily relate to the optimal strategy.

Appendix 3: Calculating the EVPI

The following table gives 3 iterations from a Monte Carlo simulation involving 2 treatments (A and B).

Net benefits in monetary terms

	Treatment A	Treatment B	Perfect Information
Iteration 1	15	9	15
Iteration 2	11	12	12
Iteration 3	13	15	15
Expected NB	**13**	**12**	**14**

Given current information the *a priori* decision is to choose Treatment A which generates an expected net benefit of 13.

However, given perfect information at each iteration Treatment A would only be chosen for the first iteration, with Treatment B chosen in each of the other two iterations. Hence, perfect information generates an expected net benefit of 14.

The difference between the expected net benefit given perfect information and that given current information represents the expected improvement associated with the perfect information. Hence it represents the value in decision payoff terms (net benefit) of the perfect information.

EVPI = E(NB given perfect information) - E(NB given current information)
= 14 - 13
= 1