

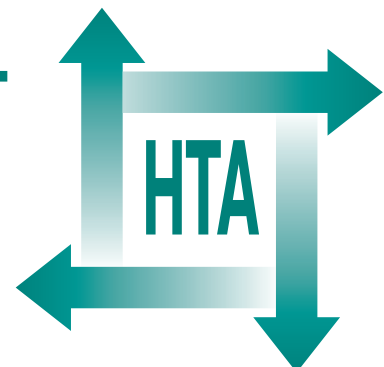
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme

K Claxton, L Ginnelly, M Sculpher, Z Philips
and S Palmer



July 2004

**Health Technology Assessment
NHS R&D HTA Programme**





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A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme

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Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

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Abstract

A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme

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Objectives: To demonstrate the benefits of using appropriate decision-analytic methods and value of information analysis (DA-VOI). Also to establish the feasibility and implications of applying these methods to inform the prioritisation process of the NHS Health Technology Assessment (HTA) programme, and possibly extending their use therein.

Data sources: Three research topics that were considered by the HTA panels in the September 2002 and February 2003 prioritisation rounds.

Review methods: A brief and non-technical overview of DA-VOI methods was circulated to the panels and Prioritisation Strategy Group (PSG). For each case study the results were presented to the panels and the PSG in the form of brief case-study reports. Feedback on the DA-VOI analysis and its presentation was obtained in the form of completed questionnaires from panel members, and reports from panel senior lecturers and PSG members.

Results: Although none of the research topics identified met all of the original selection criteria for inclusion as case studies in the pilot, it was possible to construct appropriate decision-analytic models and conduct probabilistic analysis for each topic. In each case, the tasks were completed within the time-frame required by the existing HTA research prioritisation process. The brief case-study reports provided a description of the decision problem, a summary of the current evidence base and a characterisation of decision uncertainty in the form of cost-effectiveness acceptability curves. Estimates of value of information for the decision problem were presented for relevant patient groups and clinical settings, as well as the value of information associated with particular model inputs. The implications for the value of research in each of the areas were presented in general terms. Details were also provided on what the analysis suggested

regarding the design of any future research in terms of features such as the relevant patient groups and comparators, and whether experimental design was likely to be required.

Conclusions: The pilot study showed that, even with very short timelines, it is possible to undertake DA-VOI that can feed into the priority-setting process that has been developed for the HTA programme. There are however a number of areas that need to be established at the beginning of the process, such as clarification of the nature of the decision problem for which additional research is being considered, explicitness about which existing data should be used and how data that exhibit particular weaknesses should be down-weighted in the analysis. Other areas, including optimum application of researcher time, integrating the vignette (a summary of the clinical problem and existing evidence) and the use of DA-VOI, training, use of sensitivity analyses, and deployment of clinical expertise, are also considered in terms of the potential implementation of DA-VOI within the HTA programme. Recommendations for further research include how literature searching should focus on those variables to which the model's results are most sensitive and with the highest expected value of perfect information; methods of evidence synthesis (multiple parameter synthesis) to consider the evidence surrounding multiple comparators and networks of evidence; and ways in which the value of sample information can be used by the NHS HTA programme and other research funders to decide on the most efficient design of new evaluative research. There is also a need for an analytical framework to be developed that can jointly address the question of whether additional resources would better be devoted to additional research or interventions to change clinical practice.



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Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Bias Deviation of results or inferences from the truth, processes leading to systematic deviation. Any trend in the collection, analysis, interpretation, publication or review of data that can lead to conclusions that are systematically different from the truth.

Cost-effectiveness The consequences of the alternatives are measured in natural units, such as years of life gained. The consequences are not given a monetary value.

Cost-effectiveness acceptability curve
A Bayesian approach to the presentation of cost-effectiveness. The curve illustrates the probability of intervention A being more cost-effective than intervention B given a range of values that a decision-maker might attach to an additional quality-adjusted life-year.

Decision analysis A structured way of thinking about how an action taken in a current decision would lead to a result. Will usually involve the construction of a logical model, which is a mathematical representation of the relationships between inputs and results.

Expected value of perfect information The difference between the expected value of a model with perfect information and the expected value with current information.

Incremental cost-effectiveness ratio

The ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives.

National Coordinating Centre for Health Technology Assessment Coordinates the Health Technology Assessment Programme under contract from the Department of Health's R&D Division.

Quality-adjusted life-years An index of survival that is weighted or adjusted by a value associated with patients' quality of life during the survival period.

Randomised controlled trials In healthcare evaluation, these are designed for particular measurements; in particular, relative treatment effects that are potentially subject to selection bias, such as hazard ratios. Selection bias is minimised by randomly assigning people to one, two or more treatment groups and, where possible, blinding them and the investigators to the treatment that they are receiving. The outcome of interest is then compared between the treatment groups. Such studies are designed to minimise the possibility of an association due to confounding and to remove sources of bias present in other study designs.

List of abbreviations

AMD	age-related macular degeneration	HSE	Health Survey for England
BNF	British National Formulary	ICER	incremental cost-effectiveness ratio
CARG	Cochrane Airways Review Group	LOS	length of stay
CCTR	Cochrane Controlled Trials Register	NCCHTA	National Coordinating Centre for Health Technology Assessment
CEAC	cost-effectiveness acceptability curve	NICE	National Institute for Clinical Excellence
CI	confidence interval	PaO_2	arterial oxygen partial pressure
CIPFA	Chartered Institute of Public Finance and Accountancy	PDT	photodynamic therapy
COPD	chronic obstructive pulmonary disease	PEFR	peak expiratory flow rate
CRD	Centre for Reviews and Dissemination	PRS	progressive renal scarring
CSM	chiropractic spinal manipulation	PSG	Prioritisation Strategy Group
DARE	Database of Abstracts of Reviews of Effects	PSSRU	Personal Social Services Research Unit
DA-VOI	decision analysis and value of information	QALY	quality-adjusted life-year
EQ-5D	EuroQol 5 Dimensions	RCT	randomised controlled trial
ESRD	end-stage renal disease	TAP	treatment of age-related macular degeneration with photodynamic therapy
EVPI	expected value of perfect information	UTI	urinary tract infection
FEV ₁	forced expiratory volume in one second	VA	visual acuity
FVC	forced vital capacity	VOI	value of information
		VUR	vesicoureteral reflux

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.



Executive summary

Background

This project developed as a result of the investigations of the Research Team at the Centre for Health Economics, University of York, into the methods and application of decision analysis and value of information analysis (DA-VOI) as a means of identifying research priorities, and the interest of the National Coordinating Centre for Health Technology Assessment (NCCHTA) regarding whether these methods might contribute to priority setting in the NHS Health Technology Assessment (HTA) programme. In particular, the potential for DA-VOI to contribute to the process of achieving the greatest return, in terms of outcomes such as health gain, from the resources available to the NHS HTA programme, was a major focus.

Objectives

The specific objectives of the pilot study were to:

- demonstrate the benefits of using appropriate decision-analytic methods and value of information analysis
- establish the feasibility and resource implications of applying these methods in a timely way, to inform the prioritisation process of the HTA programme
- establish the resource implications of adopting these methods more widely within the NHS HTA programme
- identify the most appropriate way to extend the use of these methods within the programme's prioritisation process.

Methods

DA-VOI provides a methodological framework that explicitly considers the uncertainty surrounding the decision of a healthcare system to adopt a health technology. Specifically, using existing evidence, these methods focus on the likelihood of making a wrong decision if the technology is adopted. The value of additional research is based on the extent to which further information will reduce this decision uncertainty. This framework

values the additional information that may be generated by further research, in a way that is consistent with the objectives and resource constraints of healthcare provision.

The pilot study relating to the implementation of these methods within the NHS HTA programme was conducted through a series of case studies. It included the application of DA-VOI to three research topics that were considered by the HTA panels in the September 2002 and February 2003 prioritisation rounds: screening in age-related macular degeneration and manual therapy in asthma and in chronic obstructive pulmonary disease. The topic of low-dose antibiotics in children with recurrent urinary tract infections was also considered by the Prioritisation Strategy Group (PSG) in March 2003.

The application of DA-VOI requires three core tasks to be completed: (1) the construction of a decision-analytic model to represent the clinical decision problem being considered; (2) a probabilistic analysis of this model to characterise the current decision uncertainty; and (3) an estimate of the value of additional information through research to reduce decision uncertainty.

A brief and non-technical overview of DA-VOI methods was circulated to the panels and PSG. For each case study the results were presented to the panels and the PSG in the form of brief case-study reports. Feedback on the DA-VOI analysis and its presentation was obtained in the form of completed questionnaires from panel members, and reports from panel senior lecturers and PSG members.

Results

Although none of the research topics identified by NCCHTA met all of the original selection criteria for inclusion as case studies in the pilot, it was possible to construct appropriate decision-analytic models and conduct probabilistic analysis for each topic. In each case, the three core tasks were

completed within the time-frame required by the existing HTA research prioritisation process. The brief case-study reports provided a description of the decision problem, a summary of the current evidence base and a characterisation of decision uncertainty in the form of cost-effectiveness acceptability curves. Estimates of value of information for the decision problem were presented for relevant patient groups and clinical settings, as well as the value of information associated with particular model inputs.

The implications for the value of research in each of the areas were presented in general terms. Details were also provided on what the analysis suggested regarding the design of any future research in terms of features such as the relevant patient groups and comparators, and whether experimental design was likely to be required.

Conclusions

- The pilot study showed that, even with very short timelines, it is possible to undertake DA-VOI that can feed into the priority-setting process that has developed for the HTA programme.
- The use of DA-VOI requires relevant stakeholders to be clear, from an early point in the process, about the nature of the decision problem for which additional research is being considered.
- DA-VOI also needs explicitness about which existing data should be used for the first part of the analysis, and how data that exhibit particular weaknesses should be down-weighted in the analysis.
- There would be advantages to making the development of the vignette (a summary of the clinical problem and existing evidence) and the use of DA-VOI an integrated process.
- It is estimated that each of the pilot studies undertaken required approximately 6 weeks whole-time equivalent researcher input, and this was made up of a mix of experience levels. This research activity needs to be spread out over a period of 10–12 weeks, in part to allow for evidence acquisition.
- One approach to the more extensive use of DA-VOI might involve working up a proportion of topics for DA-VOI once they have been identified for a vignette based on existing methods. These analyses would be presented to the panels, along with the vignettes, and they would provide feedback. At the PSG, there

would be an analysis that directly addresses the question in the vignette and would include additional analysis to explore any concerns or issues raised by the panel.

- Practical considerations about how to implement such methods into a priority-setting system, which has evolved in a particular way, are complex. These include appropriate levels of training for individuals on the relevant panels to achieve the most from DA-VOI, and how analyses of acceptable quality can be assembled in a timely way given limitations of time and skilled resources.
- There needs to be some reflection on how the DA-VOI methods handle the heterogeneity and differing levels of quality in the evidence base. Greater use of sensitivity analysis may be a way of handling this problem. Consideration needs to be given to identifying useful scenarios and priorities for sensitivity analysis. This may be an iterative process based on concerns expressed by the panels.
- There is a need to identify, and secure access to, relevant clinical experts early in the analysis period when the decision problem is being defined, the structure of the model is being established and relevant data are being identified.
- If some degree of implementation of DA-VOI takes place within the HTA programme, careful evaluation and ongoing development will be essential.

Recommendations for research

- Methods for efficient literature searching would focus most searching and review attention on those variables to which the model's results are most sensitive and with the highest expected value of perfect information.
- Methods of evidence synthesis (multiple parameter synthesis) to consider the evidence surrounding multiple comparators and networks of evidence.
- Ways in which the value of sample information can be used by the NHS HTA programme and other research funders to decide on the most efficient design of new evaluative research.
- There is a need for an analytical framework to be developed that can jointly address the question of whether additional resources would better be devoted to additional research or interventions to change clinical practice.

Chapter I

Project details

Background to the pilot study

This project developed as a result of the investigations of the Research Team at the Centre for Health Economics, University of York, into the methods and application of decision analysis and value of information analysis (DA-VOI) as a means of identifying research priorities, and the interest of the National Coordinating Centre for Health Technology Assessment (NCCHTA) regarding whether these methods might contribute to priority setting in the NHS HTA programme. In particular, the potential for DA-VOI to contribute to the process of achieving the greatest return, in terms of outcomes such as health gain, from the resources available to the NHS HTA programme was a major focus.

General methods for setting priorities in research and development of healthcare technologies have been proposed, and some have been used to identify priority areas for research. These include measures of the burden of disease, or the technology^{1,2} measures of the expected 'payback' from research,³⁻⁵ and estimates of the welfare losses due to variations in clinical practice.⁶ However, each of these proposed methods has serious methodological problems. First, all of the approaches currently proposed view research simply as a means of changing clinical practice rather than considering research as providing additional information, which will reduce the uncertainty about what is appropriate clinical practice. Indeed, measures of payback or welfare losses due to variations in clinical practice require the analysis to identify appropriate utilisation, or which technology should be adopted a priori. Therefore, these methods implicitly assume that there is no uncertainty surrounding the decision that the proposed research is supposed to inform.

Second, these approaches, particularly measures of burden, attempt to identify research priorities using aggregate measures across broad clinical areas. However, the information generated by evaluative research is only valuable if it informs specific clinical decisions for specific groups of patients. The measures of burden methods assume that the value of research in a clinical area is simply made up of the value of research about each of the constituent

clinical decision problems faced within that area. Therefore, simply because aggregate measures such as burden of disease may suggest that a clinical area is a 'high' priority, it does not mean that specific evaluative research relating to any one clinical decision problem will be valuable. Similarly, proposed research to inform a particular decision in a 'low' priority disease area may be very valuable.

In this sense, attempts to identify research priorities across broad clinical areas using aggregate indicators may be mistaken. What is required is a measure of the societal value of particular research, which can inform specific clinical decisions for defined groups of patients. An appropriate methodological framework should consider the uncertainty surrounding the adoption of a health technology in terms of the likelihood of making a wrong decision if it is adopted. It should also view the value of research as the extent to which further information will reduce this decision uncertainty. An appropriate framework should value the additional information generated by research in a way that is consistent with the objectives and the resource constraints of healthcare provision.

Bayesian decision theory and value of information analysis provide an analytical framework to establish the value of acquiring additional information to inform a decision problem. These methods have firm foundations in statistical decision theory^{7,8} and have been successfully used in other areas of research such as engineering and environmental risk analysis.⁹⁻¹¹ More recently, these methods have been extended to setting priorities in the evaluation of healthcare technologies.¹¹⁻¹⁶ In addition, they have been usefully applied to a number of different health technologies,¹⁷⁻²² including a series of case studies taken from guidance issues by the National Institute for Clinical Excellence (NICE).²³

Pilot objectives

The specific objectives of the pilot study were to:

- demonstrate the benefits of using appropriate decision-analytic methods and value of information analysis

- establish the feasibility and resource implications of applying these methods in a timely way, to inform the prioritisation process within the NHS HTA programme
- establish the resource implications of adopting these methods more widely within the HTA programme
- identify the most appropriate way to extend the use of these methods within the prioritisation process.

Priority setting in the NHS HTA programme

The NHS HTA programme is a national programme of evaluative research funded as part of the Department of Health's Research and Development programme (www.ncchta.org). Its purpose is to provide high-quality evidence on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. The HTA programme commissions both primary and secondary research. The programme is coordinated by the NCCHTA, which is based at the University of Southampton.

The process of setting priorities within the NHS HTA programme begins with suggestions for research topics being widely drawn from a range of individuals and institutions. Subject to particular criteria, such as the need for a clear research question, these are presented to three advisory panels which, with NCCHTA support, are the core of the priority-setting process within the programme. These panels are the HTA Diagnostic Technologies and Screening Panel, Pharmaceuticals Panel and Therapeutic Procedures Panel. The panels are asked on which topics they would like additional information, and should hence be taken to the next stage of the priority-setting process through the creation of a vignette – a summary of the clinical problem and existing evidence. The panels meet again and, based on the vignettes, decide which topics they would like to recommend for commissioning. The Prioritisation Strategy Group (PSG) decides for which topics commissioning briefs will be prepared, ensuring that the NHS HTA programme has a high-quality research portfolio that best reflects the research needs of the NHS. The Commissioning Board is responsible for assessing the research proposals submitted to the programme following open advertising for proposed research.²⁴

Potential benefits to the NHS HTA programme

A number of potential benefits to the NHS HTA programme from DA-VOI can be identified.

- Establishing the expected value of perfect information (EVPI) related to a clinical decision problem places an upper bound on the value to the healthcare system of further research about the choice of technology. This measure of value of information can be used to rule out research proposals (either primary or secondary) where the cost of investigation exceeds the potential benefit, identify those proposals that are potentially cost-effective (where EVPI exceeds the cost of investigation); and identify proposals and clinical decision problems where the potential value of further research will be greatest.
- The EVPI associated with each uncertain parameter relevant to the choice between technologies can also be established (partial EVPI). These measures of partial EVPI can be used to focus further research on those parameters where more precise estimates would be most valuable.
- The estimates of the partial EVPI can be used to identify appropriate research designs. In some circumstances this analysis will indicate which end-points should be included in further experimental research, whereas in others it may focus research on obtaining more precise estimates for particular inputs, which may not necessarily require experimental design and can be provided relatively quickly. For example, if information about the duration and the magnitude of effect is most valuable, then this may indicate that further experimental research with longer follow-up may be worthwhile. Alternatively, if information about health-related quality of life, resource use, or baseline risks and natural history are most valuable, then observational studies or secondary research may be appropriate.
- These methods could provide potential benefits at each stage of the research prioritisation process within the NHS HTA programme. The stages at which this analysis may be useful include, among others: when vignettes are presented to priority-setting panels, when the vignettes are considered by the PSG, application to suggestions made by affiliates; inclusion in Technology Assessment Group (TAG) briefing documents, application to suggestions from NICE guidance and as part of the monitoring of ongoing research commissioned by NHS HTA.

Although the normative value of a decision-theoretic value of information approach to these policy issues is well established, there are unresolved questions about the feasibility of their application and the most appropriate way to implement them. The purpose of the pilot is to address these questions of feasibility of the methods as a practical policy tool.

Conducting the pilot

The pilot study of implementing these methods was conducted through a series of case studies. The pilot study included the application of DA-VOI to three research topics, which were considered by the panels in the September 2002 and February 2003 prioritisation rounds, and to one topic considered by the PSG in March 2003.

The application of value of information methods requires the following three core tasks to be completed for each case study.

- A decision-analytic model is constructed, which appropriately represents the clinical decision problem under consideration. Each model needs to be sufficiently sophisticated to capture the key characteristics of the decision, but also needs to simplify the decision problem in order to deliver results in a timely way, using the evidence currently available. This task requires advice from clinical experts in each field to ensure that the model structure is clinically appropriate and maintains an acceptable balance between descriptive realism and analytical parsimony.²⁵
- The uncertainty surrounding each of the parameters in the model is characterised by assigning prior distributions. Therefore, the existing evidence for each model input is reviewed (from secondary sources already available) and appropriate distributions are assigned. These are propagated through the model using Monte Carlo simulation.
- The EVPI is established by applying non-parametric methods to the simulated output. The partial EVPIs require some additional programming and computing time, but are also established using non-parametric methods.

Selection of case studies

Following consultation with NCCHTA, it was decided to select one case study from each of the following sources:

- suggestions for further research contained in NICE guidance

- suggestions from affiliates
- vignettes considered by panels in September 2002 and taken forward to the PSG.

Following consultation with NCCHTA, it was initially agreed that, for the purposes of the pilot study, the case studies would ideally fulfil the following criteria:

- availability of earlier secondary research (systematic review)
- availability of a Technology Assessment Report completed for NICE
- an existing high-quality decision model in the literature
- particular interesting features of the disease/technology (e.g. time horizon, surrogate end-points, or multiple management strategies), which require probabilistic decision-analytic methods to characterise uncertainty.

The final selection of case studies was made by NCCHTA in late October 2002. Three case studies were identified in which DA-VOI would be undertaken. Two of these case studies were topics that had been identified as potential priorities by the panels, and DA-VOI was to be undertaken concurrently with the production of the vignettes [screening in age-related macular degeneration (AMD) and manual therapy in respiratory disease]. The analyses undertaken for these case studies were presented to the relevant panels in February 2003 and the panels' feedback was obtained. A further case study related to a topic that had been identified as a priority by the relevant panel and was due to be considered by the PSG in October 2002 [prophylactic antibiotics in children with recurrent urinary tract infections (UTIs)]. NCCHTA, in consultation with the PSG, decided to delay consideration of this topic to the next meeting of the PSG so that it could be included in the pilot study. The results of this case study were presented to the PSG in March 2003. All the DA-VOI analysis and reporting of the cases studies was conducted within the timelines set by NCCHTA and their existing process.

Manual chest physiotherapy techniques

This topic was suggested by the NCCHTA affiliates and was to be considered by the Therapeutic Procedures Panel in February 2003. The production of a vignette for this topic was undertaken independently and in parallel with the DA-VOI analysis over this period. The topic did not meet any of the selection criteria for case studies outlined above (availability of earlier secondary research, availability of a completed NICE Technology Assessment Report and an

existing high-quality decision model in the literature). Furthermore, given the paucity of relevant research in the literature, there was a danger that the quality of the modelling which would be possible for this topic would not be sufficient for adequate consideration by the panel. The topic description was also very broad and mentioned a range of manual physiotherapy techniques for chronic obstructive pulmonary disease (COPD) and cystic fibrosis, and cited Cochrane reviews of these interventions in asthma as well as COPD and cystic fibrosis. The topic description did not specify particular techniques, settings, disease or patient groups. Considering the paucity of literature and broad topic description, the NCCHTA agreed that an initial focus on asthma (which came closest to the selection criteria) was appropriate. However, in late November NCCHTA requested that the group also conduct DA-VOI for manual physiotherapy in COPD.

Both of these analyses and completed reports were submitted in mid-January 2003 in time to inform the panel meeting in early February. Therefore, two DA-VOI analyses were conducted for this topic. The analysis for asthma is reported fully in Chapter 3 of this report, and the analysis for COPD is presented in Chapter 4. The two brief case-study reports, which were considered by the panel for this topic, can be found in Appendix 1.

Screening for age-related macular degeneration

This topic was identified as a priority for research following the provisional guidance based on the then recently completed NICE appraisal of the use of photodynamic therapy (PDT) in AMD. This topic was due to be considered by the Diagnostic Technologies and Screening Panel in February 2003. The production of the vignette for this topic was undertaken independently and in parallel with the DA-VOI analysis over this period. This topic met the first two selection criteria (secondary research and a completed Technology Assessment Report) and, although no model of screening for AMD was available in the literature, a high-quality model of PDT treatment was available, which provided an important component of the screening model. The DA-VOI analysis for screening for AMD is fully reported in Chapter 5. The brief case-study report, which was considered by the panel in March 2003, can be found in Appendix 2.

Long-term antibiotics for preventing urinary tract infections in children

This topic had already been considered by the Pharmaceuticals Panel and identified as a priority. A

vignette for this topic had also been produced and was due to be considered by the PSG in October 2002. However, NCCHTA and PSG decided that this topic would be most suitable for DA-VOI analysis to inform the deliberations of the PSG. Therefore, consideration of this topic by the PSG was delayed until its next meeting in March 2003 to allow time for the DA-VOI analysis to be conducted and reported. This topic did not meet two of the initial selection criteria (availability of a completed NICE Technology Assessment Report and an existing high-quality decision model in the literature). However, the initial review of the literature did identify a number of useful sources of evidence, including a published model in a related area. The DA-VOI analysis for long-term antibiotics for preventing UTIs in children is fully reported in Chapter 6. The brief case-study report considered by the PSG in March 2003 can be found in Appendix 3.

Reporting and feedback

Important aspects of the pilot study were to demonstrate that DA-VOI could be conducted in a timely way to inform the NCCHTA process, and that the methods and results could be communicated in a way that could usefully inform decision-makers at the panels and PSG. To this end, a brief and non-technical overview of DA-VOI methods was circulated to the panels and the PSG. This forms the basis of Chapter 2 of this report. For each case study, the results were presented to panels and the PSG in the form of brief case-study reports (two case-study reports were submitted to the Therapeutic Procedures Panel). These brief reports can be found in Appendices 1–3. The full reporting of the analysis conducted can be found in Chapters 3–6. In addition, the senior lecturers on the Therapeutic Procedures Panel and the Diagnostic Technologies and Screening Panel made short presentations of DA-VOI methods following a briefing meeting from the York team in January. The Pharmaceuticals Panel senior lecturer also made a presentation to his panel. This enabled some general comments from the panel to be made and prepared the chair of the panel for discussion of the topics at the PSG. The York team presented an overview of the methods and results of the each of the case studies to the PSG in March 2003. Feedback, in the form of completed questionnaires from panel members, and reports from panel senior lecturers and PSG members, is presented and discussed in Chapter 7. Some of the possible implications of the results of this pilot study for the NCCHTA research prioritisation process are discussed in Chapter 8.

Chapter 2

Overview of methods

Bayesian decision theory and value of information analysis provides an analytical framework that can be used to establish the value of acquiring additional information to inform a decision problem. These methods have firm foundations in statistical decision theory^{7,8} and have been successfully used in other areas of research such as engineering and environmental risk analysis.^{9,10,26} More recently, these methods have been extended to setting priorities in the evaluation of healthcare technologies.¹¹⁻¹⁶ In addition, they have been usefully applied to a number of different health technologies,¹⁷⁻²² including a series of case studies taken from guidance issued by NICE.²³

The application of these methods requires three core tasks to be completed: (1) the construction of a decision-analytic model to represent the decision problem; (2) a probabilistic analysis of this model to characterise the current decision uncertainty; and (3) establishing the value of additional information.¹⁹

Decision analysis

Evaluative research is useful in so far as it informs the choice between alternative strategies for patient management. Decision analysis presents these decision problems and the key inputs to these decisions explicitly.^{27,28} Decision modelling requires all of the relevant inputs to the decision to be explicitly identified, and facilitates the synthesis of data from a variety of sources.¹⁶ Randomised trials are a crucial source of parameter estimates for decision models, particularly estimates of the magnitude of treatment effects. Other sources of data (for example, the baseline risk and resource implications of particular clinical events) may be taken from non-trial sources such as observational studies and administrative data sets. In some circumstances, where no evidence exists for particular inputs, clinical judgement may also be incorporated.

Probabilistic analysis

All decisions about the cost-effectiveness of interventions are based on uncertain information

about variables such as clinical effects, health-related quality of life and resource use. Decision-analytic models can be used to combine evidence on each parameter to assess the extent of uncertainty in the decision.²⁸ The extent and the quality of the evidence available, for each of the inputs, can be reflected in probability distributions assigned to these estimates, where more uncertainty about an input (less information or information of poorer quality) is represented by assigning a more diffuse distribution. Without access to patient-level data, these distributions are assigned based on secondary sources (e.g. published literature, meta-analysis and evidence synthesis). The choice of the type of distribution and its parameters for a particular model input is not arbitrary, but should be based on the existing evidence and what type of distribution would be most appropriate. For example, probabilities should be represented by beta distributions, which are bounded by zero and one, and their parameters can be based either on the number of observations or on mean and variance.^{3,28-30}

The uncertainty surrounding the decision problem can be characterised by propagating these distributions through the model using Monte Carlo simulation methods, where values for the input parameters are drawn at random from the probability distributions that have been assigned.^{3,28-30} This random sampling is repeated a large number of times. The output of these simulations provides a distribution of expected costs and outcomes for each strategy being compared. The uncertainty surrounding the cost-effectiveness of a technology, for a range of thresholds for cost-effectiveness, can be represented as a cost-effectiveness acceptability curve (CEAC).¹¹ *Figure 1* illustrates an example of a CEAC where the probability that the intervention is cost-effective increases as the willingness to pay for additional health [quality adjusted life-years (QALYs)] or the threshold for cost-effectiveness increases.

If the objective underlying health technology assessment is to make decisions that are consistent with maximising health gains from available resources, then decisions should be based on expected cost-effectiveness given the existing

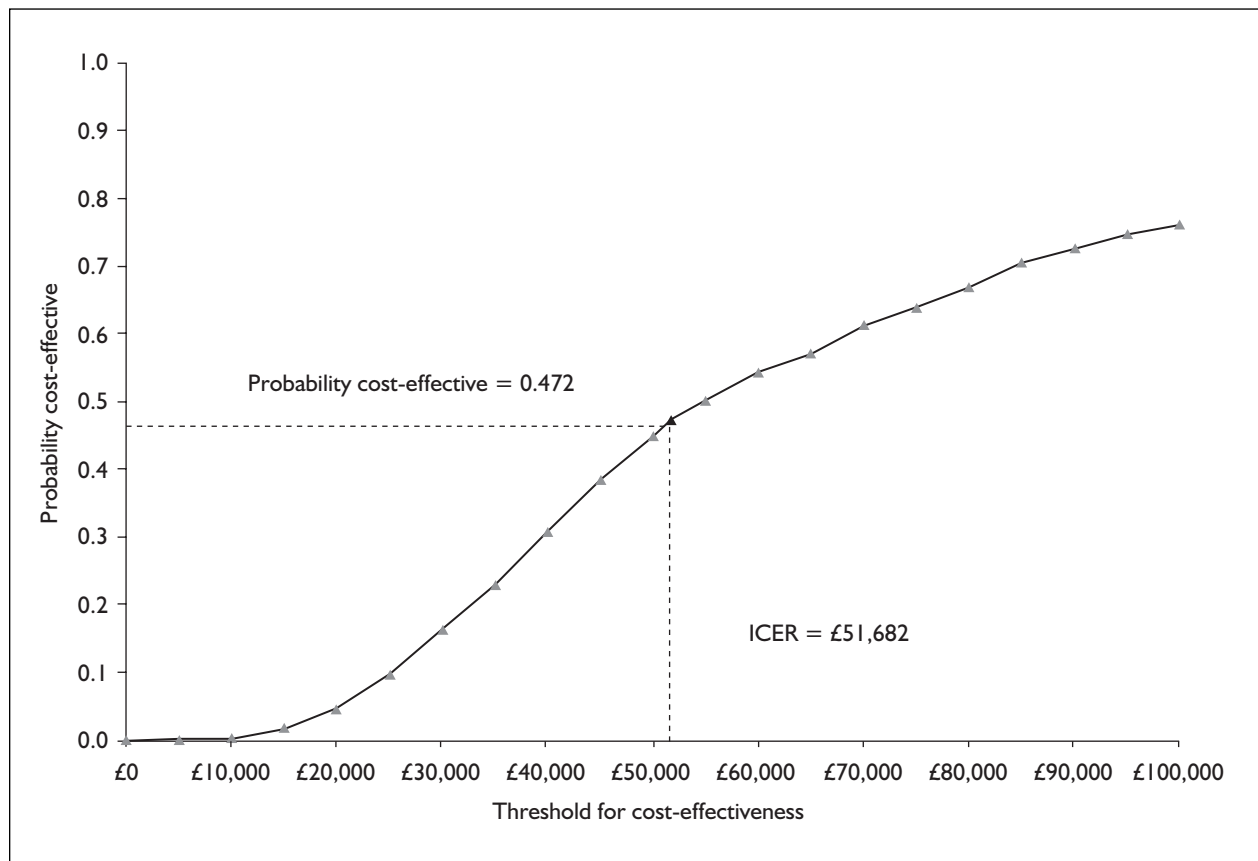


FIGURE 1 Cost-effectiveness acceptability curve example. ICER, incremental cost-effectiveness ratio.

information (i.e. using the mean differential costs and outcomes between the scenarios being compared). This does not necessarily mean that the intervention that has the highest probability of being cost-effective should be adopted. For example, in *Figure 1* if the threshold for cost-effectiveness was just greater than £51,682 (the ICER) then the intervention should be adopted even though the probability that it is cost-effective is less than 0.5 (0.472). This is because the distribution of the additional net benefits (where health outcomes are rescaled in monetary terms using the cost-effectiveness threshold)^{31,32} is positively skewed, with a mean greater than its median value. The adoption decision can be represented with a CEAC by including a cost-effectiveness frontier, which indicates which of the alternatives will be cost-effective.¹¹

Although decisions should be based on expected cost-effectiveness given the existing information, this does not mean that adoption decisions can simply be based on little, or poor-quality evidence, as long as the decision to conduct further research to support adoption (or rejection) is made simultaneously.^{12,19}

The value of information

Decisions based on existing information will be uncertain, and there will always be a chance that the wrong decision will be made. If the wrong decision is made, there will be costs in terms of health benefit and resources forgone. Therefore, the expected cost of uncertainty is determined jointly by the probability that a decision based on existing information will be wrong and the consequences of a wrong decision.

The expected costs of uncertainty can be interpreted as the EVPI, since perfect information can eliminate the possibility of making the wrong decision. If the objective of the healthcare system is to maximise gains in health outcome subject to a budget constraint then this is also the maximum that the healthcare system should be willing to pay for additional evidence to inform this decision in the future, and it places an upper bound on the value of conducting further research.^{12,13,17,19,33} However, there may be other objectives of healthcare provision such as equity. If these other objectives can be identified and valued then these can be incorporated into the analysis and the societal value of information.¹²

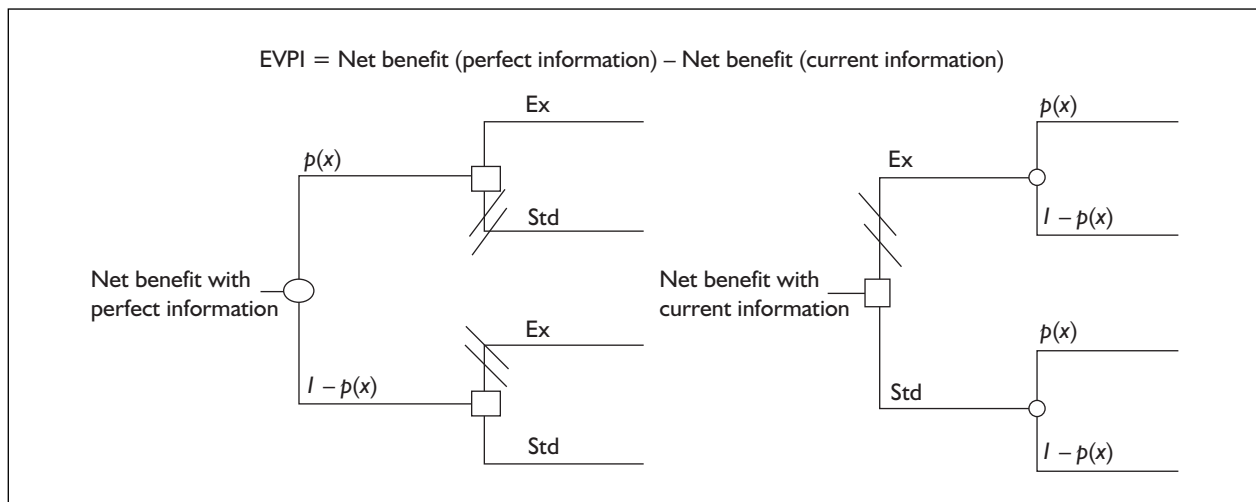


FIGURE 2 Calculating EVPI example

This general idea is illustrated in *Figure 2*. With current information, decisions must be made before it is known how the uncertainties $[p(x)]$ will be resolved; that is, a decision must be made now based on the expected values of all of the model inputs (choose Std in *Figure 2*). However, with perfect information these decisions can be made once it is known how these uncertainties $[p(x)]$ are resolved; that is, different decisions can be made for different resolutions of the uncertainties [choose Std if $1 - p(x)$ but choose Ex if $p(x)$]. The EVPI is simply the difference between the payoff (expected net benefit) with perfect and current information.^{21,33}

EVPI can be worked out directly from the simulated output from our model as it relates to the individual patient.^{9,21,33,34} Because information can be of value to more than one patient, EVPI can also be expressed for the total population of patients who stand to benefit over the expected lifetime of the technology (based on incidence over the lifetime of the technology). If the EVPI for the population of current and future patients exceeds the expected costs of additional research, then it is potentially cost-effective to conduct further research.^{12,13}

Figure 3 illustrates the population EVPI for the example used in *Figure 1*. When the threshold for cost-effectiveness (maximum value of health outcome) is low, the technology is not expected to be cost-effective and additional information is unlikely to change that decision (EVPI is low). Similarly, when the threshold is higher, the intervention is expected to be cost-effective and this decision is less likely to be changed by further research (EVPI falls). In this case, the population

EVPI reaches maximum when the threshold is equal to the expected ICER of this technology. In other words, the EVPI reaches a maximum when there is most uncertainty about whether to adopt or reject the technology based on existing evidence.^{12,13,17}

The value of reducing the uncertainty surrounding particular input parameters in the decision model can also be established (partial EVPI). This type of analysis can be used to focus further research by identifying those inputs for which more precise estimates would be most valuable. In some circumstances, this will indicate which end-points should be included in further experimental research. In other circumstances, it may focus research into obtaining more precise estimates of particular inputs that may not necessarily require experimental design and can be provided relatively quickly. The analysis of the value of information associated with each of the model inputs (partial EVPI) is, in principle, conducted in a very similar way to the EVPI for the decision as a whole.^{9,17,21,33,34} However, this does require substantial additional computation for models where the relationship between the inputs and expected cost and outcomes is not linear, for example in Markov models.^{21,33}

Figure 4 illustrates the partial EVPIs associated with the overall EVPI in *Figure 3*. In this example, the EVPI associated with reduction in symptom days is relatively high and suggests that further experimental research may be worthwhile. However, other inputs with lower partial EVPI, such as the baseline probability of hospitalisation, may not require experimental research but may also be important if the costs of further

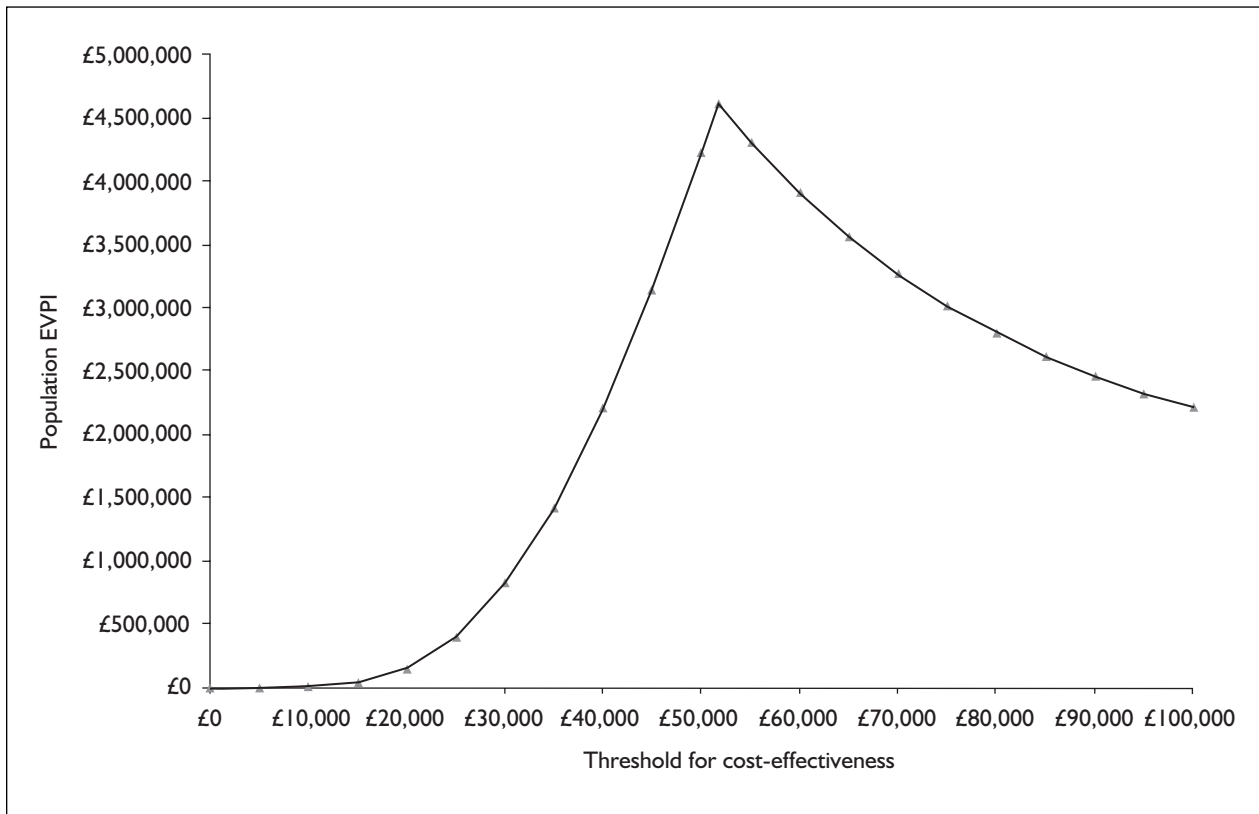


FIGURE 3 EVPI curve example

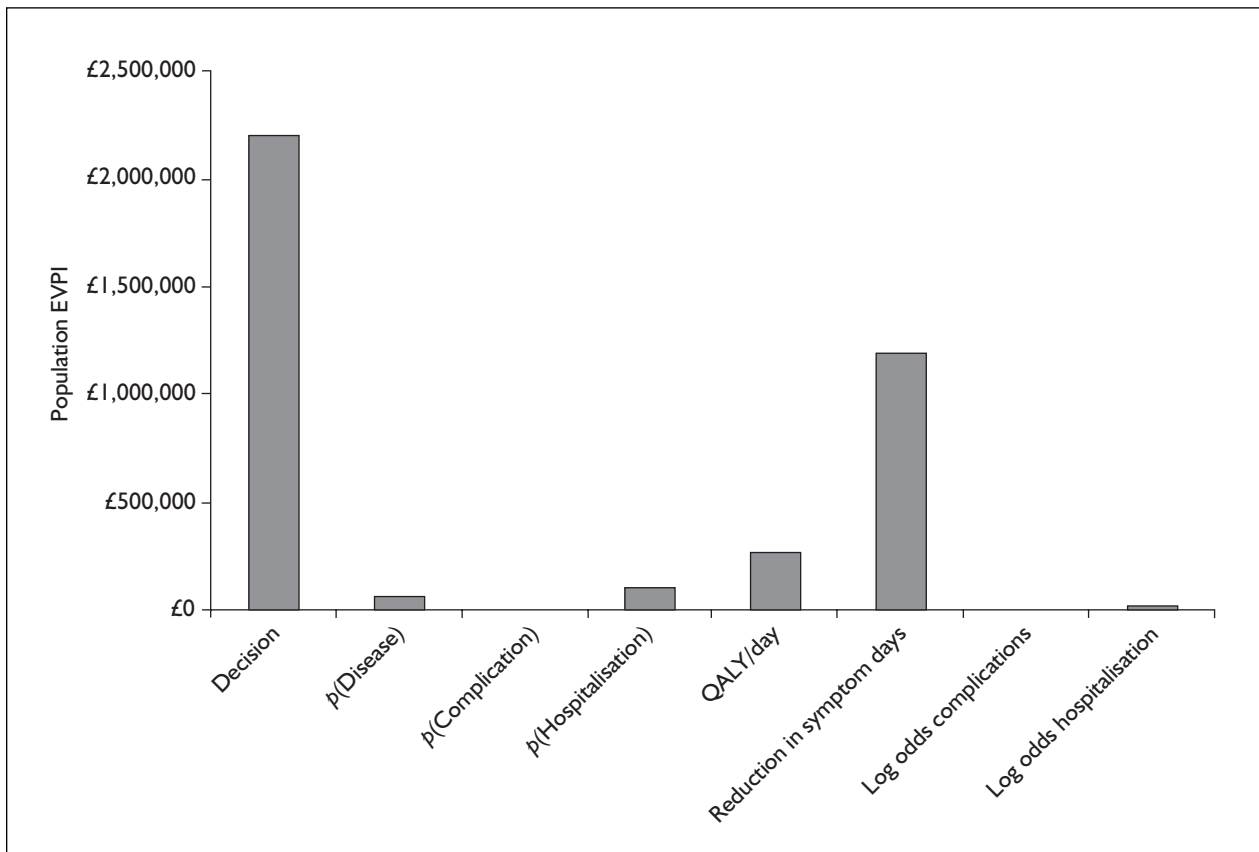


FIGURE 4 Partial EVPI example

investigation (resources and delay) are low. It should be noted that the partial EVPIs will not sum to the overall EVPI owing to the interactions within the model structure.

Setting priorities in research

The EVPI places an upper bound on the returns to further investigation. The EVPI for the decision problem can be used as a first hurdle for proposed research.^{12,13,17,19,21} If the costs of investigation exceed the EVPI, then the proposed research will not be cost-effective. It is possible to compare EVPIs across patient groups and different technologies. In general, additional research will be more valuable for a patient group or technology with higher EVPI. However, it should be noted that this comparison requires the marginal cost and benefits of research to be similar across the technologies. The same framework can be extended to establish the expected value of sample information for particular research designs and to compare these marginal benefits of research with the marginal costs. However, this type of analysis is beyond the scope of the current pilot.^{12,14,18,33}

The partial EVPIs can be used to focus potentially cost-effective research on those inputs for which more precise estimates would be most valuable. This may indicate which end-points should be included in further experimental research, or it may focus research on obtaining more precise estimates of particular inputs, which may not necessarily require experimental design or can be provided relatively quickly.^{17,21,33}

Conclusion

Bayesian decision analysis and value of information analysis provide a methodological framework that explicitly considers the uncertainty surrounding the decision to adopt a health technology based on existing evidence in terms of the likelihood of making a wrong decision if it is adopted. The value of additional research is based on the extent to which further information will reduce this decision uncertainty. This framework values additional information, which may be generated by further research, in a way that is consistent with the objectives and resource constraints of healthcare provision.

Chapter 3

Assessing the cost-effectiveness of manual chest physiotherapy techniques for asthma

Background

Topic origin

Manual chest physiotherapy for respiratory diseases was a topic identified as a potential priority by the Therapeutics Procedures Panel. DA-VOI was to be undertaken concurrently with the production of the vignette. The topic did not meet any of the selection criteria for case studies (availability of earlier secondary research, availability of a completed NICE Technology Assessment Report and an existing high-quality decision model in the literature) and, given the paucity of literature, there was a danger that the quality of the modelling that would be possible for this topic may not be sufficient for adequate consideration by the panel. After discussion with the NCCHTA it was, however, decided to proceed with this case study.

Policy background

The Asthma Audit 2001 estimated that 1 in 8 children and 1 in 13 adults in the UK are currently being treated for asthma. Each year 1500 people die from asthma, although many of these are people over the age of 65.³⁵

Treatments for asthma mainly focus around a range of pharmaceutical interventions, often delivered via inhalers, which can prevent and relieve symptoms. Most drug treatment of asthma is provided in primary care. In addition to the more conventional forms of treatment, some asthmatics are treated using non-pharmaceutical treatments such as breathing exercises and physiotherapy.

Manual chest physiotherapy is used for a range of respiratory disorders including asthma, COPD and cystic fibrosis. It is directed at increasing lung function and quality of life, amongst other outcomes. Manual therapy practitioners are varied, including physiotherapists, respiratory therapists, chiropractors and occupational therapists.

A recent Cochrane review³⁶ aimed to “evaluate the evidence for the effects of manual therapies for

treatment of patients with bronchial asthma”. Manual therapy was compared with control treatments in terms of physiological outcomes, morbidity and mortality, and side-effects of therapy. The review concluded that there is insufficient evidence either to support or to refute the use of manual chest physiotherapy techniques in asthma patients and that there is a need to conduct adequately sized randomised controlled trials (RCTs) that examine the effects of manual therapies on clinically relevant outcomes.

Decision problem

Given the view that RCTs are needed to examine the effects of manual therapies in asthma, as expressed in the Cochrane review,³⁶ and in the suggestions for research from the NCCHTA vignette, the analysis reported here assesses the cost-effectiveness of, and potential value of future research for, manual chest physiotherapy interventions compared with no intervention in asthmatic children treated in the community, asthmatic adults treated in the community and asthmatic children treated in hospital. The specific interventions under investigation were massage therapy (by parents for children and by physiotherapists for adults), chiropractic spinal manipulation (CSM) and physical therapy.

Methods

Definition of the decision problem

Based on the trial evidence,^{37–40} three different techniques for manual therapy were evaluated: massage therapy, CSM and physical therapy.

Based on the evidence from the four trials, massage therapy and CSM were evaluated for both children (administered by parents) and adults (administered by physiotherapists) treated in the community. Physical therapy was evaluated for children treated in hospital.

Description of the model

The structure of the decision model is illustrated in *Figure 5*. The effect of each intervention is based on changes in lung function measured by the forced expiratory volume in one second

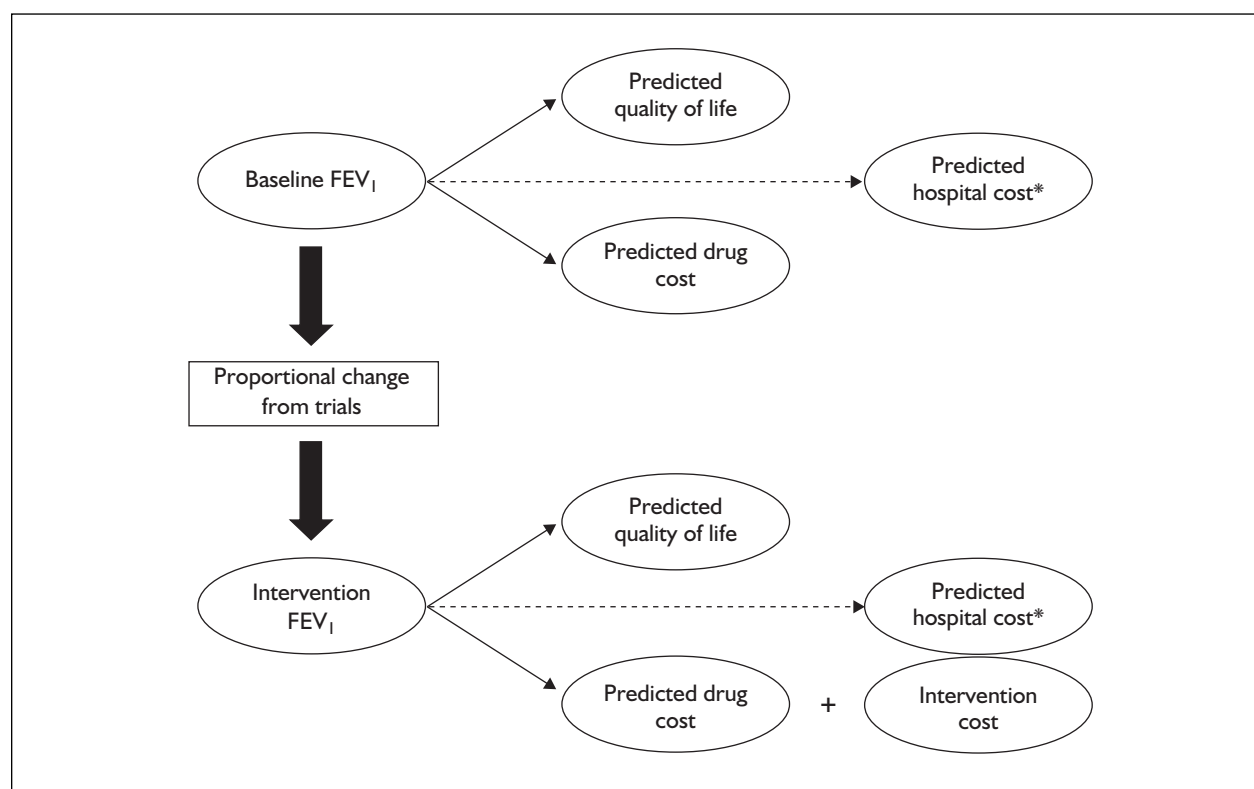


FIGURE 5 Model structure. *Physical therapy in children with severe asthma only.

(FEV₁), as this was the only outcome reported in the trials that could be linked to quality of life using EuroQol 5 Dimensions (EQ-5D) data reported in the Health Survey for England (HSE), 1996. The proportional change from the baseline FEV₁ (FEV₁ with no intervention for each patient group) is based on reported trial results.

EQ-5D⁴¹ quality of life scores (in terms of 0 to 1 'utilities') and daily medication costs were predicted contingent on FEV₁ values using a series of equations derived using a Tobit regression model⁴² based on data from the 1996 Survey for England HSE.⁴³ Additional explanatory variables, such as age and gender, were omitted from the prediction equations owing to lack of comparable data from the trials and low explanatory power. These equations are shown below, with standard errors in parentheses:

$$\text{EQ-5D} = \text{FEV}_1 * 0.1175812 (0.1535) + 0.5611784 (0.0438)$$

$$\text{Daily drug cost} = \text{FEV}_1 * -0.0676445 (0.0144) + 0.4214391 (0.0424)$$

Predicted EQ-5D scores were used to calculate expected QALYs for each intervention and the

baseline (no manual therapy) using under-the-curve methods.⁴⁴ The correlation between the constant and β coefficients in both equations was reflected in the Monte Carlo simulation based on the covariance matrix.

An NHS cost perspective was used for the analysis. Total expected costs of community-based interventions include the cost of medications and intervention costs. Physical therapy for the hospitalised children also includes an inpatient admission cost. Baseline length of stay (LOS) and change in LOS were taken from the relevant trial³⁸ and added as an additional parameter in the model. FEV₁ scores were assumed to be independent of LOS as no data were available from the trials to model any association. However, a negative correlation between the two variables is expected. The total cost of physical therapy, therefore, consisted of the cost of medications, intervention costs and inpatient hospitalisation.

The model assumes that treatment effect and costs are only sustained while treatment continues. After this period FEV₁ returns to preintervention level. The time horizon of the model is 30 days, which is consistent with the follow-up considered in the trials.

The evidence

Effectiveness

A search was conducted to update the results produced for the Cochrane review.³⁶ The Cochrane search strategy developed previously was used, and can be seen in Appendix 4. No additional trials were identified in the update searches, thus four (English language) trials³⁷⁻⁴⁰ that evaluated the use of chest physiotherapy in patients with asthma were used to provide effect estimates for the model. One additional trial⁴⁵ was identified in the Cochrane review. However, since this was in Danish, it was not included here because of time constraints, which precluded translation. The trials used for the model are summarised in Appendix 5.

The Cochrane review reported that the quality of two of the trials was moderate⁴⁰ to good,³⁷ while the remaining three trials had poor methodological quality. Balon³⁷ had the highest Jadad score of (2-1-1), a measure of study design/reporting quality consisting of three items: randomisation, blinding, and description of withdrawals and dropouts.³⁶

Outcomes reported in the trials were varied, including measures of lung, use of asthma medication and quality of life descriptive profiles. All four of the trials reported on FEV₁, which is the only outcome that could be related to quality of life (measured using the EQ-5D) using the 1996 HSE,⁴³ an observational dataset containing over 400 asthmatic patients. There is no available evidence to relate other reported outcomes to quality of life or resource use. The EQ-5D is a generic measure of health status, where health is characterised by five dimensions (mobility, self-care, ability to undertake usual activities, pain and anxiety/depression).⁴¹ Each response to this instrument locates an individual into one of 245 mutually exclusive health states, each of which has previously been valued on the 0 (equivalent to dead) to 1 (equivalent to good health) utility scale based on interviews with a sample of 3395 members of the UK public.⁴⁶

Two trials^{37,39} looked at the use of manual therapy techniques in asthmatic children treated in the community. To provide a common baseline measure for children treated in the community random effects meta-analysis was used to pool FEV₁ data from the two trials, 1.537% (95% CI 0.92 to 2.16).

The proportional change from baseline as reported in trials was used to obtain the treatment

effect of each intervention for each patient group. Two trials^{37,40} looked at the effectiveness of CSM. Thus, the effect changes from these trials were pooled using random effects meta-analysis, -0.062% (95% CI -0.188 to 0.065).

Distributions were assigned to baseline and effect estimates based on the standard errors reported in the trials or estimated from the meta-analysis. Distributions were also assigned to the coefficients of the prediction equations. The correlations between the coefficients of the prediction equations were based on the variance-covariance matrix from the regression analysis. The sources of data used in the asthma model are summarised in *Table 1*.

Incidence and prevalence data

In addition, to calculate the population EVPI values, the incidence and prevalence for each of the three patient groups was required. This was calculated using data collected in the National Asthma Campaign asthma audit 2001.³⁵

Analysis

The model was developed in Excel with the Crystal Ball add-on. Monte Carlo simulation was used to propagate the prior distributions assigned to model inputs and to estimate the expected costs and outcomes associated with each alternative therapy. ICERs were then calculated. To conduct the simulations, the distributions reported in *Table 1* were assigned to the model inputs to characterise the current (prior) uncertainty surrounding their values.²⁸ The simulation recalculated the results over a number of iterations. For each iteration the value of each variable was sampled at random from the distributions specified. By repeating the calculations of expected costs and outcomes in this way, distributions of estimates are obtained, which allow estimation of the mean expected costs and QALYs and associated distributions.

The results of the model are presented in two ways. First, mean costs and QALYs for the various comparators are presented and their cost-effectiveness compared, estimating ICERs as appropriate, using standard decision rules.⁵² Given that mean costs and QALYs gained are estimated with uncertainty, the output from the simulations was then used to generate CEACs^{11,53} for the three patient groups.

The output of these simulations was also used to estimate the EVPI^{12,21} for individual patients. Population EVPIs were based on the incidence of

TABLE 1 Sources of data in the asthma model

Parameter name	Value	Distribution	Source
Baseline FEV ₁ in children treated in community	1.537	Log-normal 95% CI 0.92 to 2.16	Meta-analysis: Balon <i>et al.</i> ³⁷ , Field <i>et al.</i> ³⁹
Baseline FEV ₁ in adults treated in community	2.97	Log-normal SD 0.92	Nielsen <i>et al.</i> ⁴⁰
Baseline FEV ₁ in children treated in hospital	2.14	Log-normal SD 0.52	Asher <i>et al.</i> ³⁸
Effect of CSM (% change)	-0.062%	Normal 95% CI -0.188 to 0.065	Meta-analysis: Balon <i>et al.</i> ³⁷ , Nielsen <i>et al.</i> ⁴⁰
Effect of massage therapy (% change)	0.201%	Normal 95% CI -0.006 to 0.407	Field <i>et al.</i> ³⁹
Effect of physical therapy (% change)	0.0092%	Normal 95% CI -0.364 to 0.409	Asher <i>et al.</i> ³⁸
Baseline LOS (days)	3.9	Log-normal SD 2.50	Asher <i>et al.</i> ³⁸
Effect of physical therapy on LOS (days)	-1.4	Normal 95% CI -2.87 to 0.07	Asher <i>et al.</i> ³⁸
EQ-5D prediction	FEV*0.117 + 0.561	Normal 95% CI 0.087 to 0.147 95% CI 0.475 to 0.647	HSE ⁴³
Drugs cost prediction	FEV* -0.067 + 0.421	Normal 95% CI -0.095 to -0.039 95% CI 0.338 to 0.50	HSE ⁴³
Cost of CSM (per session)	£27.5	Uniform (£20–35)	Green Guide online ⁴⁷
Cost of massage for children (training cost: one-off + demonstration video)	£31.70	Uniform (£17–28 for training component)	Filey-therapist.co.uk ⁴⁸
Cost of massage for adults (per session)	£22.50	Uniform (£17–28)	Filey-therapist.co.uk ⁴⁸
Cost of physical therapy (per session)	£16.24	Uniform (£20–30 for 30 minutes of physical therapy)	BNF ⁴⁹ and Netten <i>et al.</i> (PSSRU) ⁵⁰
Hospitalisation cost for severe group (cost per year)	£208	Fixed	CIPFA ⁵¹

asthma for the different patient groups (based on overall asthma incidence and evidence of the proportion of asthma patients in each group from trial evidence), and on alternative assumptions of 5, 10 and 15 years for the expected lifetime of the technology. An analysis of the parameter EVPIs associated with groups of model inputs was also conducted.

Results

Cost-effectiveness

The results are presented below for each patient group.

Children treated in the community

The costs and QALYs generated from the model are shown in *Table 2*.

TABLE 2 Results for children treated in the community

Comparator	QALY	Cost	
CSM	0.059184	£230.24	Dominated
Massage	0.062868	£40.81	£11,012.93
Baseline	0.060045	£9.72	

CSM is dominated by no intervention and massage as it is associated with higher costs and lower QALYs. Massage is likely to be regarded as cost-effective, given recent decisions made in the NHS,⁵⁴ with an incremental cost per QALY gained of £11,012 compared with no intervention. The cost-effectiveness of massage is partly due to the low costs of administration in the community by parents. However, the cost-effectiveness of massage is uncertain and the probability that massage is

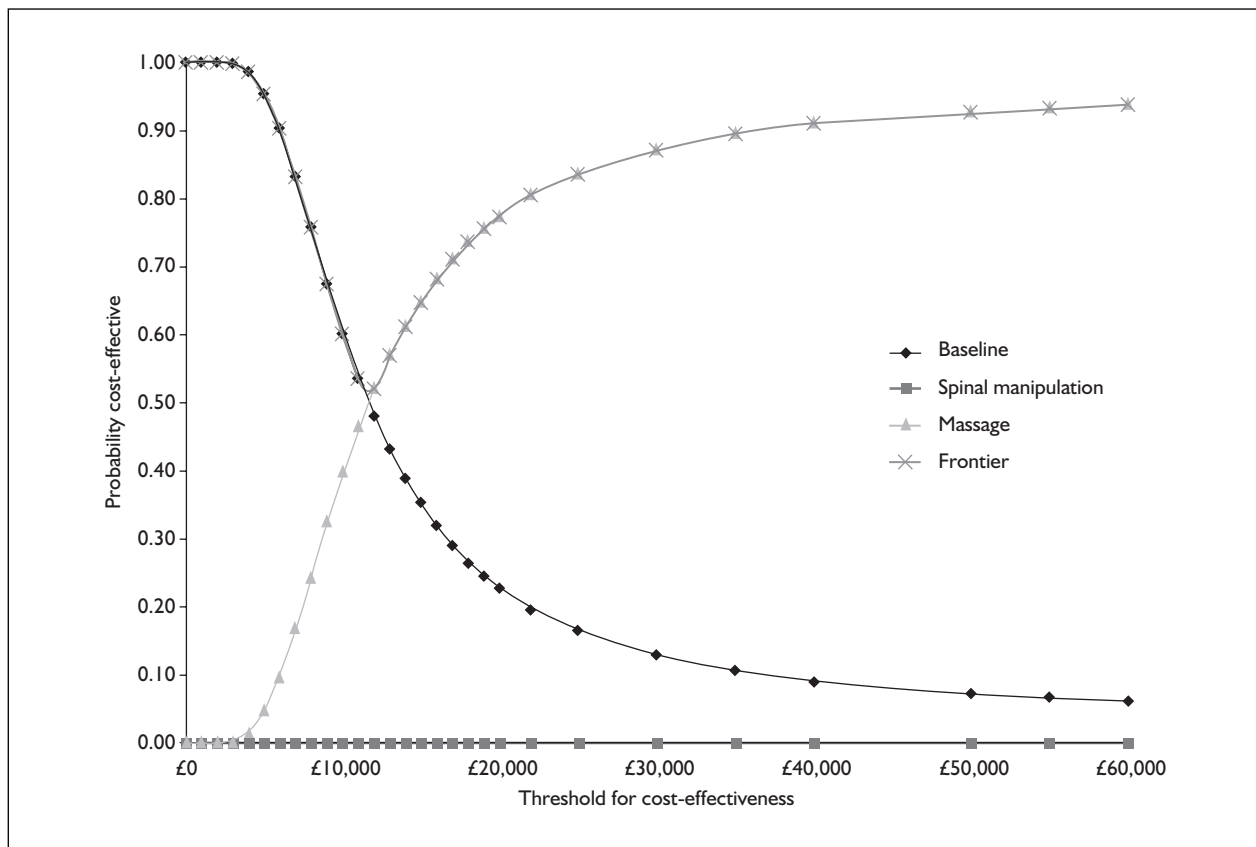


FIGURE 6 Cost-effectiveness acceptability curve (children treated in the community)

cost-effective at the threshold of £30,000 per QALY is 0.87. The decision uncertainty surrounding these interventions for children treated in the community is illustrated in *Figure 6*.

Adults treated in the community

The costs and QALYs generated from the model are shown in *Table 3*.

CSM is again dominated by no intervention and massage. However, for this patient group, massage is very unlikely to be regarded as cost-effective, with an incremental cost per QALY gained of over £200,000 compared with no intervention. This is due to the much higher cost of massage in adults, which is administered by physiotherapists as opposed to parents in the children subgroup. The probability that no intervention is cost-effective at

a threshold of £30,000 per QALY is 1, and remains very high over a range of cost-effectiveness threshold values.

Children treated in hospital

The costs and QALYs generated from the model for children treated in hospital are shown in *Table 4*.

Physical therapy can be regarded as cost-effective as it is associated with higher QALYs and lower costs than no intervention (owing to expected reductions in length of hospital stay). There is also little uncertainty associated with this decision. The probability that physical therapy is cost-effective is above 0.92 at a threshold value of £30,000 and remains high over a wide range of threshold values.

TABLE 3 Results for adults treated in the community

Comparator	QALY	Cost	
Massage	0.0769	£679.64	£201,891.37
CSM	0.072194	£227.32	Dominated
Baseline	0.073589	£6.61	

TABLE 4 Results for children treated in hospital

Comparator	QALY	Cost	
Physical therapy	0.004466	£586.52	
Baseline	0.004455	£813.73	Dominated

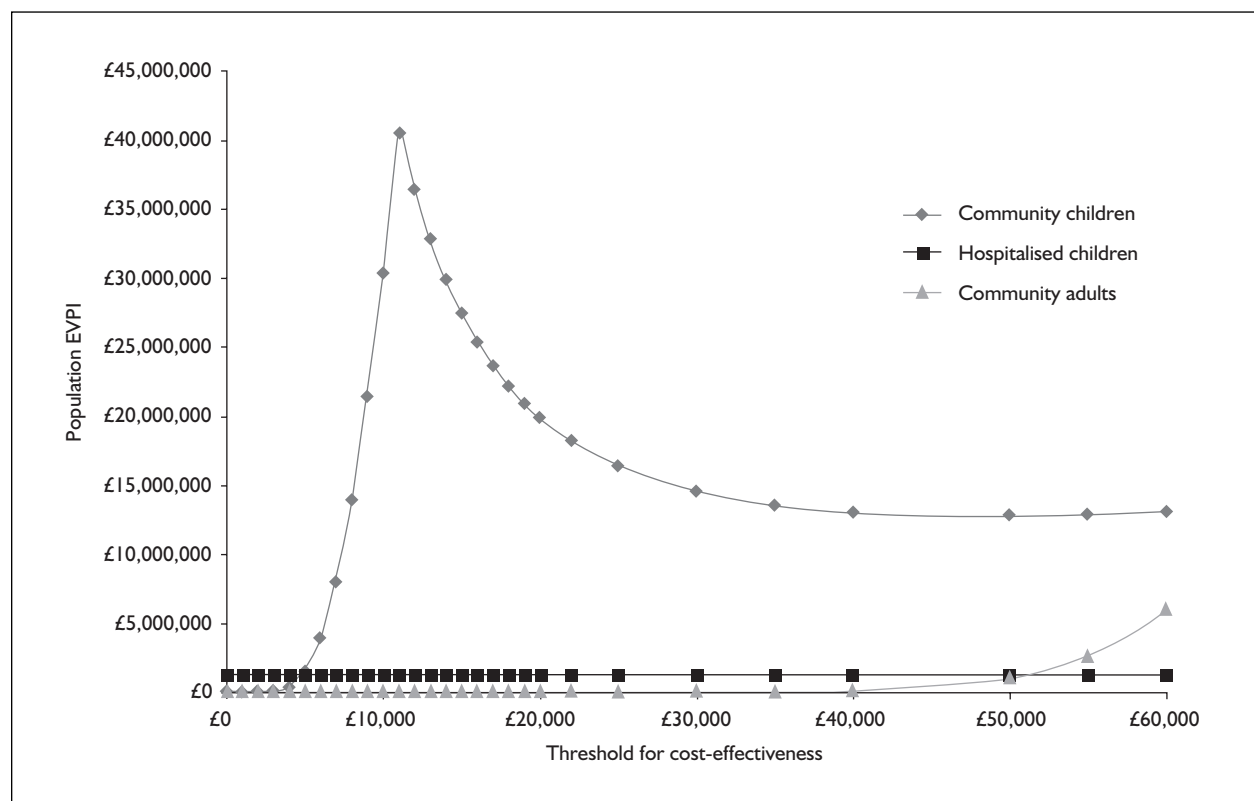


FIGURE 7 Population EVPIs

Expected value of perfect information

The population EVPI was calculated for the three groups by multiplying the episode EVPI by the cumulative incidence for the respective populations, assuming a 10-year technology lifetime in the first instance, but also calculating EVPI for 5- and 15-year lifetimes. The results are shown in *Figure 7*.

Adults treated in the community

Since the intervention is not cost-effective and there is little uncertainty surrounding this decision, the population EVPI is zero for a 5-, 10- and 15-year lifetime of the technology at a threshold for cost-effectiveness of £30,000 per QALY. At threshold values greater than £40,000 per QALY, the population EVPI becomes positive and is £1,029,063 at £50,000 per QALY.

Children treated in the community

Given the size of the population of children treated in the community and the fact that the decision uncertainty regarding which is the most cost-effective treatment is higher than in the other two populations, it is not surprising that the population EVPI for this group is the largest. At a threshold for cost-effectiveness of

£30,000 per QALY, the population EVPI for children treated in the community is above £14.5 million assuming a 10-year lifetime for the technology. The population EVPI for 5- and 15-year lifetimes is £9 and £18.5 million, respectively.

Children treated in hospital

At a threshold for cost-effectiveness of £30,000 per QALY, the population EVPI for children treated in hospital is £1.2 million assuming a 10-year lifetime for the technology. The population EVPI for 5- and 15-year lifetimes is £0.7 and £1.6 million, respectively. This is lower than the EVPI for children treated in the community owing to lower decision uncertainty (intervention appears more cost-effective for this patient group) and a smaller patient population.

EVPI for individual parameters

Adults treated in the community

As the population EVPI for the decision is zero at a threshold of £30,000, the EVPIs associated with each of the model inputs are also zero.

Children treated in the community

The EVPIs associated with the inputs of the model for children treated in the community are

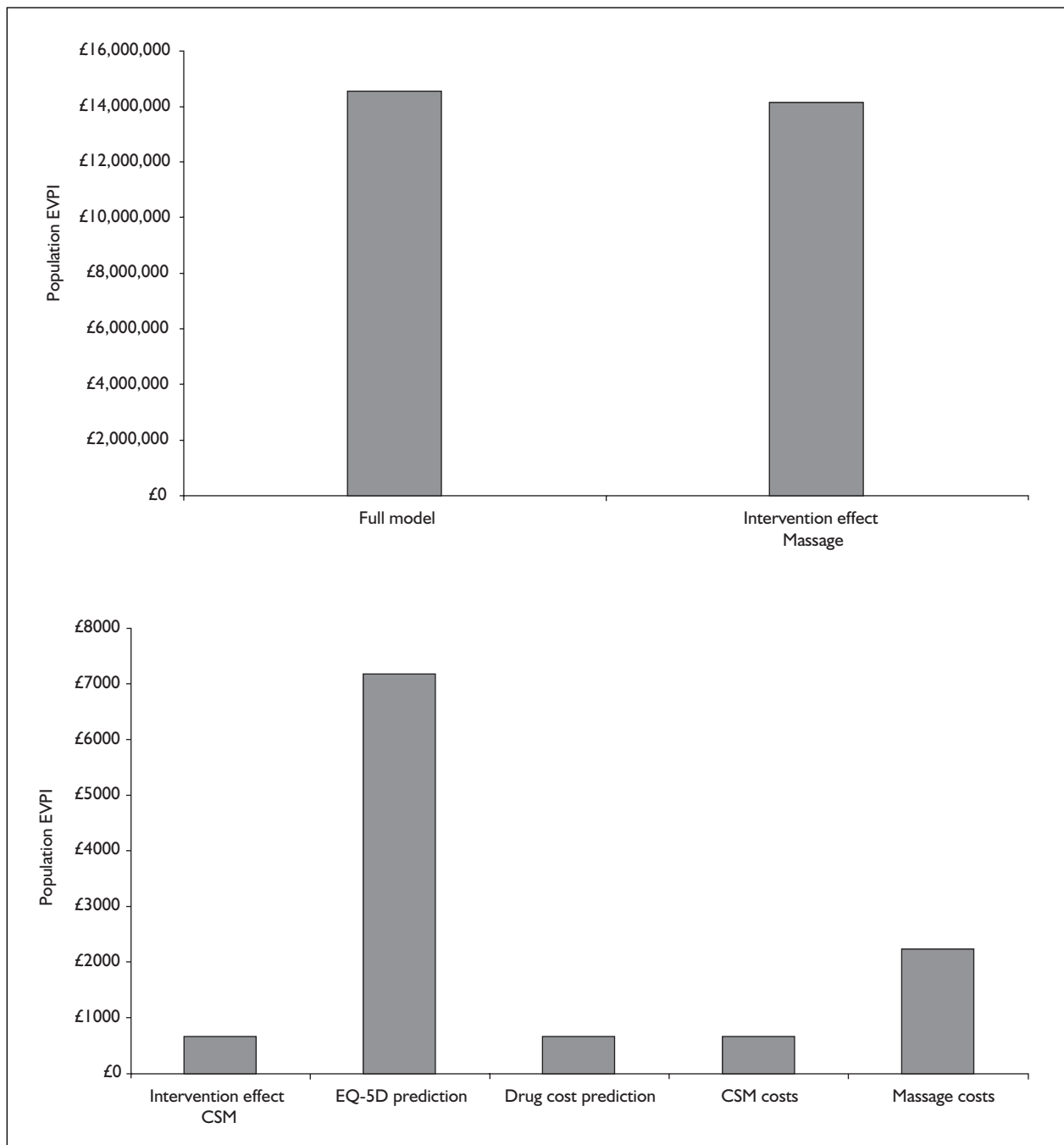


FIGURE 8 Partial EVPI (children treated in the community)

illustrated in *Figure 8* for a threshold of £30,000 per QALY and a 10-year lifetime for the technology. All model inputs have positive EVPIs, but the value of information associated with the effect of massage on FEV₁ is £14.2 million, which is substantially higher than any other model input and accounts for most of the decision EVPI. The EVPIs associated with the effect of CSM on FEV₁ are low because there is little uncertainty that CSM will not be cost-effective.

Children treated in hospital

The EVPIs associated with the inputs for the children treated in hospital model are shown in *Figure 9* for a threshold of £30,000 per QALY and a 10-year lifetime for the technology. The value of information associated with the effect of physical therapy on LOS is £1.2 million and accounts for almost all of the decision EVPI. This is because it is the evidence of reductions in hospital LOS, which largely determines the cost-effectiveness

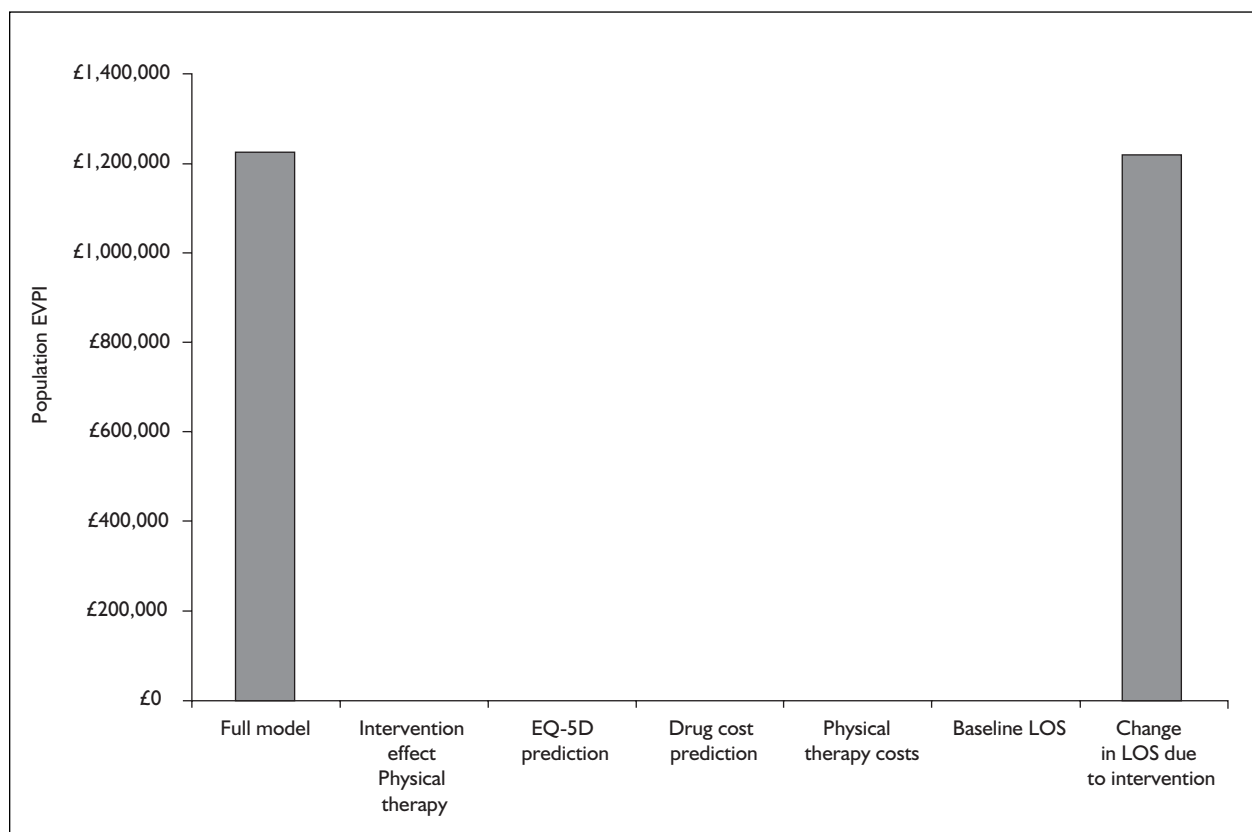


FIGURE 9 Partial EVPI (children treated in hospital)

of physical therapy. Other inputs individually have zero value of information associated with them.

Discussion and conclusions

Manual physiotherapy (massage or CSM) for adults treated in the community is unlikely to be cost-effective. Furthermore, there is very little decision uncertainty and the value of additional information is negligible. The costs of any proposed research in this patient group are likely to exceed the population EVPI over a range of plausible cost-effectiveness thresholds and additional research is unlikely to be cost-effective.

Massage for children treated in the community may be cost-effective, but CSM is unlikely to be cost-effective. The value of information is substantial (£14.5 million) at a cost-effectiveness threshold of £30,000, and is likely to exceed the costs of additional investigation. This suggests that further research will be potentially cost-effective in this patient group. The EVPI associated with the model inputs suggests that any further research would require experimental design and should focus on the effect of massage on lung function.

However, additional investigation of CSM is unlikely to be worthwhile and should be excluded as a comparator in proposed trial designs. It is possible that, in practice, lower parental compliance with training in massage will reduce the expected benefits and increase the expected cost of massage intervention. This would make the intervention less cost-effective and increase the decision EVPI.

Physical therapy for children treated in hospital may be cost-effective. The value of information is £1.2 million, at a cost-effectiveness threshold of £30,000 and, if the cost of additional investigation is lower than the population EVPI, then further research may be worthwhile. The EVPI associated with the model inputs suggests that if further research is conducted it should focus on the effect of physical therapy on hospital LOS. This research would require experimental design, as the intervention effect on LOS will be vulnerable to selection bias. In addition, access to patient-level data would enable the relationship between effect on lung function and LOS to be established. If lung function and LOS are negatively correlated (as would be expected), then the cost-effectiveness of physical therapy may be overestimated and the EVPI underestimated.

The analysis of this research topic has identified those patient groups and settings where further research would be most valuable (children in the community and in hospital). It has been able to identify the type of research that may be worthwhile (in both cases experimental design is required) and which comparators (CSM children in the community should be excluded) and end-point (LOS for children in hospital) should be

included in any proposed research designs. This analysis, however, is limited to considering the link between FEV₁ and EQ-5D. It is recognised that other measures of respiratory function may be important. Therefore, value of information surrounding the effect of interventions on FEV₁ may be more broadly interpreted as the value of more evidence about the effect of respiratory function, which could be linked to quality of life.

Chapter 4

Assessing the cost-effectiveness of manual chest physiotherapy techniques for adults with chronic obstructive pulmonary disease

Background

Topic origin

Manual chest physiotherapy for respiratory diseases was a topic identified as a potential priority by the Therapeutic Procedures Panel. DA-VOI was to be undertaken concurrently with the production of the vignette. The topic did not meet any of the selection criteria for case studies (availability of earlier secondary research, availability of a completed NICE Technology Assessment Report and an existing high-quality decision model in the literature) and given the paucity of literature, there was a danger that the quality of the modelling that would be possible for this topic may not be sufficient for adequate consideration by the panel. After discussion with the NCCHTA, however, a decision was made to proceed with this case study.

Policy background

COPD, which includes both chronic bronchitis and emphysema, is one of the most common respiratory conditions of adults in the developed world. There are few data on the prevalence of COPD in the UK. The General Household Survey⁵⁵ records self-reported diagnoses of chronic bronchitis and emphysema. This showed a prevalence of 0.9% in men and 0.7% in women in 2001.

There is no cure for COPD, although some treatments exist that can provide symptom relief and help to slow the progression of the disease. Although pharmaceutical interventions provide the mainstay of therapy, bronchial hygiene physical therapy is also used for a range of respiratory disorders, including COPD. The techniques used include postural drainage, chest percussion, vibration, chest shaking, directed coughing and autogenic drainage. These techniques aim to improve the patients' pulmonary condition by mobilising secretions from the lungs. Despite controversy in the literature regarding its efficacy, it remains in use in a variety of clinical settings.⁵⁶

A Cochrane review⁵⁶ was recently undertaken to assess the effects of bronchial hygiene physical therapy in people with COPD and bronchiectasis. Manual therapy, such as postural drainage, chest percussion, vibration, chest shaking, directed coughing or forced exhalation technique, was compared with no intervention, placebo, coughing or mechanical interventions. Outcomes considered included pulmonary function variables such as FEV₁, morbidity, mortality and adverse outcomes such as respiratory distress.

The review found that the trials identified were small and not generally of high quality. In addition, the evidence could not be synthesised as trials addressed different patient groups and outcomes. Although, in most comparisons, manual therapy had no significant effect on pulmonary function, the review concluded that there was insufficient evidence either to support or to refute the use of manual chest physiotherapy techniques in COPD patients.

Decision problem

The analysis reported here assessed the cost-effectiveness of, and potential value of future research for, manual chest physiotherapy interventions compared with no intervention in adults with COPD. The specific interventions under investigation were autogenic drainage, active breathing, the use of a heat lamp and chest percussion with drainage.

Methods

Description of model

Based on the trial evidence,^{57,58} four different techniques for manual therapy were evaluated in comparison with a common baseline: autogenic drainage, active cycle of breathing, chest percussion with drainage, and use of a heat lamp. The effect of the alternative strategies was evaluated in adults treated in the community.

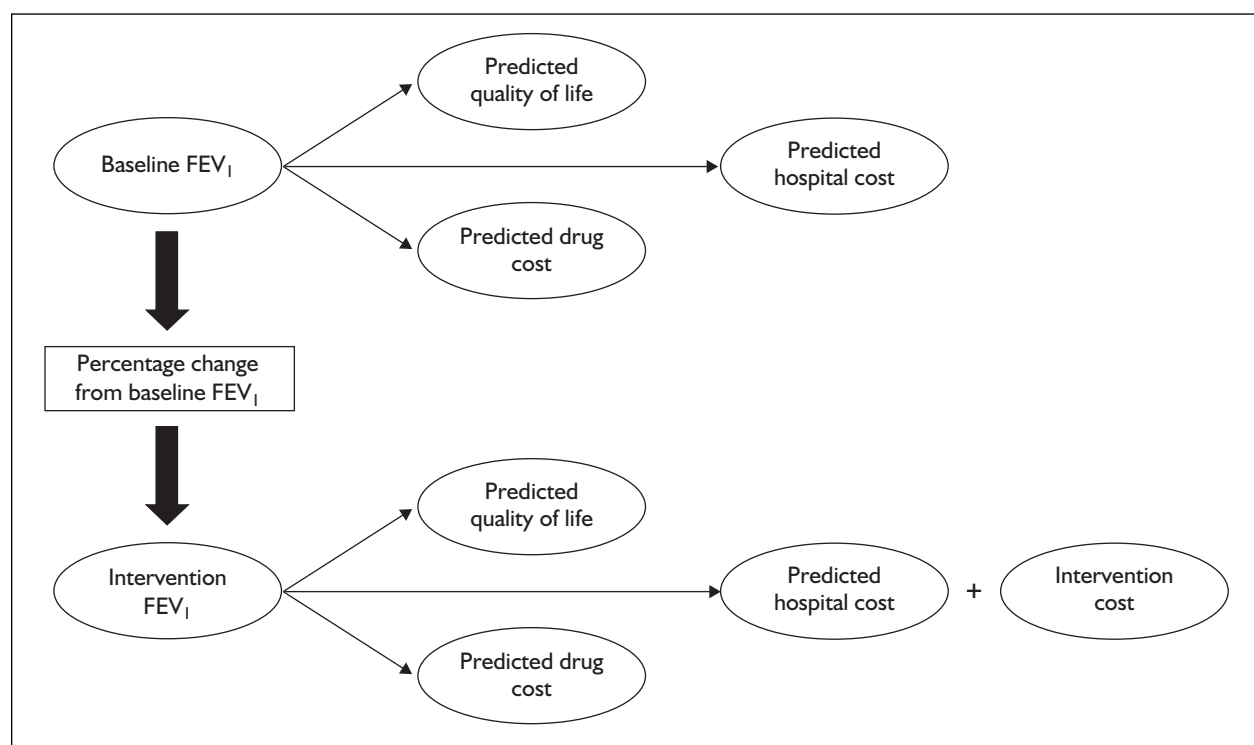


FIGURE 10 Model structure

The structure of the decision model is illustrated in *Figure 10* and is similar to that used to model the cost-effectiveness of manual therapy in asthma (reported in Chapter 3). The effect of each intervention is modelled in terms of changes in lung function measured by FEV₁, as this was the only outcome reported in the trials that could be linked to quality of life using EQ-5D data reported in the HSE, 1996. The proportional change from the baseline FEV₁ (FEV₁ with no intervention for each patient group) was based on reported trial results.

EQ-5D⁴¹ quality of life scores (in terms of 0 to 1 'utilities'),⁴⁶ daily medication costs and costs of inpatient admissions were predicted contingent on FEV₁ values using a series of equations derived using a Tobit regression model⁴² using data from the 1996 HSE.⁴³ Additional explanatory variables such as age and gender were omitted from the prediction equations owing to a lack of comparable data from the trials and low explanatory power. These equations are shown below with standard errors in parentheses:

$$\text{EQ-5D} = \text{FEV} * 0.033651 (0.0207) + 0.5374052 (0.0465)$$

$$\text{Daily drug cost} = \text{FEV} * -0.02149 (0.0435) + 0.3022287 (0.0834)$$

$$\text{Hospital costs} = \text{FEV} * -31.33919 (11.55) + 123.1737 (25.32)$$

Predicted EQ-5D scores were used to calculate expected QALYs for each intervention and the baseline (no manual therapy) using under-the-curve methods.⁴⁴ The correlation between the constant and β coefficients in both equations was based on the covariance matrix. The total cost of physical therapy consists of the cost of medications, intervention costs and inpatient hospitalisation.

The model assumes that treatment effect and costs are only sustained while treatment continues. After this period FEV₁ returns to the preintervention level. The time horizon of the model is 30 days, which is consistent with the follow-up considered in the trials. An NHS perspective was used for the analysis.

The evidence

Effectiveness

A search was conducted to update the results produced for the Cochrane review and identify relevant effectiveness evidence.⁵⁶ The Cochrane search strategy developed previously was used, and can be seen in Appendix 4. One extra trial⁵⁸ was identified in the update searches, in addition to the seven trials^{57,59-64} that evaluated the use of chest physiotherapy in patients with COPD from the Cochrane review. The quality of all the trials was moderate to poor.

TABLE 5 Sources of data used in the COPD model

Parameter	Value	Distribution	Source
No intervention (baseline FEV ₁)	1.202	Log-normal 95% CI 0.54 to 1.85	Savci <i>et al.</i> ⁵⁸
% Change in FEV ₁ using autogenic drainage on	31%	Normal SD 0.04	Savci <i>et al.</i> ⁵⁸
% Change in FEV ₁ using active cycle of breathing	7%	Normal SD 0.04	Savci <i>et al.</i> ⁵⁸
% Change in FEV ₁ using chest percussion and drainage	4%	Normal SD 0.02	May and Munt ⁵⁷
% Change in FEV ₁ using heat lamp	3%	Normal SD 0.01	May and Munt ⁵⁷
EQ-5D prediction	FEV*0.03+0.54	Normal 95% CI -0.01 to 0.07 95% CI 0.45 to 0.63	HSE ⁴³
Medication costs	FEV*0.02+0.30	Normal 95% CI -0.10 to 0.05 95% CI 0.16 to 0.44	HSE ⁴³
Hospitalisations prediction	FEV*-31.34+123.17	Normal 95% CI -62.13 to -0.55 95% CI 55.87 to 190.48	HSE ⁴³
Intervention cost	£220	Fixed	PSSRU ⁵⁰

The outcomes used in the trials were varied and include sputum weight, sputum production, radioaerosol clearance from the lung and peripheral lung, radioaerosol retention in the lung, arterial oxygen partial pressure (PaO_2) and lung function measures such as FEV₁, peak expiratory flow rate (PEFR) and forced vital capacity (FVC). Beneficial effects have been confined to sputum production and radioaerosol clearance outcomes, but there is no evidence to relate these outcomes to quality of life. The only end-point that could be related to quality of life was FEV₁. This was through the equations detailed above, estimated to predict the relationship between FEV₁ and EQ-5D using the 1996 HSE.⁴³ Without patient-level data, it was not possible to link FEV₁ with other outcomes, such as sputum production.

Two trials reported FEV₁ as an outcome. Savci and colleagues⁵⁸ compared autogenic drainage and the active cycle of breathing in adult male patients with stable clinical COPD. May and Munt⁵⁷ compared the physiological effects of chest percussion and drainage with heat-lamp therapy in adults with stable chronic bronchitis. Details of the trials included in the analysis are reported in Appendix 5.

Baseline FEV₁ in the model was based on a pooled estimate from the two arms (before intervention) of the Savci trial⁵⁸ with a distribution based on the 95% CI of the pooled data, 1.202 (0.547 to 1.858). The May and Munt trial⁵⁷ was not used to obtain a baseline estimate of effect as the paper reported medians as opposed to mean baseline FEV₁ values. The proportional change from baseline, as reported in both trials, is used to obtain the treatment effect of each intervention, and distributions were assigned based on the standard errors reported in the trials: autogenic drainage = 0.308 (0.044), active cycle of breathing = 0.074 (0.041), chest percussion with drainage = 0.044 (0.024) and heat lamp = 0.034 (0.012).

Distributions were also assigned to the coefficients of the equations (derived from the 1996 HSE), which predict quality of life scores, daily medication costs and hospitalisations, based on estimated standard errors. Correlations between the coefficients of the prediction equation were also accounted for. Each intervention was assigned a fixed cost, which was derived from a standard NHS cost estimate for a hospital-based physiotherapist.⁵⁰

The distributions and sources of data used in the model are summarised in Table 5.

TABLE 6 Results from the COPD model

Strategy	QALYs	Costs	
Heat lamp	0.047134	£317.90	Dominated
Chest percussion and drainage	0.047163	£316.85	Dominated
Active cycle of breathing	0.047249	£315.84	Dominated
Autogenic drainage	0.047934	£307.98	£232,673
No manual therapy	0.047033	£98.35	

Incidence and prevalence data

In addition, to calculate the population EVPI values, the incidence and prevalence of COPD in England and Wales were required. These were calculated using data collected in a report published by the Scottish parliament on lung disease in Scotland,⁶⁵ applied to England and Wales population figures.⁶⁶

Analysis

Similar methods of probabilistic analysis and EVPI were used for this model as for those in the asthma model detailed in Chapter 3.

Results**Cost-effectiveness**

The costs and QALYs generated from the model are shown in *Table 6*.

Manual chest physiotherapy techniques are unlikely to be regarded as cost-effective compared with no physiotherapy. The incremental cost per additional QALY for autogenic drainage compared with no therapy is £232,673. All other interventions are dominated by autogenic drainage. Moreover, this decision is not uncertain with the probability that no chest physiotherapy is cost-effective at a threshold of £30,000 being 1, falling to 0.9963 at a threshold of £60,000. The decision uncertainty over a range of threshold values is illustrated in the CEAC in *Figure 11*.

Expected value of perfect information

The population EVPI for adults with COPD is illustrated in *Figure 12*. At a cost-effectiveness threshold of £30,000, the population EVPI is zero for a 5-, 10- and 15-year lifetime for the technology. At cost-effectiveness thresholds greater than £40,000 per QALY, the population EVPI becomes positive (£205,556 at a threshold of £60,000 per QALY and a 10-year lifetime for the technology).

EVPI for individual parameters

As the population EVPI for the decision is zero at a threshold of £30,000, the EVPIs for each of the

model inputs are also zero. It is only at very high cost-effectiveness thresholds that a small degree of decision uncertainty results in substantial population EVPI (£6.1 million at a threshold of £100,000 per QALY, with a 10-year lifetime for the technology). In this case, there are also positive EVPIs associated with the proportional change in FEV₁ from autogenic drainage, breathing, the use of a heat lamp and chest percussion with drainage. However, the highest EVPI is associated with the equation predicting quality of life from FEV₁ (£5.2 million). Other inputs, such as the equations predicting hospitalisations and medications from FEV₁, also have positive EVPIs.

Discussion and conclusions

Manual chest physiotherapy for adults with COPD is very unlikely to be considered cost-effective at conventional threshold values of cost-effectiveness. Furthermore, there is very little decision uncertainty, and the value of additional information is negligible at these thresholds. The costs of proposed research are likely to exceed the population EVPI over a range of plausible cost-effectiveness thresholds and additional research is unlikely to be cost-effective.

In addition, there are some reasons why the model may overestimate the cost-effectiveness of the interventions and the population EVPI. First, FEV outcomes may be overestimated owing to uncontrolled placebo effects in the trials. Second, the costs associated with physiotherapy equipment have been excluded here. Third, the calculation of population EVPIs is based on all-age average incidence rates applied to the total population of England and Wales, which may overestimate the population of current and future adult COPD patients.

This analysis is based on the use of manual physiotherapy for COPD patients in the community setting. The only trials reporting FEV₁, which could be linked to quality of life and resource use (including subsequent

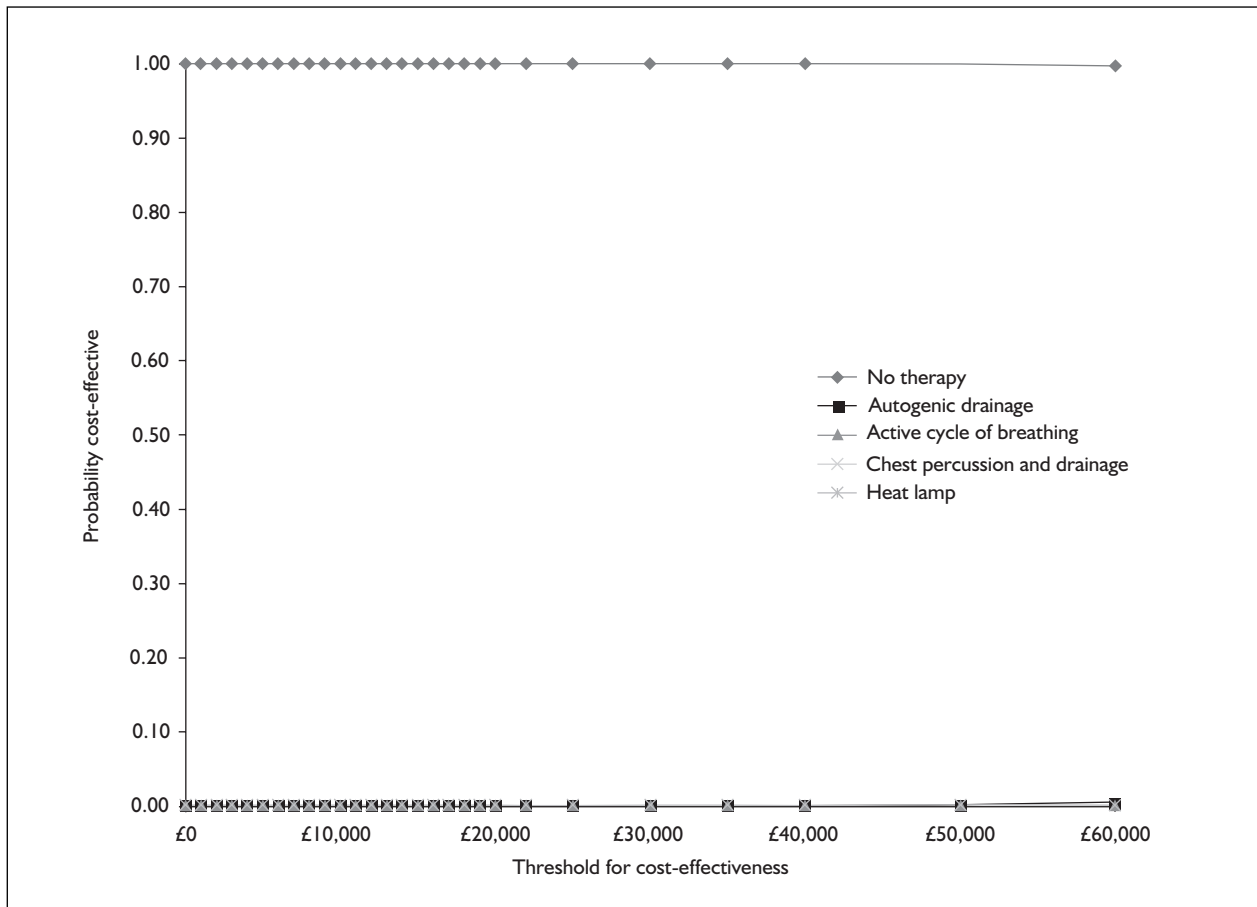


FIGURE 11 Cost-effectiveness acceptability curve

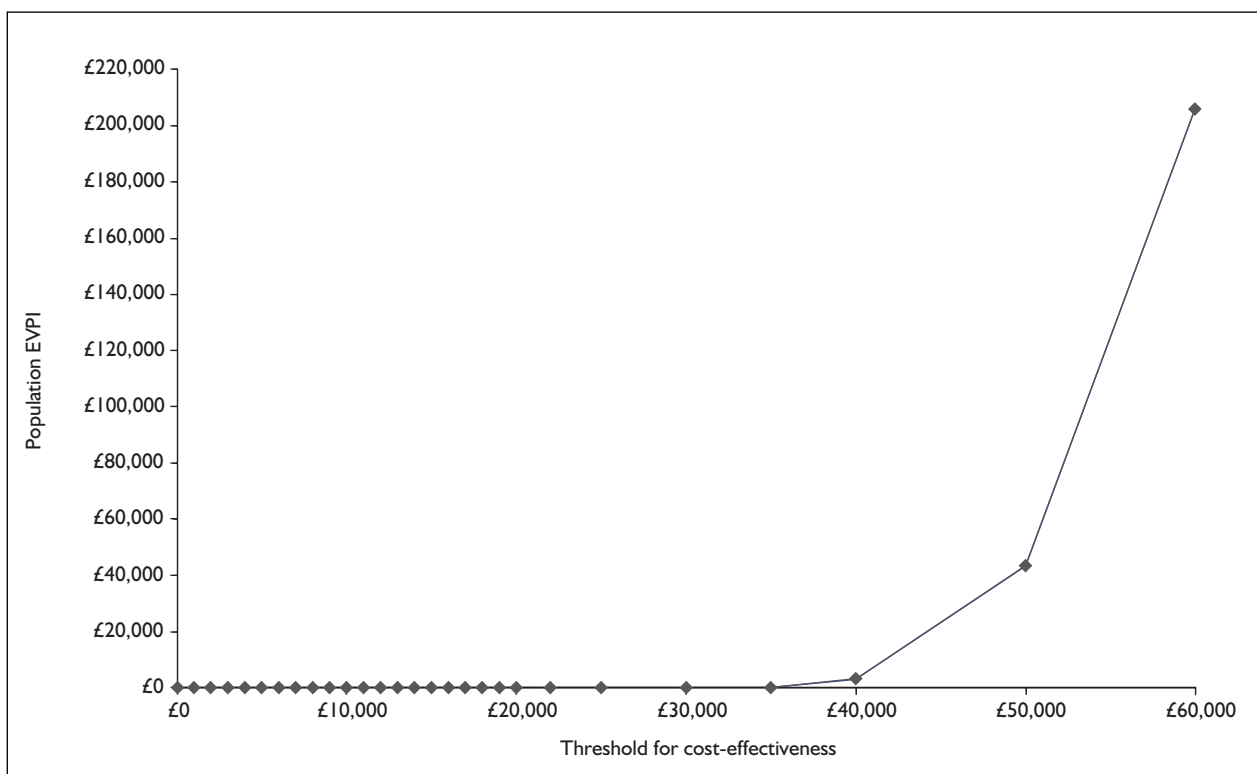


FIGURE 12 Population EVPI

hospitalisations), were for community-based interventions. Therefore, there is no evidence of effect in a hospital setting that can be linked to quality of life or resource use. Some of the trials that reported other end-points were conducted in the hospital setting. However, the results of these trials did not provide any evidence that the interventions are likely to be more effective in the hospital setting. In addition, none of these trials reported effects on LOS or other end-points that

can be linked to a reduction in resource use. Although not modelled directly, the balance of the very limited evidence suggests that these interventions are unlikely to be cost-effective in the hospital setting and the value for information surrounding this may also be limited. However, if further research is conducted in this setting, then end-points that can be linked directly to quality of life and resource use (particularly LOS) should be included to establish cost-effectiveness.

Chapter 5

Is there an effective method for screening for age-related macular degeneration?

Background

Topic origin

Screening for AMD was identified as a priority for research in a recently completed NICE appraisal⁶⁷ of the use of PDT in AMD. The topic met the first two selection criteria (secondary research and a completed NICE Technology Assessment Report) and although no model of screening for AMD was available in the literature a high-quality model of PDT treatment was available, which would provide an important component of the screening model.

Policy background

AMD is a degenerative condition of the macula. It is one of the most common causes of vision loss in people over 50. The disease varies in severity, from a slight loss in vision to near blindness. AMD is classified as either wet (neovascular) or dry (non-neovascular). Neovascular AMD progresses more rapidly and causes the more severe vision loss. About 10% of patients who suffer from macular degeneration have wet AMD. If one eye develops a neovascular membrane, the other eye is at moderate risk of having the same problem. Neovascular AMD is further defined by its location in the choroidal neovascular vessels (subfoveal, juxtafoveal or extrafoveal) and by its pattern of leakage (classic, occult, mixed or recurrent).⁶⁸

Treatments for certain types of AMD have developed over the past few years and include confluent argon laser photocoagulation, verteporfin photodynamic therapy, radiotherapy and transpupillary thermotherapy.⁶⁸ Photodynamic therapy for AMD has recently been appraised by NICE.⁶⁷ The evidence from the Assessment Report, and the provisional guidance issued by NICE, indicated that PDT will only be potentially cost-effective for the treatment of AMD in the better seeing eye (after first eye involvement) and only for certain types of AMD (neovascular, predominantly classic, subfoveal). AMD can progress rapidly (declining visual acuity) and is a significant cause of blindness. Early PDT can halt or slow the decline in visual acuity. Earlier treatment with PDT at better starting visual

acuity is more cost-effective, and treatment is not recommended for starting visual acuities lower than 20/100.

Given that treatment with PDT is more effective the earlier it is initiated in the course of the disease, there is a prima facie case that screening would be cost-effective by identifying patients with AMD before their visual acuity declines. A self-screening test of central vision distortion, called the Amsler grid,⁶⁹ is available and it has been suggested that this could be used as a basis of screening.

Decision problem

Following the conclusions of the Assessment Report undertaken for NICE⁶⁷ and the provisional guidance regarding the use of PDT, this study focused on the use of weekly self-screening following first eye involvement with neovascular AMD. This self-screening strategy is compared with two alternatives: no screening, but diagnosis and treatment of eligible AMD following self-referral (due to declining visual acuity) to an ophthalmologist (this strategy is consistent with provisional NICE guidance); and a strategy of no screening and no PDT. The analysis reported here assessed the cost-effectiveness of, and potential value of future research for, these alternative strategies.

Methods

Description of the model

The structure of the decision model is illustrated in *Figure 13*. A Markov process⁷⁰ is used to model the incidence of second eye neovascular AMD over 10 years and the associated decline in visual acuity following undiagnosed second eye involvement.

Patients enter the model with neovascular AMD previously diagnosed in the first eye. Two alternative starting visual acuities are modelled, 20/40 or 20/80. The implication of this is that individuals with the worst vision would generally receive PDT or no PDT at a lower visual acuity. Each week patients can decide to self-screen

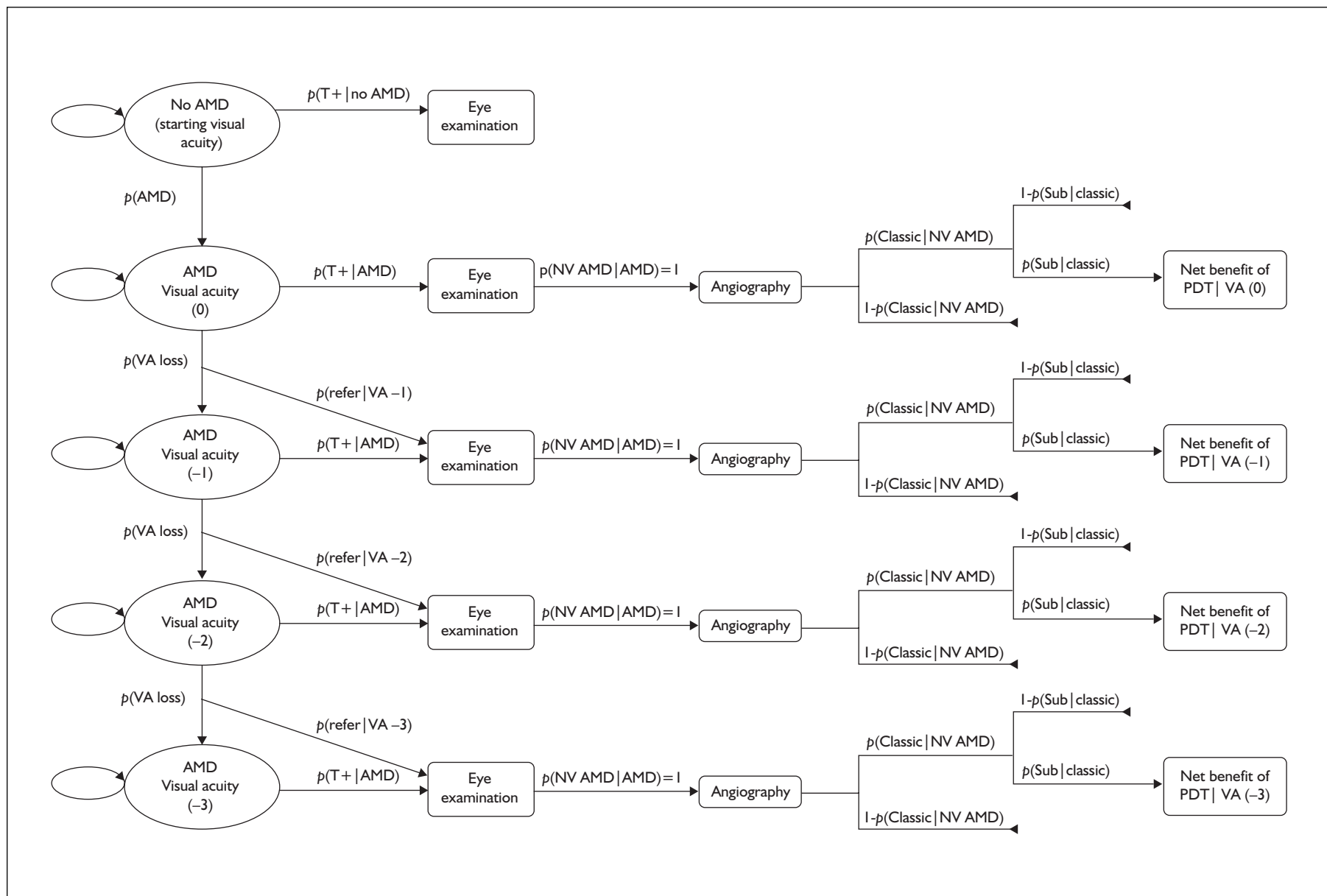


FIGURE 13 Model structure for AMD self-screening

(comply) using the Amsler grid, which is an A4 sheet of paper containing a series of lines, which appear distorted if a change in vision has occurred.

Patients with positive screen results (self-diagnosed) will self-refer for a full eye examination by an ophthalmologist. Patients may also self-refer owing to declining visual acuity, measured as a loss of one or more lines. At a loss of four or more lines, all patients will have self-referred to the ophthalmologist (in the absence of data, expert judgement was used to specify the probability that patients self-refer on loss of visual acuity). The full eye examination will identify patients with neovascular AMD in the second eye (i.e. false positives are identified). Angiography is then undertaken in those with confirmed neovascular AMD to identify the type of neovascular disease that is present, and thus determine whether the patient is eligible for PDT. Since angiography is used to identify and monitor AMD in the clinical trials of PDT, it is taken to be the gold-standard test in this model.

Patients with diagnosed AMD that is eligible for PDT will then either have PDT (screen plus PDT and no screen plus PDT strategy) or not have PDT (no screen + no PDT strategy). The expected costs and QALYs over 2 years following diagnosis, which are associated with the use or non-use of PDT, are then assigned.⁷¹ The expected quality of life with PDT depends on the visual acuity at diagnosis, where patients with better visual acuities will experience better quality of life. The costs of PDT are constant throughout the visual acuity groups.⁷¹

A 10-year time horizon for incidence, development and diagnosis was used in the model as, during this period, almost all patients developed second eye disease (96%), and this disease was diagnosed in most patients in both screen and no-screen groups (92%). In other words, all patients with second eye involvement will be diagnosed at some point. The question is when, and at what visual acuity, this happens. Given the decision problem to be addressed, an NHS perspective was used for the analysis. Health benefits are expressed in terms of QALYs.

The evidence

The sources of all inputs into the model can be seen in *Table 7*.

Clinical events

The incidence of second eye neovascular AMD,⁷² the eligibility for PDT (subtypes of AMD),⁷⁵ the sensitivity and specificity of the Amsler grid

screen⁷³ and compliance with self-screening⁷⁴ were all based on observational studies. Beta distributions were assigned to reflect the amount of evidence available for each of these parameters using measures of variance reported in the studies. Although two trials of PDT for AMD are available, only the (TAP) trial included predominantly classic AMD. The decline in visual acuity for undiagnosed second eye involvement was based on the 2-year results of the control arm of the TAP trial of PDT⁶⁷ as reported in the NICE Assessment Report, with beta distributions assigned to these transition probabilities.

No evidence was available regarding the probability that patients will self-refer following each decline in visual acuity. Therefore, expert judgements from a primary care physician with specialist research interest in AMD were used, with beta distributions reflecting the additional uncertainty about a range of possible values.

Costs and QALYs

The expected costs and QALYs (over 2 years following diagnosis) associated with the use and non-use of PDT at the different visual acuity levels (20/40, 20/50, 20/64, 20/80, 20/100, 20/126) were taken from the output of a cost-effectiveness model of PDT developed as part of the NICE appraisal of PDT.⁷¹ The authors used a Markov model to estimate the costs and outcomes of PDT with verteporfin using patient-level data taken from the TAP trial.⁷⁶ Two-year (within-trial estimate) and 5-year periods were used to assess cost and outcomes. Time-trade-off methods were used by Brown and colleagues⁷⁷ to elicit utilities for various visual acuity levels in the model, and utility decrements from adverse events were estimated through the expert panel.⁷⁷ Gamma distributions were assigned to expected QALY gains on PDT using the reported means and variances taken from the simulated model output. Costs used in the model were taken from Meads and colleagues⁶⁷ and the model output suggested that costs were constant across visual acuity states.

The costs of ophthalmologist screening and angiography (diagnosis) were based on the NICE Assessment Report.⁶⁷ If self-administered, the costs of self-screening are zero (given that the Amsler grid only constitutes an A4 sheet of paper).

Mortality

All-cause mortality was also incorporated into the model (for a male and female population aged

TABLE 7 AMD model data sources

Parameters	Value	Distribution	Source
Incidence of second eye neovascular AMD	Year 1 = 0.00198	Beta $\alpha = 9, \beta = 95$	Gregor <i>et al.</i> ⁷²
	Year 2 = 0.00404	$\alpha = 18, \beta = 56$	
	Year 3 = 0.00685	$\alpha = 17, \beta = 36$	
	Year 4 = 0.0124	$\alpha = 11, \beta = 12$	
	Year 5 = 0.0114	$\alpha = 5, \beta = 6$	
Progression of visual acuity with second eye involvement	VA0 to VA1 = 0.014	Beta $\alpha = 2.93, \beta = 204.06$	Meads <i>et al.</i> ⁶⁷
	VA1 to VA2 = 0.062	$\alpha = 12.54, \beta = 189.16$	
	VA2 to VA3 = 0.062	$\alpha = 12.44, \beta = 187.70$	
	VA3 to VA4 = 0.060	$\alpha = 11.93, \beta = 186.19$	
Accuracy of Amsler grid	Sensitivity 0.59 Specificity 0.04	Beta $\alpha = 65.65, \beta = 44.35$ $\alpha = 5.28, \beta = 104.72$	Schuchard ⁷³
Compliance with self-screening	0.55	Beta $\alpha = 49, \beta = 40$	Fine <i>et al.</i> ⁷⁴
Eligibility for PDT (AMD subgroups)	0.56	Beta $\alpha = 17, \beta = 829$	Margherio <i>et al.</i> ⁷⁵
Self-referral on decline in visual acuity	VA1 = 0.2	Beta $\alpha = 2, \beta = 8$	Clinical judgement
	VA2 = 0.6	$\alpha = 6, \beta = 4$	
	VA3 = 0.8	$\alpha = 8, \beta = 2$	
	VA4 = 1	Constant	
QALYs with PDT	VA0 = 2.34	Gamma $\alpha = 193.58, \beta = 0.012$	Smith <i>et al.</i> ⁷¹
	VA1 = 2.26	$\alpha = 218.58, \beta = 0.010$	
	VA2 = 2.12	$\alpha = 406.31, \beta = 0.005$	
	VA3 = 2.10	$\alpha = 404.02, \beta = 0.005$	
	VA4 = 2.	$\alpha = 370.49, \beta = 0.005$	
QALYs without PDT	VA0 = 2.17	Gamma $\alpha = 217.67, \beta = 0.010$	Smith <i>et al.</i> ⁷¹
	VA1 = 2.12	$\alpha = 178.15, \beta = 0.011$	
	VA2 = 2.03	$\alpha = 287.43, \beta = 0.007$	
	VA3 = 2.01	$\alpha = 286.02, \beta = 0.007$	
	VA4 = 1.99	$\alpha = 287.30, \beta = 0.006$	
Costs of PDT	£6475.35	Constant	Smith <i>et al.</i> ⁷¹
Costs of diagnosis and screen	£55.88 + £112 + £108	Constant	Meads <i>et al.</i> ⁶⁷ , CIPFA ⁵¹

55–64 years) based on UK life tables.⁶⁶ Advice about model structure and sources of evidence was taken from clinical experts.

Incidence and prevalence

For expected value of information measures, estimates of the size of the current and future patient population relevant to the decision problem were based on the incidence of first eye AMD taken from the NICE Assessment Report.⁶⁷

Analysis

Similar methods of probabilistic analysis and expected value of perfect information were used for this model as for the asthma model detailed in Chapter 3.

Results

Costs

Table 8 shows the costs associated with each of the three strategies. As expected, the screen and treatment option has the highest costs for both 20/40 and 20/80 starting visual acuities, £3688 and £3685 respectively. The no-screen and no-treatment strategy is associated with the lowest costs for both starting visual acuities.

Outcomes

Treatment with PDT is associated with additional QALYs. Therefore, the two strategies that involve treatment have higher QALYs than the no-treatment strategy. However, there are large

TABLE 8 Results from the AMD model

Strategy	QALYs	Costs	
<i>Starting visual acuity = 20/40</i>			
Screen and treat	1.2253	£3688	£12,740
No screen and treat	0.9904	£2662	E dominated ^a
No screen and no treatment	0.9435	£98	
<i>Starting visual acuity = 20/80</i>			
Screen and treat	1.0973	£3685	£17,881
No screen and treat	0.9296	£2660	E dominated
No screen and no treatment	0.8967	£98	

^a E dominated is subject to extended dominance.⁵²

differences between the numbers of QALYs gained in the screen plus treat and no-screen plus treat strategies. This is because the screening allows patients to be diagnosed at a better visual acuity level (i.e. before it has declined significantly), and those higher visual acuity groups are associated with better outcomes (QALYs).

Cost-effectiveness

The results for both 20/40 and 20/80 starting visual acuity patients are shown in *Table 8*. Cost-effectiveness and decision uncertainty are extremely similar for both males and females. Hence, only the results for males are reported here.

For patients with a starting visual acuity of 20/40, screening can be regarded as cost-effective compared with no treatment, with an incremental cost per additional QALY of £12,740. The strategy of no screen but treatment on diagnosis is not cost-effective compared with no treatment (incremental cost per additional QALY equals £54,670), and is subject to extended dominance.⁵²

The cost-effectiveness of screening is, however, uncertain and this is shown in the cost-acceptability curve in *Figure 14*. The probability that screening is cost-effective with a threshold for cost-effectiveness of £30,000 is 0.866.

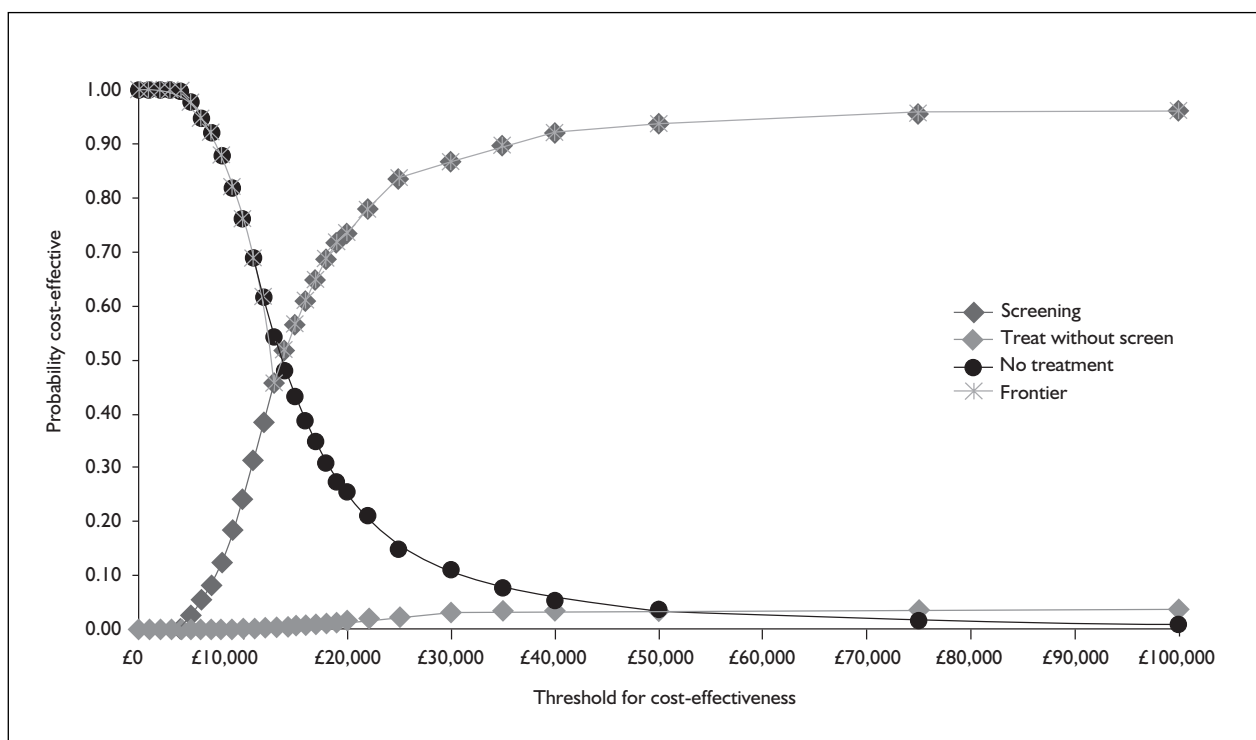


FIGURE 14 Cost acceptability curve for starting visual acuity of 20/40

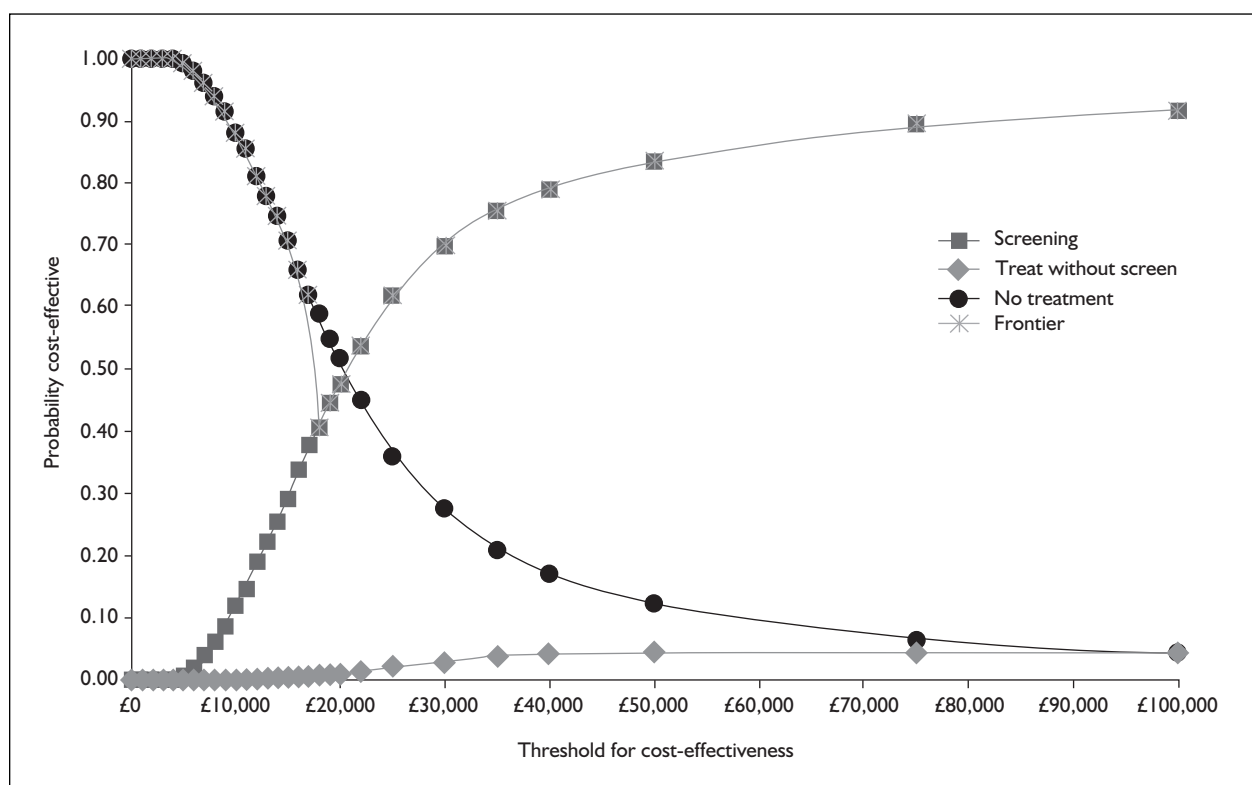


FIGURE 15 Cost acceptability curve for starting visual acuity of 20/80

For patients with a lower starting visual acuity of 20/80, screening is less likely to be considered cost-effective compared with no treatment, although the incremental cost per additional QALY (£17,881) is higher than in the group with higher starting visual acuity and is more uncertain (probability that screening is cost-effective with a threshold for cost-effectiveness of £30,000 is 0.7). The decision uncertainty is shown in Figure 15.

Expected value of perfect information

The population EVPI for a starting visual acuity of 20/40 is illustrated in Figure 16. At a threshold for cost-effectiveness of £30,000, the population EVPI is £6.95 million assuming a 10-year lifetime for the technology (£178 for individual patients) or £3.91 and £9.18 million assuming a lifetime of 5 and 15 years, respectively. The population EVPI with starting visual acuity of 20/80 is higher: £18.26 million assuming a 10-year lifetime of the technology (£468 for individual patients), or £10.45 and £24.09 million assuming a lifetime of 5 and 15 years, respectively. Estimates of EVPI for male and female populations are very similar.

EVPI for individual parameters

The EVPI for each of the groups of model inputs for the 20/40 model is illustrated in Figure 17 for a threshold for cost-effectiveness of £30,000 and a

10-year lifetime for the technology. For patients with a starting visual acuity of 20/40, the value of information associated with the expected QALYs from PDT is £1.35 million. The other groups of model inputs, such as screening accuracy, have no value of information associated with them. At a starting visual acuity of 20/80 (Figure 18), the value of information associated with the expected QALY from PDT is £2.83 million and the value associated with the expected QALYs with no treatment is £1.05 million. The other groups of model inputs have no value of information associated with them.

In general, individual EVPIs will not sum to the EVPI for the decision as a whole. In this case many of the groups of model inputs have no value associated with them. This does not mean that the uncertainty surrounding their values is unimportant (together, they generate the EVPI for the decision), but it does mean that more information about these inputs individually may not be valuable.

Discussion and conclusions

Self-screening following first eye neovascular AMD appears to be a potentially cost-effective

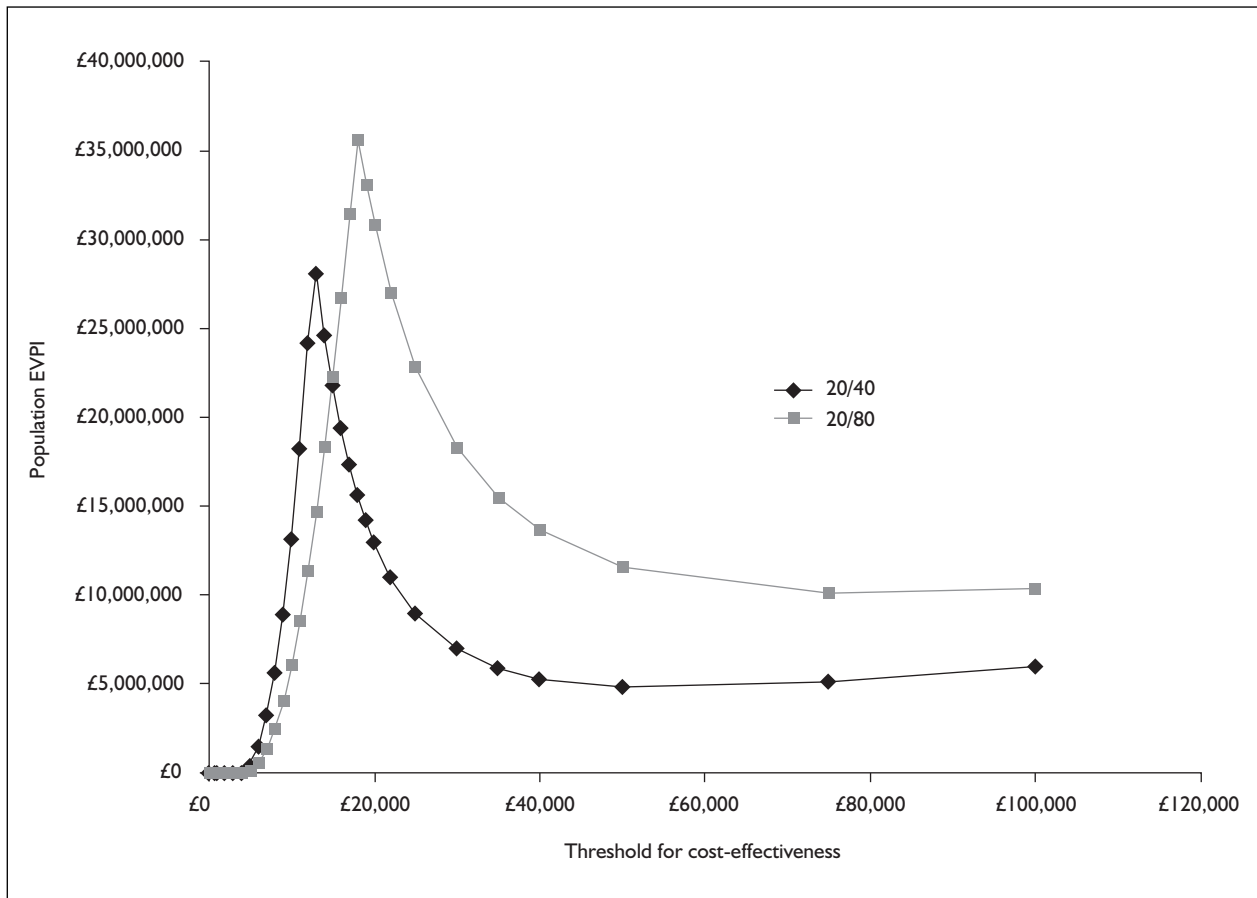


FIGURE 16 Population EVPI for 20/40 and 20/80 starting visual acuity

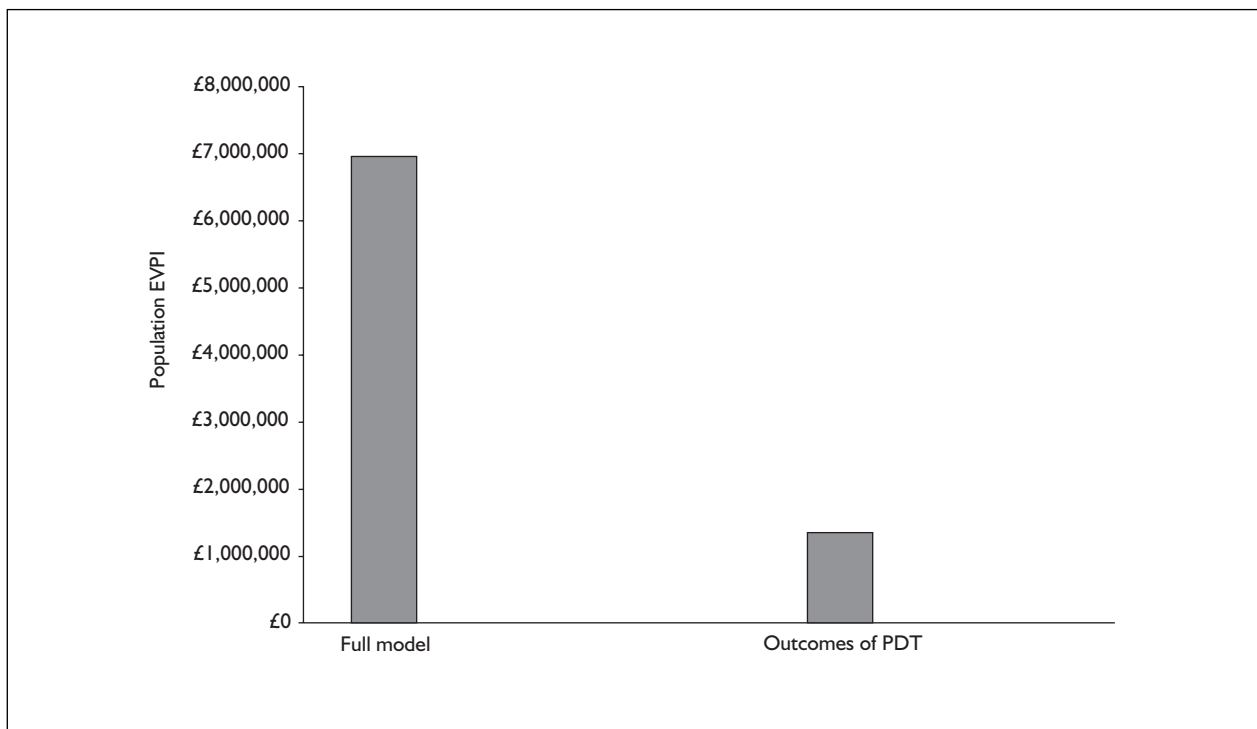


FIGURE 17 Partial EVPI for a starting visual acuity of 20/40

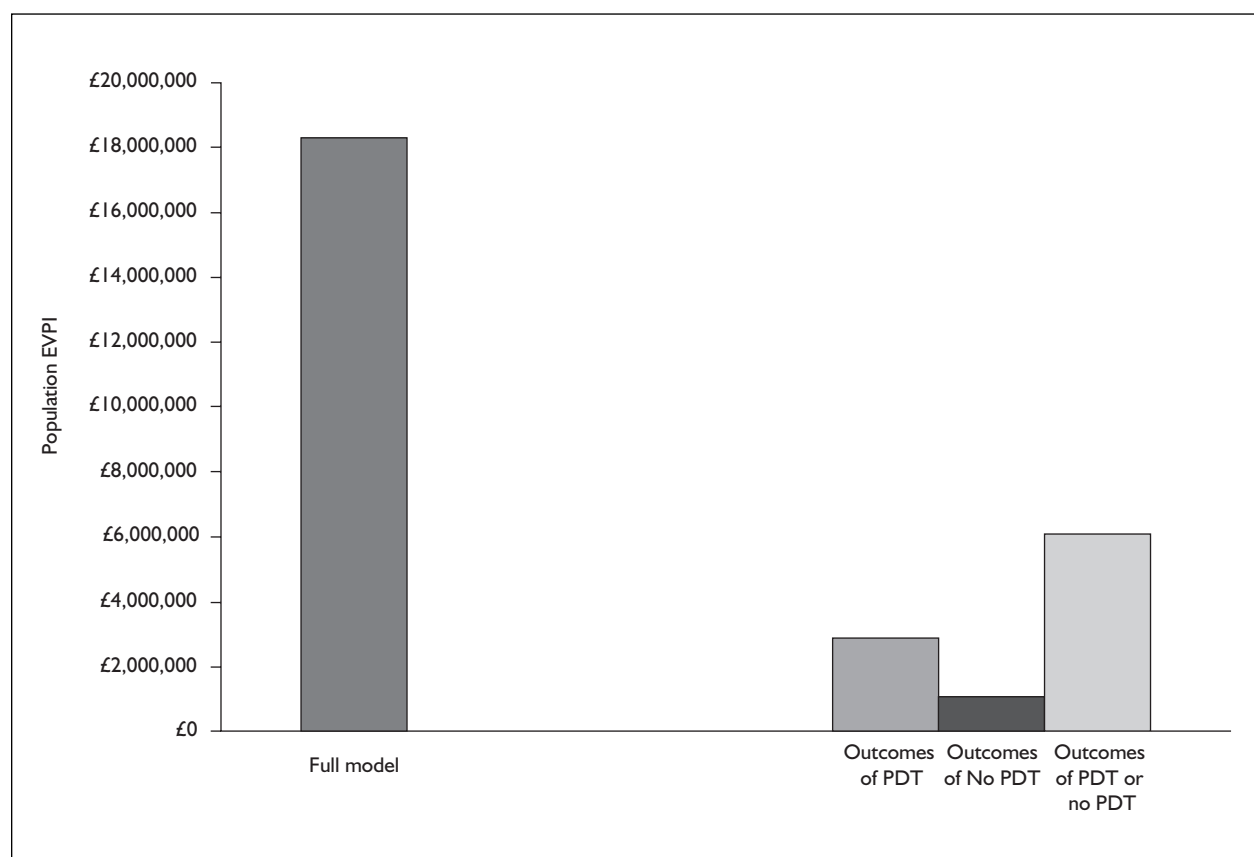


FIGURE 18 Partial EVPI for a starting visual acuity of 20/80

intervention for patients with initial visual acuities ranging from 20/40 to 20/80. However, the cost-effectiveness of self-screening is uncertain and, at a threshold for cost-effectiveness of £30,000 per additional QALY, the value of information surrounding the decision problem is significant, particularly when patients have lower initial visual acuities. The EVPI may exceed the cost of further investigation, which suggests that further research will be potentially cost-effective. The EVPI associated with model inputs indicates that more evidence about the impact of PDT on expected quality of life, and the quality of life for those not treated with PDT, would be most valuable and would require experimental design. It also suggests that additional evidence about other inputs individually, such as screening accuracy alone, may be of little value. However, this does not mean that additional information about all the model inputs combined would not be valuable.

This model has focused on self-screening patients with first eye neovascular AMD. A policy of self-screening for AMD before first eye involvement could be considered and modelled. However, the results of this model and previous analysis in the

previous assessment report⁶⁷ demonstrate that policy would not be cost-effective for a number of reasons: treatment will not be cost-effective in the worse seeing eye as it will not have an impact on overall visual acuity; the very low incidence in this group of patients will generate a very large number of false-positive results and unnecessary eye examinations; and the gains in quality of life offered by this strategy will only be realised years in the future for the small number of patients who have treatable neovascular AMD in the first eye but develop untreatable neovascular AMD in the second eye. Since this strategy will not be cost-effective, the decision uncertainty and EVPI surrounding this policy would also be very low. A policy of regular (3 monthly) repeated eye examinations could also be considered but again this analysis indicates that this strategy would also not be cost-effective. This is because it would be very costly (many more negative eye examinations) and is unlikely to be effective as visual acuity can decline rapidly in the period between examinations.

In addition, there are two issues with the way in which the screening programme has been

modelled at present. Currently, the effect of the Amsler grid, in terms of identifying patients with AMD, can occur before AMD develops and at each stage of visual acuity loss. However, it may be that there is no additional benefit from the Amsler grid after a patient has developed visual acuity problems, that is, after a loss of one or more lines. In addition, patients only self-refer to see an ophthalmologist once they have a decline in visual acuity (i.e. when there are noticeable changes in their eyesight). However, given that patients in the

model have already had first eye involvement and may, therefore, be expected to be more vigilant in recognising changes in their vision, patients may self-refer when there is no loss in visual acuity (AMD state). This may be because they are using other stationary objects to imitate the Amsler grid. Both of these issues are likely to make the screening strategy less cost-effective and, unless the ICER is greater than £100,000 (screening is unlikely to be cost-effective), will increase the expected value of information.

Chapter 6

What is the cost-effectiveness of long-term antibiotic treatment for preventing recurrent urinary tract infections in children?

Background

Topic origin

Long-term antibiotics for preventing UTIs in children had already been considered by the Pharmaceuticals Panel and identified as a priority. A vignette for this topic had also been produced which was due to be considered by the PSG in October 2002. However, NCCHTA and PSG decided that this topic would be most suitable for DA-VOI analysis to inform the deliberations of PSG. Therefore, consideration of this topic by PSG was delayed until its next meeting in March 2003 to allow time for the DA-VOI analysis to be conducted and reported. The topic did not meet the initial selection criteria: there was no assessment report available, nor was there a pre-existing model to work on. It was felt that given the paucity of literature and the complexity of the disease area, the quality of the modelling undertaken may not be sufficient for adequate consideration by the panel. After discussion with the NCCHTA, it was, however, decided to proceed with the modelling exercise.

Policy background

UTIs occur when the kidneys, ureter, bladder or urethra become infected. By the age of 7 years, 8.4% of girls and 1.7% of boys will have suffered at least one episode.⁷⁸ Recurrent UTI occurs in up to 30% of cases.⁷⁹

Pyelonephritis is a kidney infection that can occur when infected urine flows backwards from the bladder to the kidneys or when an infection in the bloodstream reaches the kidneys. It is a more severe type of UTI, especially when of a recurrent nature in young children, where it can cause progressive renal scarring (PRS), which can lead to renal failure in later life if left untreated.⁷⁸

Long-term (up to 3 years) antibiotic treatment may be required in children and infants with recurrent UTI and normal urinary tracts, as well as for children with urinary tract abnormalities,

such as vesicoureteral reflux (VUR), who are at greater risk of renal scarring.

A Cochrane review⁷⁸ was recently undertaken to determine the efficacy and side effects of long-term antibiotics given to prevent recurrent UTI in children. Randomised comparisons of two or more antibiotics to prevent recurrent UTI in children under 18 years were considered relevant for inclusion in the review. Long-term antibiotic versus placebo/no treatment, and studies that compared two or more antibiotic regimens, were included. Outcomes considered were: the number of repeat UTIs, total number of recurrent UTIs, adverse reactions to treatment, hospitalisation with UTI, and UTI with fever.

The review found evidence that three long-term antibiotics – trimethoprim, nitrofurantoin and cotrimoxazole – may reduce the risk of recurrent UTI in children. However, the evidence for the widespread use of long-term prophylactic antibiotics was regarded as “weak”.

Decision problem

The analysis reported here has assessed the cost-effectiveness of, and potential value of future research for, long-term (3-year) treatment with trimethoprim, nitrofurantoin or cotrimoxazole, compared with intermittent short-term antibiotic treatment of UTIs when they occur. The analysis considers the cost-effectiveness of these interventions for children with confirmed diagnosis of recurrent (three or more infections in the previous year) UTI but no urinary tract abnormality, and for those with confirmed mild (grade I and II) VUR. Severe VUR was excluded because interventions for this group are well established and additional primary (randomised trial) research is unlikely to be regarded as ethical. Analysis for recurrent UTI and mild VUR was conducted for boys and girls aged either 1 year or 3 years as clinical experts suggested these were the two most relevant age groups. In total, four alternative treatments were considered for eight patient groups.

Methods

Description of the model

The structure of the decision model is illustrated in *Figure 19*. For each of the eight patient groups, the frequency of recurrent UTI over 3 years is modelled as a Markov process,⁷⁰ with the impact on quality of life and resource use recorded. Each time a recurrent UTI occurs there is a chance that this will be a pyelonephritic attack, which will also have an impact on quality of life and costs.

VUR status and the cumulative number of pyelonephritic attacks are important determinants of the risk of developing PRS.⁸⁰ Those children who develop PRS face a risk that this will lead to end-stage renal disease (ESRD) at some time in the future. The age at which they will develop ESRD is uncertain. This is therefore represented by a distribution of ages (7–24 years). Two consequences of ESRD are considered: transplant and by long-term home dialysis. ESRD, whether managed by transplant or long-term home dialysis, is associated with a reduction in quality-adjusted life expectancy, as well as resource costs. Hypertension was not included as an outcome of

renal scarring owing to a lack of data concerning its long-term effects and contradictory evidence regarding its link to renal scarring.

The effect of long-term antibiotics is, therefore, established through a series of links of evidence: a reduction in the frequency of recurrent UTI may reduce the number of pyelonephritic attacks, which may reduce the risk of PRS and the development of ESRD in later life. In this way, the model uses RCT evidence of treatment effect on frequency of UTI, combined with natural history evidence, to estimate the short-run and longer term impacts on quality-adjusted life expectancy and resource use.

The evidence

Effectiveness

The structure of the model was used to define a number of systematic searches around natural history. These searches were carried out by the Information Service at the University of York. A number of questions for each data requirement was identified, along with keywords. These questions are presented in Appendix 6, along with the full details of the searches conducted. These

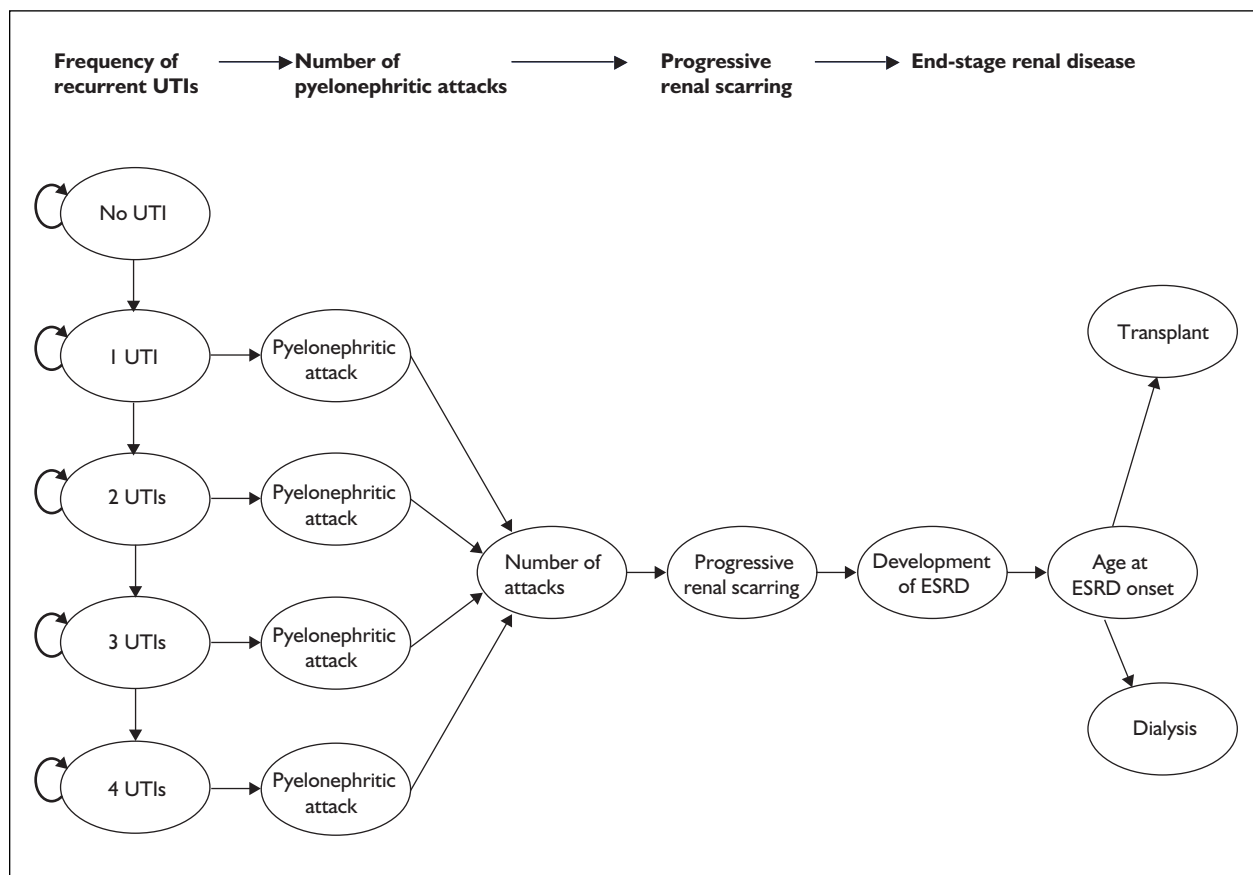


FIGURE 19 Model structure

TABLE 9 Sources of data used in the UTI model

	Value	Distribution	Source
Baseline probability of recurrent UTI (annual recurrence)	0.68	Beta 95% CI 0.547 to 0.685	Control arms of trials in Smellie <i>et al.</i> ⁸¹ , Savage <i>et al.</i> ⁸² and Stansfeld ⁸³
Log odds of cotrimoxazole	-2.70	Normal SD 0.73	Smellie <i>et al.</i> ⁸¹ , Stansfeld ⁸³
Log odds of nitrofurantoin	-1.92	Normal SD 0.55	Smellie <i>et al.</i> ⁸¹ , Brendstrup <i>et al.</i> ⁸⁴
Log odds trimethoprim	-0.87	Normal SD 0.57	Brendstrup <i>et al.</i> ⁸⁴
Frequency of pyelonephritic attack: girls	Age 1 = 0.83 Age 2 = 0.51 Age 3 = 0.40 Age 4 = 0.41 Age 5 = 0.44	Beta $\alpha = 110, \beta = 22$ $\alpha = 66, \beta = 63$ $\alpha = 57, \beta = 85$ $\alpha = 46, \beta = 66$ $\alpha = 45, \beta = 57$	Jodal ⁸⁵
Frequency of pyelonephritic attack: boys	Age 1 = 0.77 Age 2 = 0.42 Age 3 = 0.29 Age 4 = 0.10 Age 5 = 0	Beta $\alpha = 57, \beta = 17$ $\alpha = 9, \beta = 12$ $\alpha = 7, \beta = 17$ $\alpha = 2, \beta = 17$ $\alpha = 0, \beta = 10$	Jodal ⁸⁵
Probability of renal scarring	No pyl = 0.06 1 pyl = 0.10 2 pyl = 0.16 3 pyl = 0.30 4 pyl = 0.43	Beta $\alpha = 1.75, \beta = 27.18$ $\alpha = 8, \beta = 70.55$ $\alpha = 3.75, \beta = 18.89$ $\alpha = 3, \beta = 6.74$ $\alpha = 3.5, \beta = 4.62$	Jodal ⁸⁵
Probability of ESRD, given renal scarring	0.05	Beta $\alpha = 10.2, \beta = 193.1$	North American Pediatric Renal Transplant Cooperative study ⁸⁶
Mean age at onset of ESRD	13.67 years	Triangular Min. = 7, Max. = 24	Mean from Arant ⁸⁷ , Range from Jacobson <i>et al.</i> ⁸⁸
Cost of UTI/pyelonephritic attack	£17.23	Fixed	BNF ⁴⁹ , PSSRU ⁵⁰
Cost of dialysis per year	£19,871	Fixed	Mowatt <i>et al.</i> ⁸⁹
Cost of renal transplant	£6212.44	Fixed	CIPFA ⁵¹
Disutility of UTI	-0.00141	Normal 95% CI 0 to 0.2	Barry <i>et al.</i> ⁹⁰
Disutility of Pylonephritic attack	-0.0143	Normal 95% CI 0.01 to 0.5	
Mean survival duration after transplant	13.2 years	Normal 95% CI 12.1 to 14.4	Wahn <i>et al.</i> ⁹¹
Mean survival duration on dialysis	12.25 years	Fixed	Mowatt <i>et al.</i> ⁸⁹
Mean survival duration without ESRD	68.14 years	Uniform 66.65, 69.62	Office for National Statistics ⁶⁶

pyl, pyelonephritic attack.

searches helped to identify a number of studies that were used to populate the model. Details of the data used from these studies are given in Table 9.

In addition to the parameter searches a model of UTI in children and an associated systemic review

were identified,⁸⁰ which helped to inform the structure of the model.

The effect of each of the interventions on the frequency of UTI was based on evidence from a Cochrane review,⁷⁸ which identified four trials that have evaluated the use of long-term antibiotics⁸¹⁻⁸⁴

(trimethoprim, nitrofurantoin and cotrimoxazole) for recurrent UTI. Three trials^{81–83} compared intervention with intermittent antibiotic treatment, and one trial compared alternative long-term antibiotics.⁸⁴ The methodological quality of the trials was poor.⁷⁸

In order to use all of the RCT evidence, multiple parameter synthesis³³ (a generalisation of Bayesian meta-analysis) was conducted to estimate log odds ratios for each of the interventions (the posterior distributions and the correlations between them were used directly in the analysis). The frequency of subsequent recurrent UTI without intervention was based on the pooled control arms of three trials. The possibility of resistance to long-term antibiotics was not included owing to a lack of suitable evidence on which to base such a model.

The probability of a UTI being pyelonephritic (by age and gender) and the probability of PRS given the cumulated number of pyelonephritic attacks (by VUR status) were based on natural history evidence,⁸⁵ with beta distributions assigned reflecting the number of observations in each case. The probability of developing ESRD for children who experienced PRS was based on registry data.⁸⁶ The age at onset of ESRD for this group of patients was based on limited evidence from two observational studies,^{87–88} with a triangular distribution assigned to reported ranges. Children who develop ESRD can be managed by long-term dialysis or transplantation. The proportion of children eligible for transplantation is dependent on age of onset and is taken from a simulation model⁹² developed to examine the alternative therapies for ESRD.

Costs and QALYs

The impact of ESRD on quality-adjusted life expectancy was established by combining estimates of quality of life following transplantation and dialysis from a published time-trade-off exercise⁹³ with a number of published studies on the expected survival following transplantation⁹¹ or while on long-term dialysis.⁸⁹ Distributions were assigned to these estimates based on reported standard errors or the number of observations. The impact of UTI and pyelonephritis on quality of life was based on a published study looking at the disutility associated with UTIs in women.⁹⁰ The disutility of a pyelonephritic attack was calculated by multiplying this disutility by the number of days spent with a more severe attack. Distributions were also assigned to reflect the reported ranges. The costs of intermittent

treatment of UTI and pyelonephritis were based on dosage, duration of treatment, and primary and secondary care visits. The costs of ESRD were taken from the CIPFA database⁵¹ and estimates from a published NICE assessment report.⁸⁹ The possibility of resistance to long-term antibiotics was not included owing to a lack of suitable evidence on which to base such a model.

Analysis

Similar methods of probabilistic analysis and EVPI were used for this model as were used for the asthma model detailed in Chapter 3.

Results

Costs

Intermittent therapy is the most costly strategy for each of the eight patient groups (*Table 10*). Trimethoprim is the least expensive prophylactic antibiotic, therefore representing the cheapest treatment option.

Outcomes

For each of the eight patient groups, treatment with cotrimoxazole gives the least QALYs lost as a result of recurrent UTI attacks, and therefore gives the most QALYs gained compared with intermittent therapy (*Table 10*). The most QALYs lost are associated with intermittent therapy followed by either trimethoprim or nitrofurantoin depending on the patient group.

Cost-effectiveness

The cost-effectiveness results are summarised in *Table 10*.

In summary, the results in *Table 10* demonstrate that some form of long-term antibiotic treatment can be regarded as cost-effective for all eight patient groups (i.e. intermittent treatment is less effective and more costly in every case). The probabilities that each of the four strategies are cost-effective are also presented in *Table 10* for each of the eight models. There is very little decision uncertainty surrounding this result, and the probability that intermittent treatment will be cost-effective remains very close to zero over a range of cost-effectiveness thresholds, with the highest probability being for boys aged 3 years, with no VUR ($p = 0.02$). There is, however, substantial uncertainty in the choice of which long-term antibiotic treatment will be cost-effective. In most cases, this choice is between trimethoprim and cotrimoxazole. At a cost-effectiveness threshold of £30,000, nitrofurantoin

TABLE 10 Summary of results by patient group

Strategy	Costs	QALYs lost	
<i>Girls aged 3 with no VUR</i>			
Cotrimoxazole	92	-0.0030	£16,739
Nitrofurantoin	52	-0.0096	E dominated
Trimethoprim	15	-0.0076	
Intermittent	171	-0.2866	Dominated
<i>Girls aged 3 with VUR</i>			
Cotrimoxazole	94	-0.0058	£9,157
Nitrofurantoin	57	-0.0182	E dominated
Trimethoprim	18	-0.0141	
Intermittent	296	-0.5819	Dominated
<i>Girls aged 1 with no VUR</i>			
Cotrimoxazole	93	-0.0021	£8,333
Nitrofurantoin	53	-0.0069	£7,209
Trimethoprim	22	-0.0112	
Intermittent	171	-0.2356	Dominated
<i>Girls aged 1 with VUR</i>			
Cotrimoxazole	94	-0.0066	£2,609
Nitrofurantoin	58	-0.0198	£2,171
Trimethoprim	30	-0.0327	
Intermittent	298	-0.5957	Dominated
<i>Boys aged 3 with no VUR</i>			
Cotrimoxazole	90	-0.0002	£86,000
Nitrofurantoin	47	-0.0007	£51,428
Trimethoprim	11	-0.0014	
Intermittent	92	-0.1056	Dominated
<i>Boys aged 3 with VUR</i>			
Cotrimoxazole	91	-0.0009	£20,476
Nitrofurantoin	48	-0.0030	£18,947
Trimethoprim	12	-0.0049	
Intermittent	169	-0.3254	Dominated
<i>Boys aged 1 with no VUR</i>			
Cotrimoxazole	92	-0.0017	£11,111
Nitrofurantoin	52	-0.0053	£6,596
Trimethoprim	21	-0.0100	Dominated
Intermittent	151	-0.2028	
<i>Boys aged 1 with VUR</i>			
Cotrimoxazole	93	-0.0052	£3,246
Nitrofurantoin	56	-0.0166	£2,154
Trimethoprim	28	-0.0296	Dominated
Intermittent	267	-0.5319	

is never cost-effective. As expected, long-term treatment with the more effective but more costly antibiotic (cotrimoxazole) is more cost-effective for the more severe cases: those with VUR, younger children and girls who have a higher risk of recurrent pyelonephritic infections.

Girls aged 3 with no VUR

Long-term treatment with cotrimoxazole may be regarded as cost-effective with an incremental cost per QALY gained of £16,739. However, this is uncertain, and the probability that it is cost-

effective at a threshold of £30,000 per QALY is only 0.46. This decision uncertainty is illustrated in *Figure 20* and shows that the probability that nitrofurantoin will be cost-effective is relatively low.

Girls aged 3 with VUR

Long-term treatment with cotrimoxazole is more cost-effective than in 3-year-old girls without VUR (incremental cost per QALY gained of £9157). However, this is still uncertain, and the probability that it is cost-effective at the threshold of £30,000 per QALY is 0.58.

Girls aged 1 with no VUR

Long-term treatment with cotrimoxazole may be regarded as cost-effective (incremental cost per QALY gained of £8333) and more cost-effective than in girls aged 3 years. However, this is still uncertain, and the probability that it is cost-effective at the threshold of £30,000 per QALY is 0.50.

Girls aged 1 with VUR

Long-term treatment with cotrimoxazole is most cost-effective for this patient group (incremental cost per QALY gained of £2609). This choice is less uncertain than for other groups, and the probability that it is cost-effective at the threshold of £30,000 per QALY is 0.73. The probability that either nitrofurantoin or trimethoprim will be cost-effective is relatively low.

Boys aged 3 with no VUR

Long-term treatment with trimethoprim may be regarded as cost-effective (it is associated with lower costs and lower QALYs lost than intermittent therapy), and the probability that it is cost-effective at the threshold of £30,000 per QALY is 0.77. In this case, nitrofurantoin and cotrimoxazole may not be regarded as cost-effective (incremental cost per QALY gained of £51,428 and £86,000, respectively). The probability that they will be cost-effective at a threshold of £30,000 per QALY is 0.16 and 0.05, respectively. This decision uncertainty is demonstrated in *Figure 21*.

Boys aged 3 with VUR

Long-term treatment with cotrimoxazole is more cost-effective than in boys aged 3 years with no VUR (incremental cost per QALY gained of £20,476). However, this choice is very uncertain, and the probability that it is cost-effective at the threshold of £30,000 per QALY is only 0.29. The decision uncertainty is demonstrated in *Figure 22*.

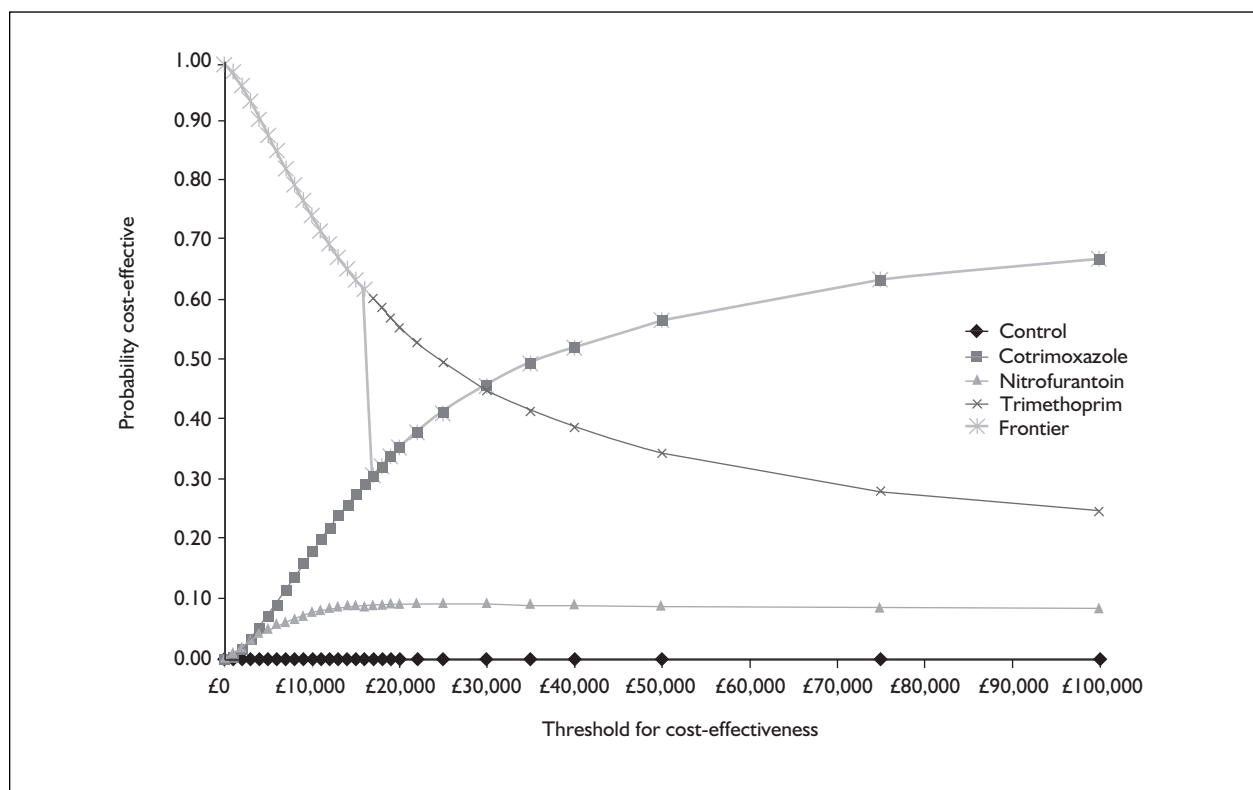


FIGURE 20 Cost-effectiveness acceptability curve (girls aged 3 with no VUR)

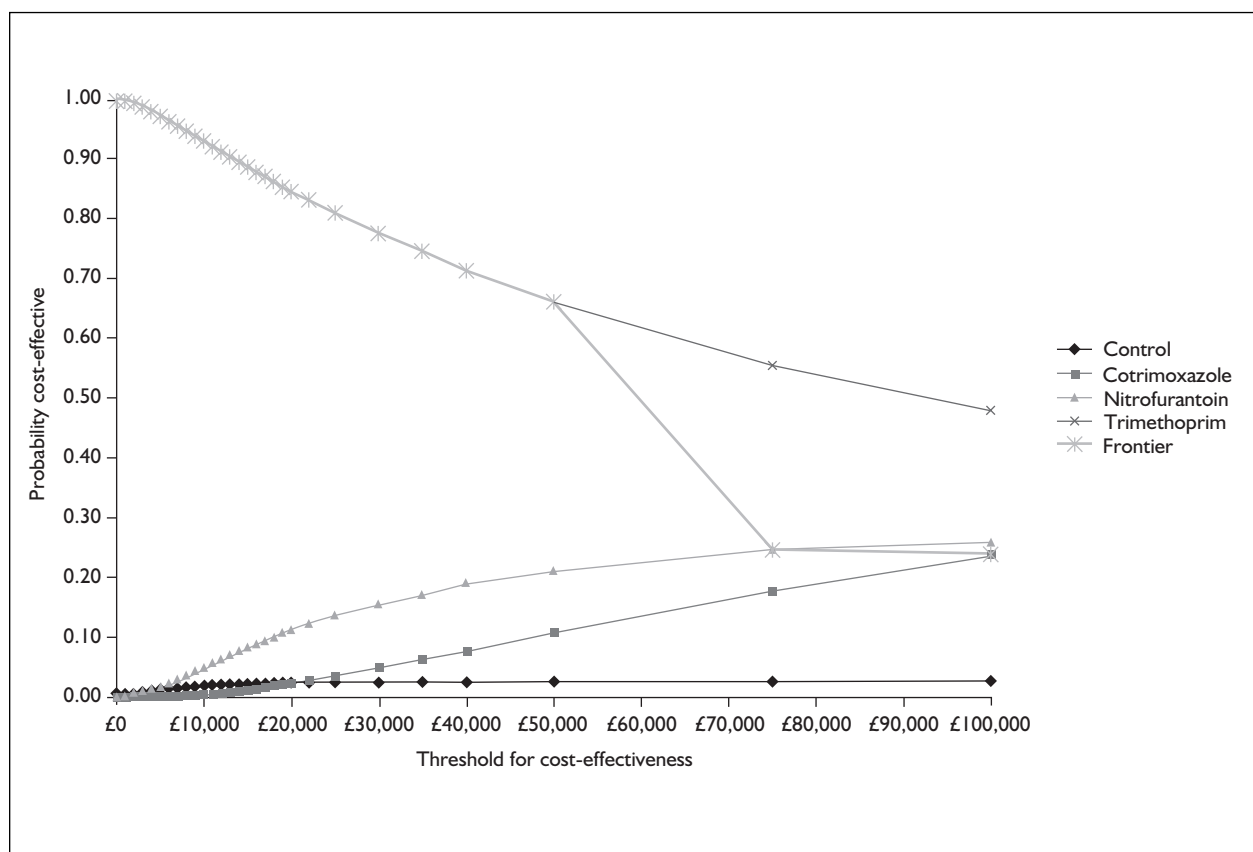


FIGURE 21 Cost-effectiveness acceptability curve (boys aged 3 with no VUR)

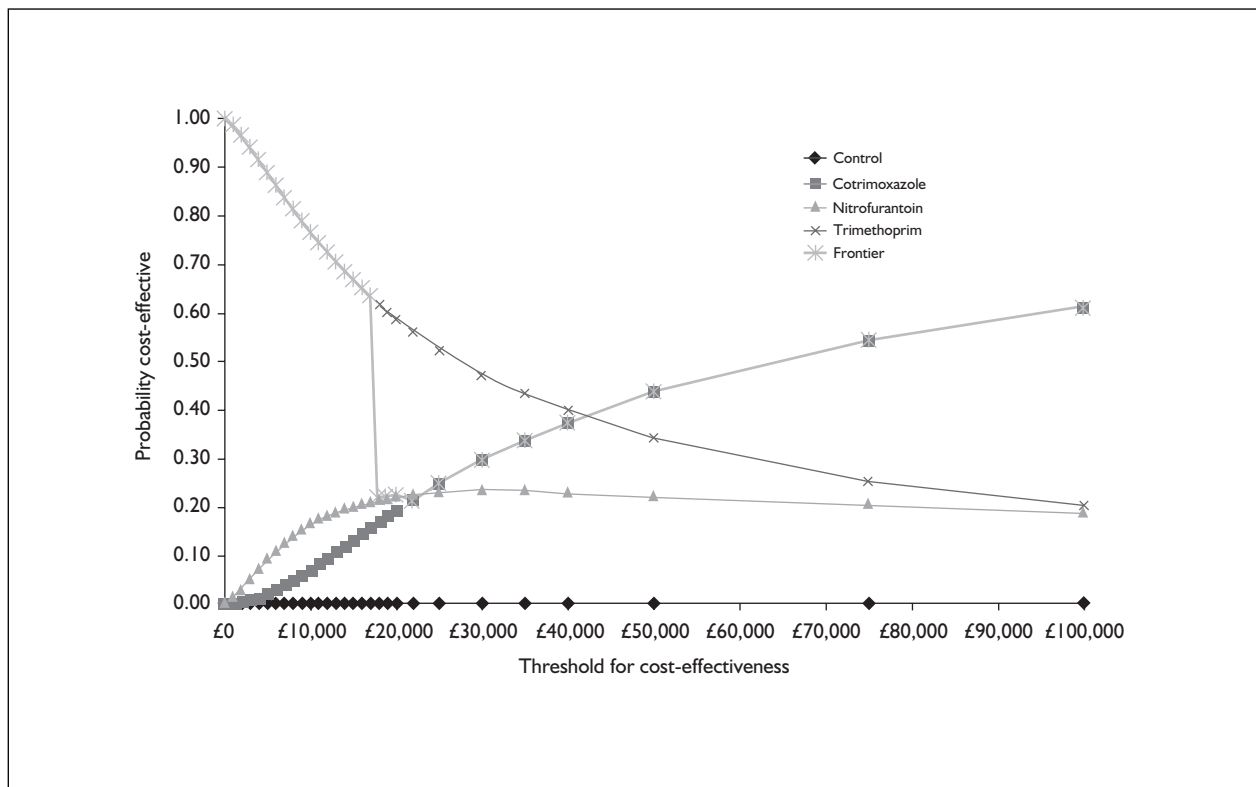


FIGURE 22 Cost-effectiveness acceptability curve (boys aged 3 with VUR)

Boys aged 1 with no VUR

Long-term treatment with cotrimoxazole is more cost-effective than in boys aged 3 years (incremental cost per QALY gained of £11,111), but this choice remains uncertain and the probability that it is cost-effective at the threshold of £30,000 per QALY is 0.45.

Boys aged 1 with VUR

Long-term treatment with cotrimoxazole is most cost-effective for this group of boys (incremental cost per QALY gained of £3246). This choice is less uncertain, and the probability that it is cost-effective at a threshold of £30,000 per QALY is 0.72.

Expected value of perfect information

The population EVPIs for all eight patient groups at a threshold for cost-effectiveness of £30,000 per QALY and assuming a 10-year lifetime for the technology are reported in *Table 11*.

Girls aged 3 with no VUR

Population EVPI is illustrated in *Figure 23* and is highest for this particular patient group. This is due to substantial decision uncertainty and the relatively high incidence. At a threshold for cost-effectiveness of £30,000 per QALY, the population EVPI is above £2.24 million, assuming a 10-year

lifetime for the technology (£1.28 and £2.95 million assuming a lifetime of 5 and 15 years, respectively).

Girls aged 3 with VUR and girls aged 1 with, and with no, VUR

The population EVPIs for these patient groups, at a threshold for cost-effectiveness of £30,000 per QALY, are similar: £612,499 for girls aged 3 years with VUR, £689,977 for girls aged 1 year with no VUR and £543,529 for girls aged 1 year with VUR assuming a 10-year lifetime for the technology.

Boys aged 3

Population EVPI is low for these patient groups owing to relatively little decision uncertainty for those with no VUR and the low incidence for those with VUR. At a threshold for cost-effectiveness of £30,000 per QALY, the population EVPI is £22,546 with VUR and £40,931 with no VUR assuming a 10-year lifetime for the technology. The population EVPIs with and without VUR are demonstrated in *Figure 24*.

Boys aged 1

The population EVPI is higher than for boys aged 3 years, for both VUR and no VUR, but remains relatively low. At a threshold for cost-effectiveness of £30,000 per QALY, the population EVPI is

TABLE 11 Expected value of information for eight UTI models

Strategy	Probability cost-effective ^a	Population EVPI ^{ab}
<i>Girls aged 3 with no VUR</i>		
Cotrimoxazole	0.46	£2,241,627.00
Nitrofurantoin	0.09	
Trimethoprim	0.45	
Intermittent	0.00	
<i>Girls aged 3 with VUR</i>		
Cotrimoxazole	0.58	£612,499.90
Nitrofurantoin	0.09	
Trimethoprim	0.33	
Intermittent	0.00	
<i>Girls aged 1 with no VUR</i>		
Cotrimoxazole	0.50	£689,977.70
Nitrofurantoin	0.20	
Trimethoprim	0.30	
Intermittent	0.00	
<i>Girls aged 1 with VUR</i>		
Cotrimoxazole	0.73	£543,529.60
Nitrofurantoin	0.15	
Trimethoprim	0.12	
Intermittent	0.00	
<i>Boys aged 3 with no VUR</i>		
Cotrimoxazole	0.05	£40,931.96
Nitrofurantoin	0.16	
Trimethoprim	0.77	
Intermittent	0.02	
<i>Boys aged 3 with VUR</i>		
Cotrimoxazole	0.30	£22,546.97
Nitrofurantoin	0.23	
Trimethoprim	0.47	
Intermittent	0.00	
<i>Boys aged 1 with no VUR</i>		
Cotrimoxazole	0.45	£267,106.00
Nitrofurantoin	0.24	
Trimethoprim	0.31	
Intermittent	0.00	
<i>Boys aged 1 with VUR</i>		
Cotrimoxazole	0.72	£172,611.30
Nitrofurantoin	0.16	
Trimethoprim	0.12	
Intermittent	0.00	

^a At a threshold for cost-effectiveness of £30,000 per QALY.
^b Assuming a 10-year lifetime for the technology.

£267,109 for those with VUR and £172,611 for those with no VUR.

EVPI for individual parameters

Girls aged 3 with no VUR

The EVPIs for model inputs are illustrated in *Figure 25* for a cost-effectiveness threshold of £30,000 per QALY and a 10-year lifetime for the technology. The value of information associated

with the effectiveness of long-term antibiotics is £2.25 million, which is substantially higher than for any other model input. This is broken down into the EVPI associated with the effectiveness of each of the three antibiotics separately (it should be noted that this breaks the correlation generated in the multiple parameter synthesis and will tend to overestimate individual EVPIs), and shows that additional evidence about cotrimoxazole and trimethoprim (EVPIs of £1.33 and £1.45 million, respectively) is higher than for nitrofurantoin (£0.53 million). The EVPI associated with effectiveness can also be broken down into effectiveness within 6 months (existing trial evidence) and a longer follow-up from 6 months to 3 years. This suggests that evidence about the longer run effectiveness of these antibiotics is more valuable than additional evidence of effect within 6 months (partial EVPIs of £1.77 million and £0.6 million, respectively). Model inputs associated with the development and the impact of ESRD also have positive but low EVPI (£8,500). The EVPI associated with other model inputs is negligible for this patient group.

Other patient groups

The pattern of partial EVPIs for other patient groups is very similar to that illustrated in *Figure 25*, with relatively high values associated with effectiveness, particularly for the longer-run effectiveness of cotrimoxazole and trimethoprim. Of the other model inputs, those associated with ESRD have the highest partial EVPI (up to £32,000 in girls aged 3 years with VUR). Also, in girls aged 3 years with VUR, the probabilities of renal scarring and the disutility of UTI/pyelonephritis have small EVPIs associated with them (£13,000 and £2000, respectively).

Discussion and conclusions

Some form of long-term antibiotic treatment can be regarded as cost-effective for all eight patient groups (intermittent treatment is more costly and less effective). There is also very little decision uncertainty surrounding this result, and the probability that intermittent treatment will be cost-effective remains close to zero over a range of cost-effectiveness thresholds. This suggests that the question for further research is which of the antibiotics should be used, rather than whether long-term antibiotics are worthwhile.

At a cost-effectiveness threshold of £30,000 per QALY, cotrimoxazole is cost-effective for every patient group with the exception of boys aged

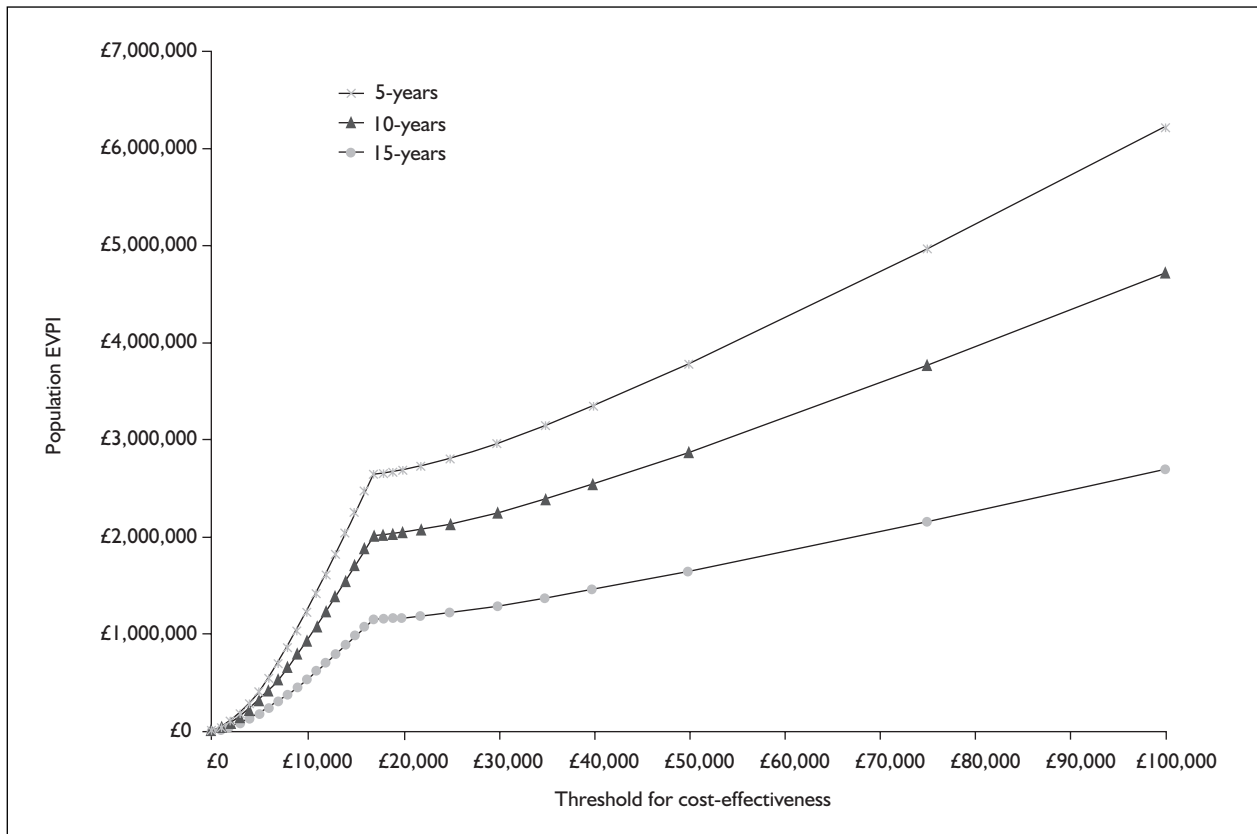


FIGURE 23 Population EVPI (girls aged 3 with no VUR)

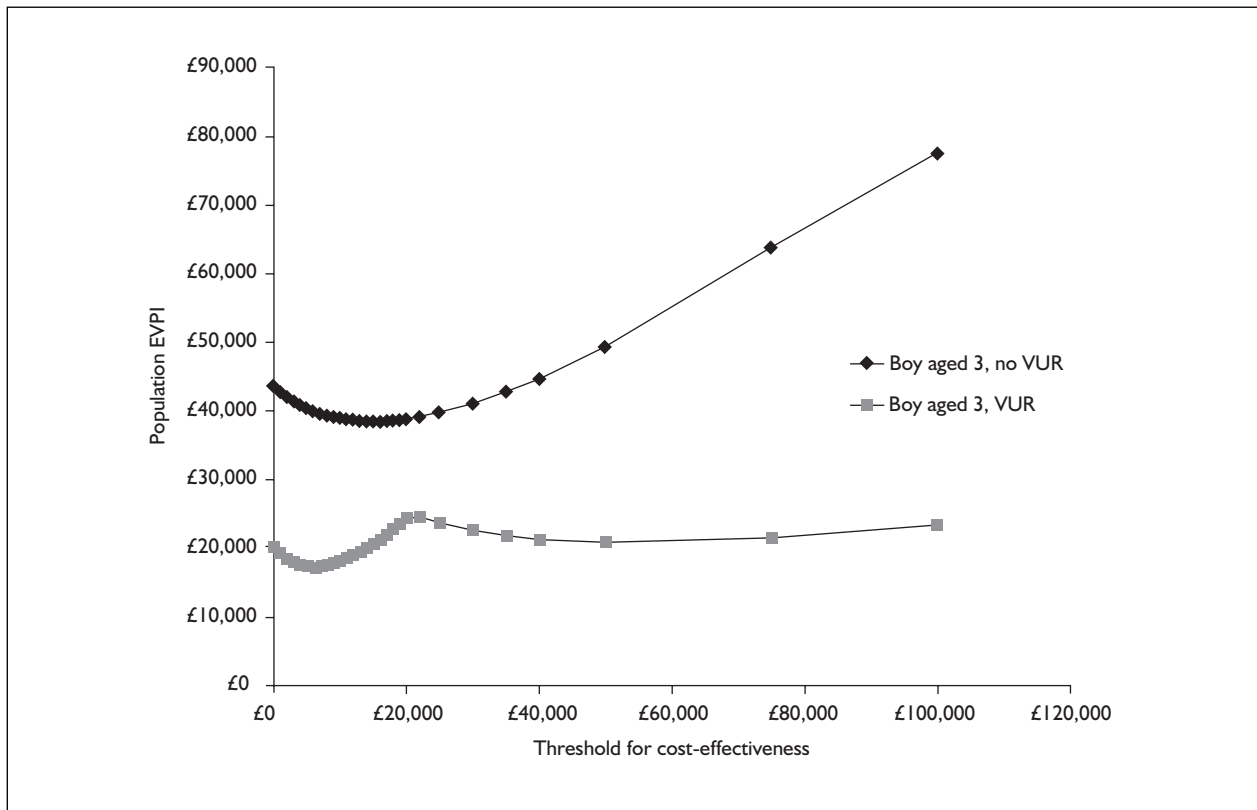


FIGURE 24 Population EVPI (boys aged 3 with and without VUR)

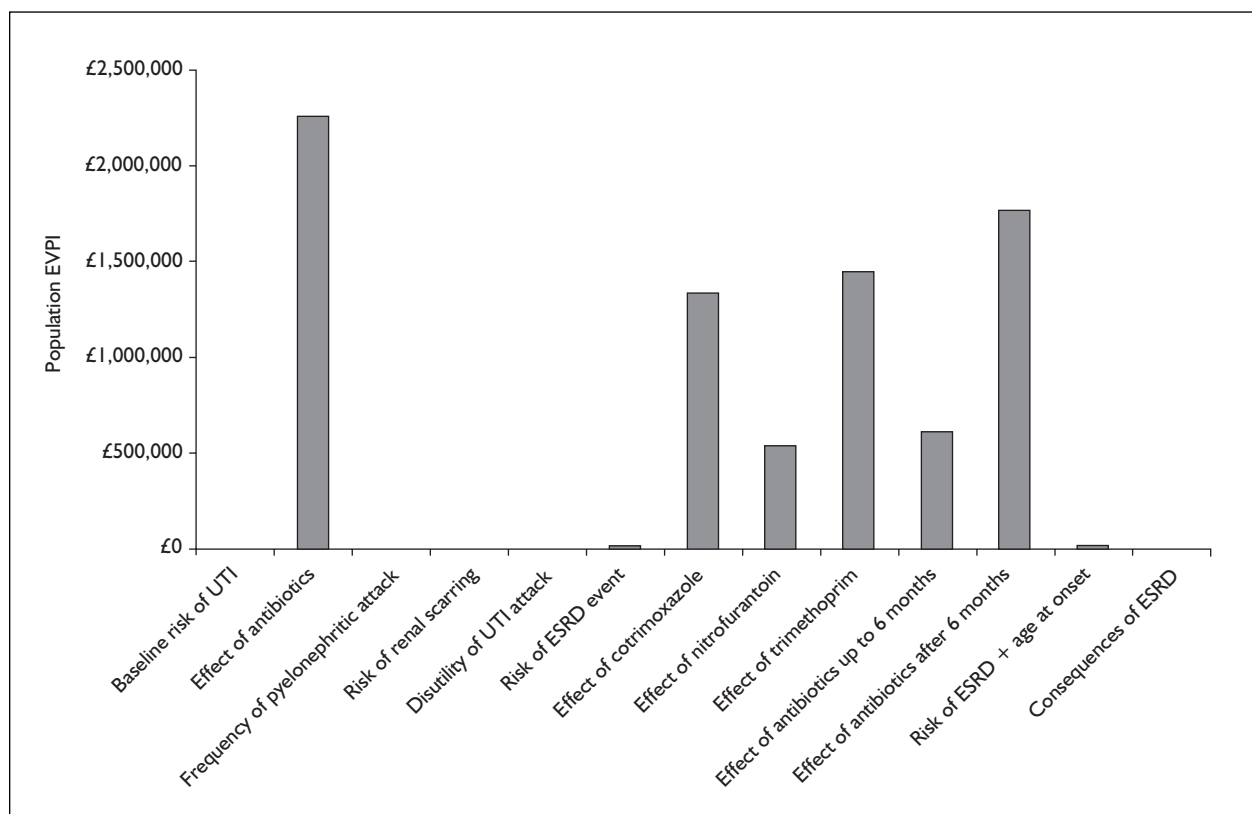


FIGURE 25 Partial EVPI (girls aged 3 with no VUR)

3 years with no VUR, where long-term treatment with trimethoprim is cost-effective. However, there is substantial decision uncertainty about which of the three long-term antibiotic treatments will be the most cost-effective. In many cases, this choice is between trimethoprim and cotrimoxazole. However, there is also a chance that nitrofurantoin will be cost-effective. For patients with mild VUR, for younger children and for girls, long-term treatment with cotrimoxazole (which is more effective and more costly) is more cost-effective, with less decision uncertainty.

In general, the population EVPI in this area is substantial (£4.6 million across all eight patient groups), but differs by patient group. The population EVPI is highest for girls aged 3 years with no VUR (£2.24 million at a threshold of £30,000) and suggests that further research in this patient group could be potentially worthwhile. The population EVPI for some other patient groups, such as girls aged 3 years with VUR and girls aged 1 year (with and without VUR), is still substantial (£612,499, £689,977 and £543,529, respectively, at a threshold of £30,000), although this may not exceed the costs of

primary research. In boys, the population EVPI is lower, particularly for boys aged 3 years, and additional research may not be cost-effective for this group.

The partial EVPIs associated with the model inputs suggest that if further research is commissioned, it should focus on the relative effectiveness of alternative long-term antibiotics in reducing the frequency of UTI, particularly their longer run effectiveness. Although additional evidence about all three interventions will be valuable, it seems that evidence about cotrimoxazole and trimethoprim would be most important.

In summary, the analysis suggests that additional primary research may be required for selected patient groups (particularly girls with no VUR). If additional trials are conducted, they should include head-to-head comparisons of either cotrimoxazole and trimethoprim or all three antibiotics. In addition, longer follow-up (6 months to 3 years) would be worthwhile, as additional trials with 6-month follow-up are unlikely to be cost-effective.

Chapter 7

Feedback

Feedback from panel members

As detailed in Chapter 1, senior lecturers on the Therapeutic Procedures and Diagnostic Technologies and Screening Panels made short presentations of the DA-VOI methods to panel members following a briefing meeting with the York Research Team in January 2003. Owing to the scheduling of panel meetings, the research team presented the UTI model to the Pharmaceuticals Panel during the PSG seminar in March 2003. The analysis was then discussed at the PSG meeting later the same day.

Following the presentation of materials to the Therapeutic Procedures and Diagnostic Technologies and Screening Panels, feedback forms were distributed. These were completed by each of the panel members and returned to the research team. *Table 12* summarises the views on the value of information material presented at the two panel meetings.

The response to the value of information methods and case-study models was mixed, with some panel members in favour of using this method for future prioritisation meetings and some members not convinced about the value of this method in this particular setting. Panels seemed to have some difficulty with the background document, which would suggest that this may need to be simplified before presentation to other non-technical audiences.

In addition, two questions asking for comments on the background material and the model(s) presented were included in the feedback forms. Comments suggested a mixed response to both value of information methods and the case-study models, in terms of their overall value and contribution towards prioritisation in this particular context. Some panel members also felt that the background material did not provide enough detail, while others felt that it was too detailed and overly technical.

Feedback from NCCHTA senior lecturers at the PSG

Informal feedback was provided from senior lecturers. This is shown in full in Appendix 7. As

with the feedback from the panels, the response to value of information methods and the case-study models was mixed. The following general comments were made:

- The increased cost of DA-VOI work, in comparison with the cost of vignette production – is this good value for money? If the question addressed is correct, the 6 weeks necessary for DA-VOI work may actually represent good value for money.
- Rather than undertake DA-VOI, it may be more appropriate to provide more information (based on vignettes) on all A-list suggestions, if additional time/resources were available for prioritisation.
- What would be the selection criteria for DA-VOI work, given that 45 vignettes are produced each year?
- When would the DA-VOI work be carried out? There are possible problems from not tying together vignette production and value of information modelling.
- The role of DA-VOI methods in panel decision-making: is there a clear role? The value of information work contributed towards a change in the decision of the Diagnostic Technologies and Screening Panel, but this may have been due to careful re-examination of the research question rather than the value of information methods and model.
- The issue of model results that do not confirm prior beliefs: does this make the results less plausible or it is simply illustrating the need for explicit modelling?
- The models must be explicit about how bias was addressed in the data sources, given that the results depend on the RCT/non-RCT data used to inform model parameters.
- The presentation of DA-VOI work: could the models be presented in a more digestible way? It would be useful to present effectiveness separately from cost-effectiveness.
- How rigorous could DA-VOI work be when undertaken in a standard fashion, that is, when outside the pilot exercise.
- The role of systematic reviews in DA-VOI work: this should be integral to the exercise, but there may be capacity/time constraints to a formal systematic review.

TABLE 12 Feedback from panel members

	Therapeutic Procedures Panels scores (n= 11 panel members)	Diagnostic Technologies and Screening Panel scores (n = 10 panel members)
Q1: How well the background presentation was presented (1 = badly to 5 = well)	Score 4 = 4 (36%) Score 5 = 7 (64%)	Score 2 = 1 (10%) Score 4 = 4 (40%) Score 5 = 5 (50%)
Q2: How easy the background presentation was to understand (1 = hard to understand to 5 = easy to understand)	Score 2 = 2 (18%) Score 3 = 5 (45%) Score 4 = 4 (37%)	Score 2 = 2 (20%) Score 3 = 2 (20%) Score 4 = 5 (50%) Score 5 = 1 (10%)
Q3: Usefulness of the background 'overview of methods' document (1 = not at all useful to 5 = very useful)	Score 2 = 1 (9%) Score 3 = 3 (27%) Score 4 = 6 (54%)	Score 2 = 4 (40%) Score 3 = 5 (50%)
Q4: How easy the model was to understand (1 = hard to understand to 5 = easy to understand)	Score 1 = 1 (9%) Score 2 = 2 (18%) Score 3 = 4 (37%) Score 4 = 4 (37%)	Score 2 = 6 (60%) Score 3 = 2 (20%) Score 4 = 1 (10%) Score 5 = 1 (10%)
Q5: How the model contributed to a decision on the A-list topic (1 = not at all to 5 = a lot)	Score 1 = 3 (27%) Score 2 = 1 (9%) Score 3 = 2 (18%) Score 4 = 2 (18%) Score 5 = 1 (9%)	Score 1 = 6 (60%) Score 2 = 2 (20%) Score 3 = 2 (20%)
Q6: How helpful this type of explicit modelling approach could be in supporting future panel decisions (1 = not at all to 5 = a lot)	Score 1 = 2 (18%) Score 2 = 1 (9%) Score 3 = 4 (37%) Score 4 = 4 (37%)	Score 2 = 2 (20%) Score 3 = 4 (40%) Score 4 = 3 (30%) Score 5 = 1 (10%)

Conclusions

Over a relatively short period, much was learned about the use of DA-VOI in the NHS HTA programme's priority setting process. Given the large volume of topics that are considered each year by the panels, the issue of how formal modelling might fit into the prioritisation process

was frequently commented on in feedback. Other recurring feedback from the panels and the senior lecturers related to how highly technical material could be presented to non-specialists on the panels and how the varying quality of available data could be adequately reflected in the models. Chapter 8 provides some responses to these points and others.

Chapter 8

Discussion

This chapter provides the reflections, on the part of the research team, of the process and outcomes of the pilot study. The chapter is structured into five sections: issues relating to process, methodological points, implementation issues, further research and achievement of study objectives.

Process issues

Several issues relating to the NHS HTA programme's priority setting process, and how DA-VOI might fit into this, were raised by the pilot study. To use DA-VOI, it is essential to have a clear definition of the decision problem. In the case of setting research priorities for the HTA, this would be defined in terms of factors such as the relevant technology, its comparators and the appropriate patient group(s). The vignettes, around which the definition of the research question is currently based, take a more general, less tightly specified, view of the decision problem. If DA-VOI is to work in tandem as part of priority setting in the NHS HTA programme, some consideration would be needed regarding the point at which the research question needs to be firmed up, and how DA-VOI can fit into, and have a role in, informing that process.

One approach would be to make the development of the vignette and the use of DA-VOI an integrated process. The key initial tasks in developing the models and the production of the vignette are very similar: identifying relevant literature and using expert opinion (e.g. clinical, managerial and administrative) to scope out the nature of the decision problem. Making the modelling work and the vignette production not just coordinated, but also part of the same task would have a number of advantages. First, it would mutually strengthen and focus both the vignette production and the model development. This would be achieved by seeking clarity about key characteristics of the research question, such as the relevant subgroups of patients, the setting of the technology and the most appropriate comparator interventions and programmes. Second, any divergence between the vignette and the model would be avoided if they were created as part of

the same process. One of the features of the pilot was that, for those topics at the relevant stage (manual physiotherapy in respiratory disease and screening for AMD), the vignette and decision models were developed largely independently and, not surprisingly, typically took differing perspectives on particular issues. Third, joint development of these two parts of the prioritisation process would also avoid duplication of effort and reduce the additional resources required for this type of work.

Feedback from the panels suggests that, while members were positive in general about a role for DA-VOI, they thought that they needed more detail about the inputs and assumptions in the model. How this might be achieved, given the time constraints on panel days and the limited space in the documentation, needs to be considered. One possible way of addressing this would be to provide more detailed documentation, which could be sent out to panel members in advance of their meetings and, given some initial training in these methods, this might lead to less discussion on the panel day. A more interactive process between those undertaking the DA-VOI analysis and the concerns of NCCHTA, panel members and the PSG may be useful in this respect. One advantage of decision modelling is that it provides a framework where alternative scenarios and sensitivity analysis can be run in response to concerns about alternative assumptions or different views about the interpretation or quality of evidence. A more interactive process, which gives some opportunity for the DA-VOI analysis to respond to particular concerns, may give decision-makers more confidence that the results of the model are robust regarding these issues.

A final issue with respect to process is the need to identify, and secure access to, relevant clinical experts early in the analysis period when the decision problem is being defined, the structure of the model is being established and relevant data are being identified. Given that this input is being provided voluntarily, there are limits to the demands that can be made on these individuals regarding the volume and timing of the inputs they provide. It may be worth considering the use

of panels of experts with ongoing links to the NHS HTA programme. There would certainly be benefits from the same experts being identified for the vignettes and the model development.

Methods

It was agreed at the outset of the pilot that the feedback that the research team would receive from NCCHTA and the panels would not relate to the methods of DA-VOI, but rather to their application to research priority setting in the HTA programme. However, a number of methodological issues was raised by the pilot study. The first issue relates to model complexity. In general, the types of model that have been developed (particularly the models of screening for AMD and prophylactic antibiotics in UTI) are more complex than was originally anticipated. The authors believe this type of modelling to have been necessary, given the characteristics of the relevant diseases and technologies, but this level of sophistication in modelling does have resource implications for implementation.

Second, there is an important issue relating to how comprehensive the literature searching for the evidence necessary to populate the models can reasonably be, given the time and resource constraints. For the two case studies for use with the panels (physical therapy in respiratory disease and screening for AMD) systematic search methods were used, but these focused on easily identified sources (e.g. the Cochrane database of RCTs).

For the third case study presented to the PSG (prophylactic antibiotics in UTI) the research team worked with information scientists at the University of York to explore other, more comprehensive, search methods. These methods did not relate solely to treatment effectiveness, but also included model parameters relating to natural history, incidence and prevalence, health-related quality of life (for QALYs) and costs. In this case, the development of the model structure was used to specify a series of very specific searchable questions for particular model parameters. Methods for *efficient* literature searching for non-effectiveness parameters are currently underdeveloped and research in this area is being undertaken. The emphasis on 'efficient' is important: in no decision model will there be the resources to identify every item of data that could feasibly be incorporated into the analysis. This will be particularly true for models

developed to prioritise research for the HTA programme. Efficiency in this regard will, in part, reflect the need to focus most searching and review attention on those variables to which the model's results are most sensitive and which will typically be the parameters with the highest EVPI. This suggests an iterative approach to searching:²⁵ build the model based on easily available data (e.g. MEDLINE, Cochrane), then undertake more comprehensive searching for those parameters with a relatively high EVPI.

A third issue relates to the data synthesis methods. More complex methods of evidence synthesis (multiple parameter synthesis) may be necessary when considering the evidence surrounding multiple comparators and networks of evidence.³³ Although the authors did not originally anticipate using this approach, these methods were used in developing the model of recurrent UTI in children. This is an important area for future methods development for evidence synthesis in general, and decision modelling for cost-effectiveness in particular.

A fourth issue is that there needs to be some reflection on how the DA-VOI methods handle the heterogeneity and differing levels of quality in the evidence base. This issue was raised by both the panels and NCCHTA. A particular issue was the problem of how variability in the quality of the studies available to populate a model should be handled when interpreting the latter's results (e.g. how to handle poorly conducted trials as a source for estimating relative treatment effect). Some important methodological work has been undertaken to consider how the risk of bias might be handled quantitatively to adjust estimates of a particular parameter,⁹⁴⁻⁹⁸ and research is needed to assess how this might be used more extensively in cost-effectiveness modelling.⁹⁹ In the context of working with groups responsible for priority setting in research, greater use of sensitivity analysis may be a more explicit way of handling this problem; that is, running the model a number of times to include different data sources. In some cases, a model will be robust to these alternative data in terms of cost-effectiveness and EVPI. However, this will not be true in other cases and, ultimately, it is then for the relevant decision-making group (e.g. the panels or the PSG) to decide how it weights the different sources of evidence. Consideration needs to be given to identifying useful scenarios and priorities for sensitivity analysis. This may be an iterative process based on concerns expressed by the relevant panel.

A fifth issue relates to the impact of research on clinical practice. The DA-VOI framework assumes that clinical practice will follow what is identified as optimal management based on the analysis. There is a strong rationale for this since the issue of how to direct clinical practice towards what research has identified as optimal is a separate activity that may require different types of intervention with associated costs and effectiveness.¹⁰⁰ In other words, estimating the value of research in reducing the cost of decision uncertainty associated with the management of a particular patient group should be separated from the issue of whether to devote resources and, if so, in what way, to changing clinical practice. However, it is recognised that, eventually, the issue of whether to spend additional resources on new research or interventions to change practice needs to be considered. The development of an analytical framework to address this question is an area for additional research.

Finally, the pilot study set out to explore the use of expected value of *perfect* information in setting research priorities as part of the HTA programme. It should be emphasised that there are other elements of statistical decision theory that have a potentially valuable role in this process. In particular, an assessment of the expected value of *sample* information directly addresses the issue of the optimal design of a primary study, such as an RCT.^{12,33} For example, the most efficient sample size of a trial can be determined using these methods to balance the marginal cost of additional samples against the marginal benefit in terms of reductions in the cost of uncertainty. In comparison, EVPI looks at the potential of additional research to be efficient as it represents a maximum value based on the total cost of uncertainty. However, EVPI can have a major role in research prioritisation in several ways. First, comparing EVPI with the likely fixed cost of a new study provides an important first step in deciding whether additional research is likely to be efficient. Second, EVPI on specific parameters can indicate which specific parameters are in particular need of more precise estimation through additional research. Depending on the type of parameter of highest value, this will indicate what type of study design should be considered (e.g. a randomised trial for a relative treatment effect or a cohort study for baseline event rates).

Implementation

If DA-VOI is to be used to help to set research priorities for the HTA programme, how might it

be implemented? The full details of any implementation would have to be worked out by NCCHTA. However, it is useful to offer some comments on this here.

It would be unrealistic to imagine that DA-VOI can be undertaken with each topic presented to the panels. This is because of the considerable resource implications of undertaking DA-VOI and the volume of topics being considered. As part of this pilot study, it has been estimated that each of the pilots undertaken required approximately 6 weeks' whole-time-equivalent researcher input, and this was made up of a mix of experience levels. This research activity needs to be spread out over a period of 10–12 weeks, in part to allow for evidence searching and acquisition. It is unlikely that a sufficient number of suitably trained researchers currently exists in the UK to undertake this work. This shortage is particularly acute, given the competing demands of other decision-making bodies for researchers with these sorts of skills (e.g. the requirements of the technology assessment process for NICE). More routine use of DA-VOI would, therefore, require significant investment in capacity in this area.

Once topics are identified for a vignette based on existing methods, however, all or some of these could be worked up for DA-VOI; but how should these topics be identified? The identification of topics could be based on the original selection criteria proposed in this pilot (availability of secondary research and existing economic models) or on some assessment of the potential costs of commissioning research for the topic (e.g. whether primary research is likely to be considered). The value of coordinated production of the vignette and the DA-VOI is discussed above.

Combined vignette production and modelling would mean that vignette and associated analysis could go to the panels. Following the panel meeting, there would be an opportunity to respond to any feedback from that meeting. This might suggest running the model for different patient subgroups, scenarios, and so on, before it goes to PSG. At PSG, there would be an analysis that directly addresses the question in the vignette and would include additional analysis to explore any concerns or issues raised by the panel. This would allow an iterative process of development from vignette production to feedback from the panel to consideration by PSG. The PSG would perhaps be the more appropriate body to consider the implications of the DA-VOI for the type of research to be commissioned (e.g. trial,

epidemiological study, quality of life survey). In due course, the use of expected value of sample information might be an option for this group.

Other ways of implementing DA-VOI in the HTA priority-setting process can be considered. One is to use it only when a decision has been made to commission primary research, when the methods would be used to assess the sort of budget that might be allocated to a project, and the design of the research. However, the authors feel that it remains true that these methods are a potential input into the decision regarding whether primary or secondary research is appropriate. Another model is to use DA-VOI only with the PSG, but the methods have a role with the panels as long as the materials that they receive are adequate and there is, if not joint production, then a much closer coordination of vignette production and DA-VOI than took place during this pilot study.

Recommendations for research

This pilot study has identified a number of areas for further research.

- For decision modelling to establish the cost-effectiveness of new healthcare technologies and the value of additional research, further methods for efficient literature searching are necessary. These methods would focus most searching and review attention on those variables to which the model's results are most sensitive and with the highest EVPI.
- Decision modelling invariably involves bringing together evidence from disparate sources so that all relevant data are used to inform decisions. More research is needed into methods of evidence synthesis (multiple parameter synthesis) that consider the evidence surrounding multiple comparators and networks of evidence.
- The pilot study explicitly considered the potential value and usefulness of expected value of *perfect* information in setting research priorities in the NHS HTA programme. Methods are also available to identify efficient research designs; for example, the optimum sample size in trials that considers the reduction in the cost of uncertainty as well as the cost of research. These expected value of *sample* information methods have been applied in the literature, but research is needed into how they might fit into research priority setting in the

NHS HTA programme and other research agencies.

- There is a need for an analytical framework to be developed that can jointly address the question of whether additional resources would better be devoted to additional research, interventions to change clinical practice (towards what analysis based on existing evidence would suggest is optimal) or, indeed, changes in service delivery.

Has the pilot study achieved its objectives?

The pilot study set out four specific objectives. The extent to which each of these has been achieved is addressed below.

Objective I: Investigate the benefits of using appropriate decision-analytic methods and value of information analysis

The starting point for the use of DA-VOI is that formal analytical techniques can provide a useful input into the process of research priority setting. This pilot study gave NCCHTA, and others involved with the HTA programme, an opportunity to see what these methods can contribute to its priority setting process. However, it is also clear that, to achieve the benefit of such methods, there are some important demands to be satisfied. In particular, there is the need for relevant stakeholders to be clear, from an early point in the process, about the nature of the research question. Only when this has been specified, in terms of clear decision problems, can DA-VOI be used to establish the most cost-effective intervention or programme based on current evidence, the cost of uncertainty associated with that current decision and, hence, the value of additional information. As well as requiring a clear definition of the decision problem, the successful use of DA-VOI needs explicitness about which existing data should be used in the first part of the analysis and how data that exhibit particular weaknesses should be down-weighted in the analysis. The use of more informal methods to set research priorities does not overcome the difficult processes of defining the decision problem and deciding on relevant and appropriate evidence to use. Rather, it implicitly subsumes these factors into an overall judgement, which precludes transparency regarding the link between how a research priority was set and available evidence.

Objective II: Establish the feasibility and resource implications of applying these methods in a timely way, which can inform the prioritisation process within the NHS HTA programme

The pilot study showed that, even with very short timelines, it is possible to undertake DA-VOI that can feed into the priority-setting process that has developed for the HTA programme. This was the case despite the case studies not fitting the criteria initially set out for their selection. Furthermore, if DA-VOI was to be used more routinely in the priority setting process, this could probably be achieved more easily than in the pilots. For example, closer coordination between the vignette production and the DA-VOI, and more involvement of the panels and NCCHTA in the DA-VOI process, would almost certainly improve the implementation process.

Objective III: Establish the resource implications of adopting these methods more widely within the HTA programme

It was possible to quantify the resource implications of the approach that was adopted in the pilots: each of the case-studies undertaken required approximately 6 weeks' whole-time-equivalent researcher input, made up of a mix of experience levels, spread over 10–12 weeks. The aggregate effect of a more extensive use of these methods would depend on the specific details of implementation. There will be other resource implications in addition to undertaking the analysis; for example, training NCCHTA staff and panel members about how to interpret and contribute to the DA-VOI process. However, it is

recognised that there are capacity constraints, in terms of appropriately trained analysts, which may limit widespread introduction of the methods, at least in the short term.

Objective IV: Identify the most appropriate way to extend the use of these methods within the prioritisation process

Several options for the extended use of DA-VOI have been considered in this chapter. It is recognised that the resource implications and capacity constraints make it unrealistic to imagine that DA-VOI can be undertaken with each topic presented to the panels. Possible options include the use of the methods to assess the sort of budget that might be allocated to a project when a decision has been made to commission primary research. Another is to use DA-VOI only with the PSG. Perhaps the most compelling approach, however, would be to work up a proportion of topics for DA-VOI once they have been identified for a vignette based on existing methods. The identification of topics could be based on the original selection criteria proposed in this pilot or on some assessment of the potential costs of commissioning research for the topic. Combined vignette production and modelling would mean that vignette and associated analysis could go to the panels and there would be an opportunity to respond to any feedback from that meeting. At PSG, there would be an analysis that directly addresses the question in the vignette and would include additional analysis to explore any concerns or issues raised by the panel. This would allow an iterative process of development from vignette production to feedback from the panel to consideration by PSG.



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Contributions of authors

Karl Claxton was the overall lead for the project. He was involved in the construction of all four

models and had primary responsibility for report writing. Laura Ginnelly was involved in the construction of all four models and contributed to report writing. Mark Sculpher provided input at all stages and contributed to report writing. Zoë Philips was involved in the construction of the asthma and COPD models. She read and commented on various drafts of the report. Steve Palmer was involved in the development of the AMD model, and read and commented on various drafts of the report.



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Appendix I

Documents presented to Therapeutic Procedures Panel

A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme

Assessing the cost-effectiveness of manual chest physiotherapy techniques for asthma

Background

Policy background

Manual chest physiotherapy is used for a range of respiratory disorders including asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis. A recent Cochrane review, 'Manual therapy for asthma', has concluded that there is insufficient evidence to either support or refute the use of manual chest physiotherapy techniques in asthma patients.

Decision problem

The analysis reported here has assessed the cost-effectiveness of, and potential value of future research for, manual chest physiotherapy interventions compared with no intervention in children treated in the community, adults treated in the community and children treated in hospital. The specific interventions under investigation are massage therapy, chiropractic spinal manipulation (CSM) and physical therapy.

Methods

Description of the model

The structure of the decision model is illustrated in *Figure 1*. Based on the trial evidence, three different techniques for manual therapy are evaluated: massage therapy, chiropractic spinal manipulation (CSM) and physical therapy. Massage therapy and CSM were evaluated for both children and adults treated in the community. Physical therapy was evaluated for

children treated in hospital. The effect of the interventions is modelled as changes in lung function measured by FEV₁ (forced expiratory volume in one second). The proportional change from the baseline FEV₁ (FEV₁ with no intervention for each patient group) is based on reported trial results. EQ-5D quality of life scores (in terms of 0 to 1 'utilities') and daily medication costs are predicted contingent on FEV₁ values using a series of equations derived from the 1996 Health Survey for England (HSE). Predicted EQ-5D scores are used to calculate expected QALYs for each intervention and baseline. Total expected costs of community based interventions include the cost of medications, and intervention costs. Physical therapy for the hospitalised children also includes an inpatient admission cost. Baseline length of stay (LOS) and change in LOS were taken from the relevant trial and added as an additional parameter in the model. The total cost of physical therapy, therefore, consisted of the cost of drugs, intervention and inpatient hospitalisation. Treatment effect and costs are only sustained while treatment continues. The time horizon of the model is 30 days and the perspective is the NHS.

The evidence

The Cochrane review and an updated search identified four (English language) trials that have evaluated the use of chest physiotherapy in patients with asthma. Although the outcomes reported in the trials are varied, all included measures of lung function such as FEV₁. The only outcome that can be related to quality of life was FEV₁ using the 1996 HSE. There is no evidence to relate other reported outcomes to quality of life or resource use. Random effects meta-analysis was used to pool data from two trials (Balon & Field) to provide a common baseline measure for children treated in the community, as well as the effects of CSM (Balon & Neilson). The proportional change from baseline as reported in trials (or meta-analysis) is used to obtain the treatment effect of each intervention for each patient group. Distributions were assigned to baseline and effect based on the standard errors reported in the trials or estimated from the meta-analysis. Distributions were also assigned to the

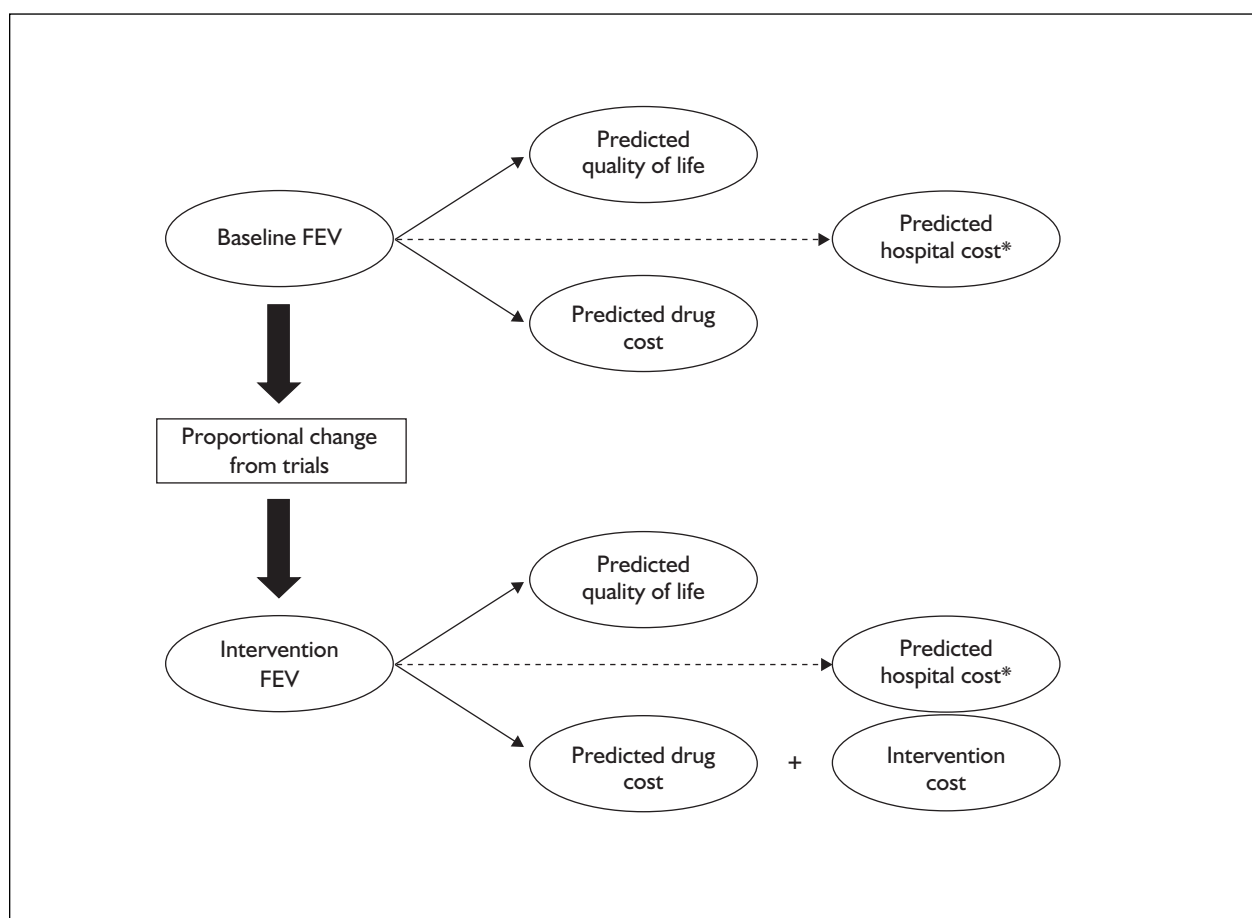


FIGURE I Model structure. *Physical therapy in children with severe asthma only.

coefficients of the equations (derived from the 1996 HSE), which predicted EQ-5D scores and daily medication costs, based on estimated standard errors (the correlation between the coefficients of the prediction equation were accounted for). Advice about the model structure and sources of evidence was taken from Dr Mike Pearson (Royal College of Physicians, London).

Analysis

Monte Carlo simulation was used to run the model and to generate cost-effectiveness acceptability curves for the three patient groups. The output of these simulations was used to estimate the expected value of perfect information (EVPI) for individual patients. Population EVPIs were based on the incidence of asthma for the different patient groups (based on overall asthma incidence and evidence of the proportion of asthma patients in each group), and alternative assumptions about the expected lifetime of the technology of 5, 10 and 15 years. An analysis of the partial EVPIs associated with groups of model inputs was also conducted.

Results

Cost-effectiveness

Adults treated in the community

Massage cannot be regarded as cost-effective (incremental cost per QALY gained of over £200,000). CSM is also not cost-effective and is dominated by no intervention. Moreover, this decision is not uncertain: the probability that no intervention is cost-effective at a threshold of £30,000 per QALY is 1, and remains very high over a range of cost-effectiveness thresholds.

Children treated in the community

Massage may be regarded as cost-effective (incremental cost per QALY gained of £11,012 compared to no intervention). However, this is uncertain and the probability that massage is cost-effective at the threshold of £30,000 per QALY is 0.87. CSM is not cost-effective and is dominated by both massage therapy and no intervention. The decision uncertainty for children treated in the community is illustrated in Figure 2.

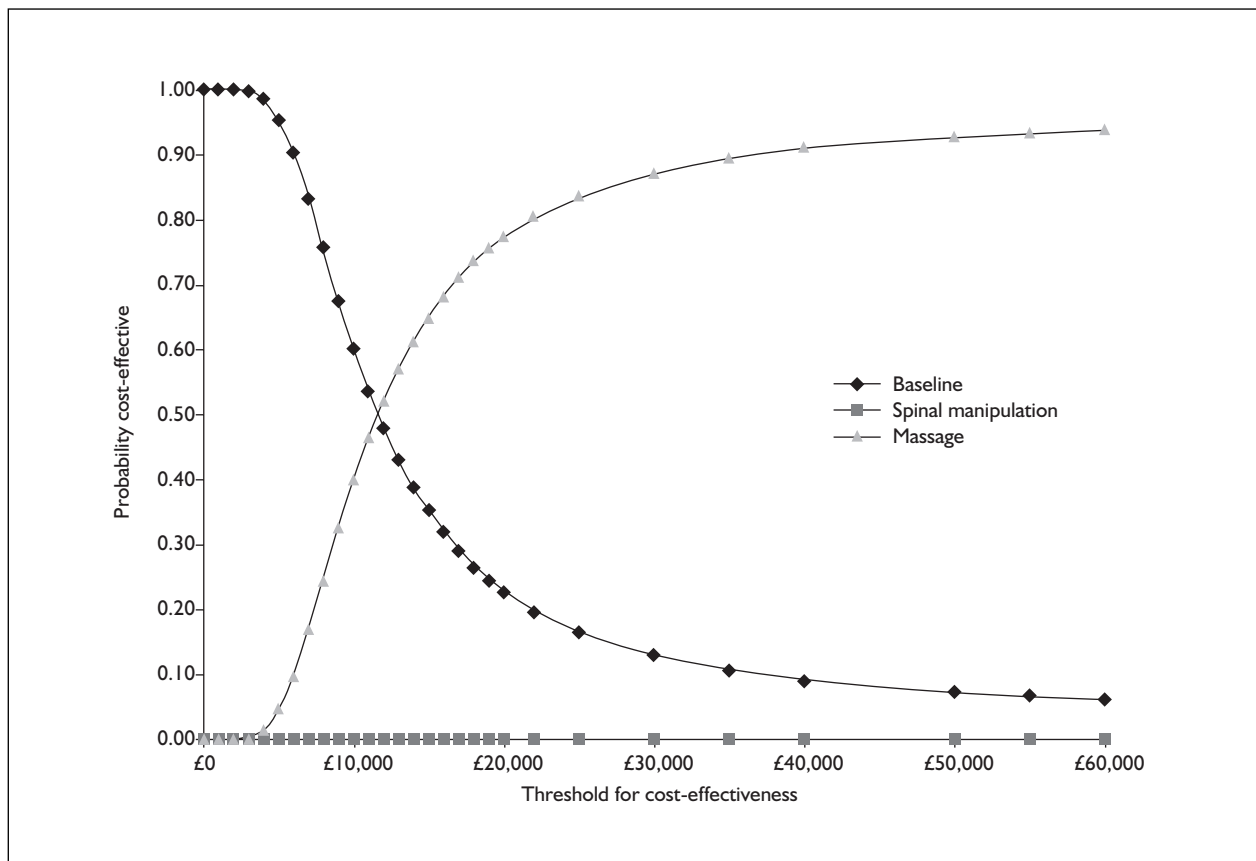


FIGURE 2 Cost-effectiveness acceptability curve (children treated in the community)

Children treated in hospital

Physical therapy can be regarded as cost-effective as it is associated with higher QALYs and lower costs than no intervention (due to expected reductions in LOS). There is little uncertainty associated with this decision. The probability that physical therapy is cost-effective is above 0.92 at a threshold value of £30,000 and remains high over a wide range of threshold values.

Expected value of perfect information

The population EVPI for the three patient groups is illustrated in *Figure 3*.

Adults treated in the community

At a threshold for cost-effectiveness of £30,000 per QALY, the population EVPI is zero for a 5-, 10- and 15-year lifetime of the technology (at thresholds greater than £40,000 per QALY the population EVPI becomes positive).

Children treated in the community

At a threshold for cost-effectiveness of £30,000 per QALY, the population EVPI is above £14.5 million assuming a 10-year lifetime for the technology (£9

and £18.5 million assuming a lifetime of 5 and 15 years, respectively).

Children treated in hospital

At a threshold for cost-effectiveness of £30,000 per QALY, the population EVPI is £1.2 million assuming a 10-year lifetime for the technology (£0.7 and £1.6 million assuming a lifetime of 5 and 15 years, respectively).

Partial EVPIs

Adults treated in the community

As the population EVPI for the decision is zero at a threshold of £30,000, the partial EVPIs for each of the model inputs are also zero.

Children treated in the community

The partial EVPIs for model inputs are illustrated in *Figure 4* for a threshold of £30,000 per QALY and a 10-year lifetime for the technology. All model inputs have positive EVPIs but the value of information associated with the effect of massage on FEV is £14.2 million which is substantially higher than any other model inputs and accounts for most of the decision EVPI.

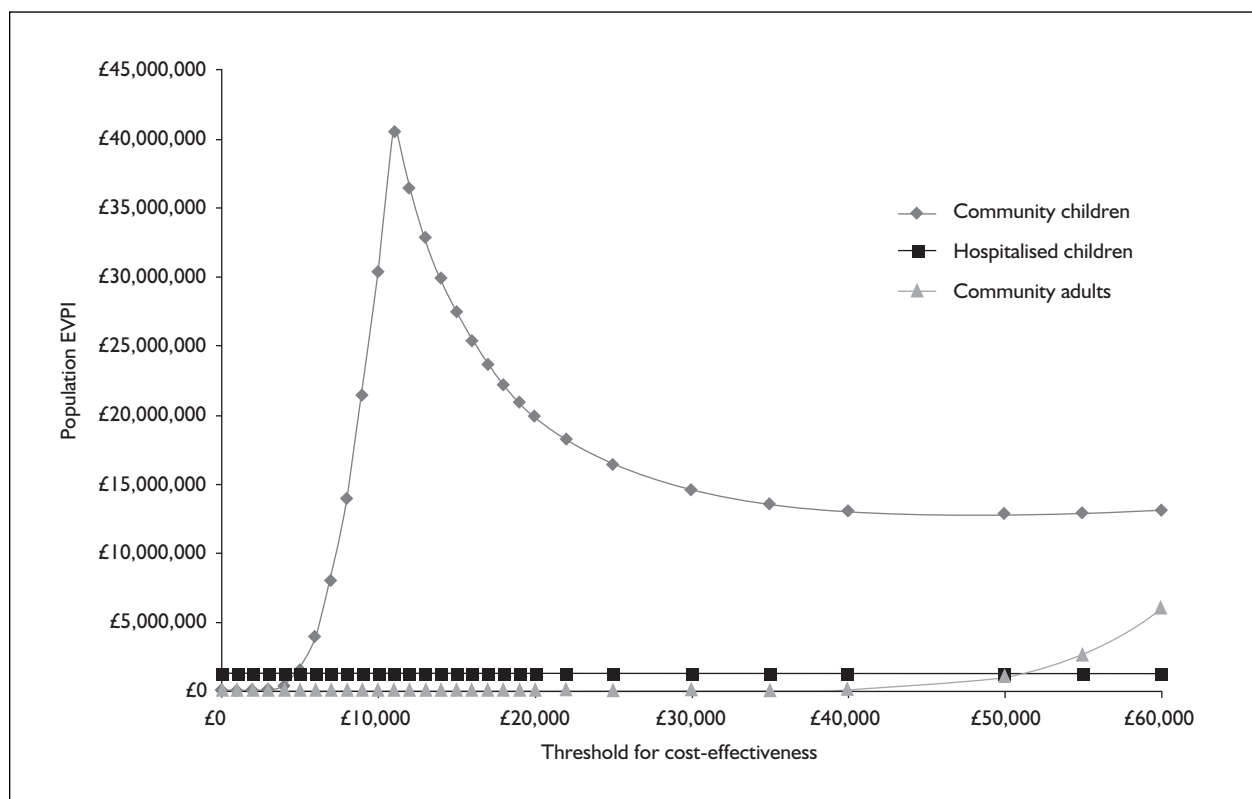


FIGURE 3 Population EVPI

Children treated in hospital

The partial EVPIs for model inputs are illustrated in *Figure 5* for a threshold of £30,000 per QALY and a 10-year lifetime for the technology. The value of information associated with the effect of physical therapy on LOS is £1.2 million and accounts for almost all of the decision EVPI. Other inputs have zero value of information associated with them.

Conclusions

Manual physiotherapy (massage or CSM) for adults treated in the community is unlikely to be cost-effective. Furthermore, there is very little decision uncertainty and the value of additional information is negligible. The costs of proposed research are likely to exceed the population EVPI over a range of plausible cost-effectiveness thresholds and additional research is unlikely to be cost-effective.

Massage for children treated in the community may be cost-effective. The value of information is substantial (£14.5 million) at a cost-effectiveness threshold of £30,000, and is likely to exceed the costs of additional investigation, which suggests that further research will be potentially cost-effective. The EVPI associated with the model inputs suggests that any further research should focus on the effect of massage on lung function. Additional investigation of CSM is unlikely to be worthwhile.

Physical therapy for children treated in hospital may be cost-effective. The value of information is £1.2 million, at a cost-effectiveness threshold of £30,000 and, if the cost of additional investigation is lower than the population EVPI, then further research may be worthwhile. The EVPI associated with the model inputs suggests that if further research is conducted it should focus on the effect of physical therapy on length of hospital stay.

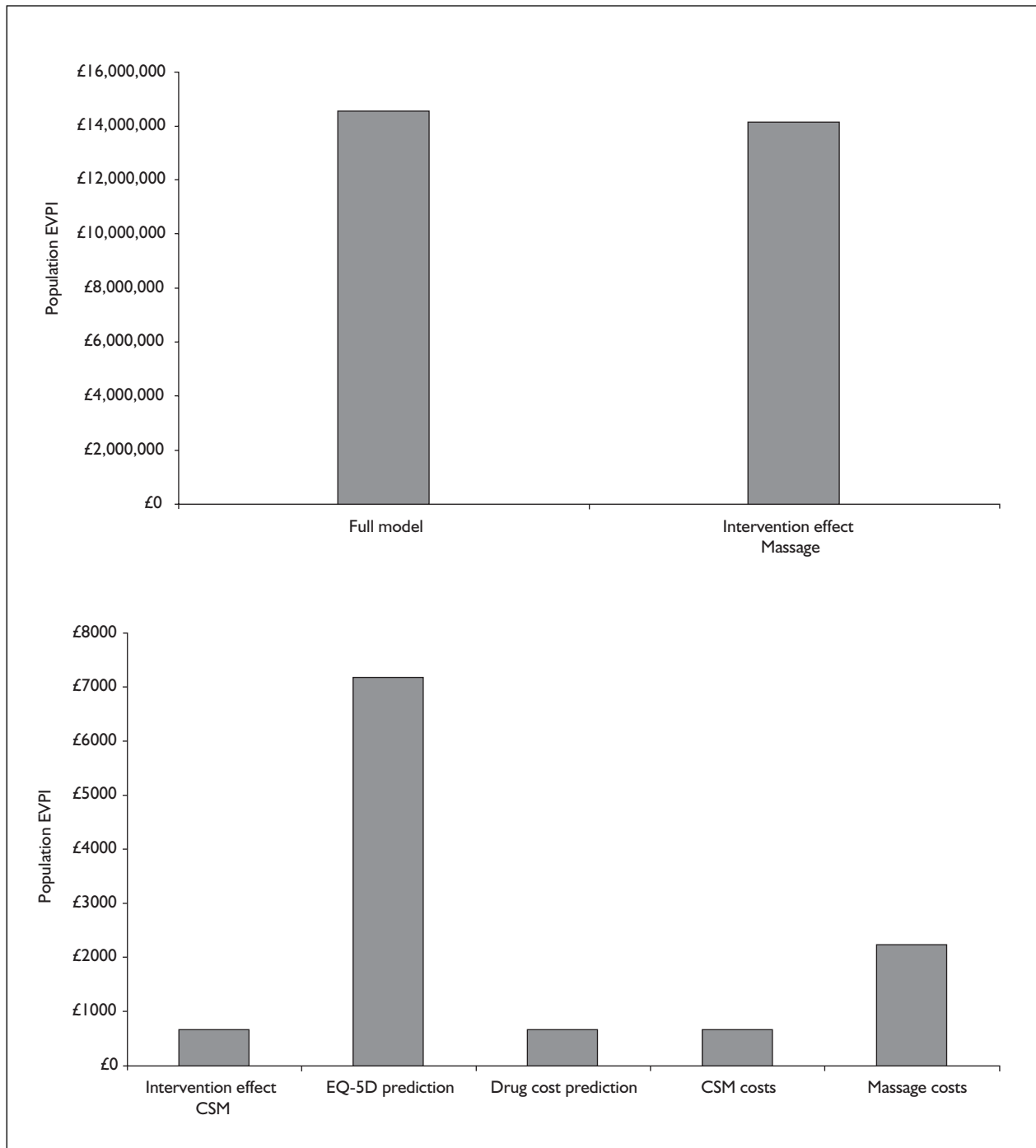


FIGURE 4 Partial EVPI (children treated in the community)

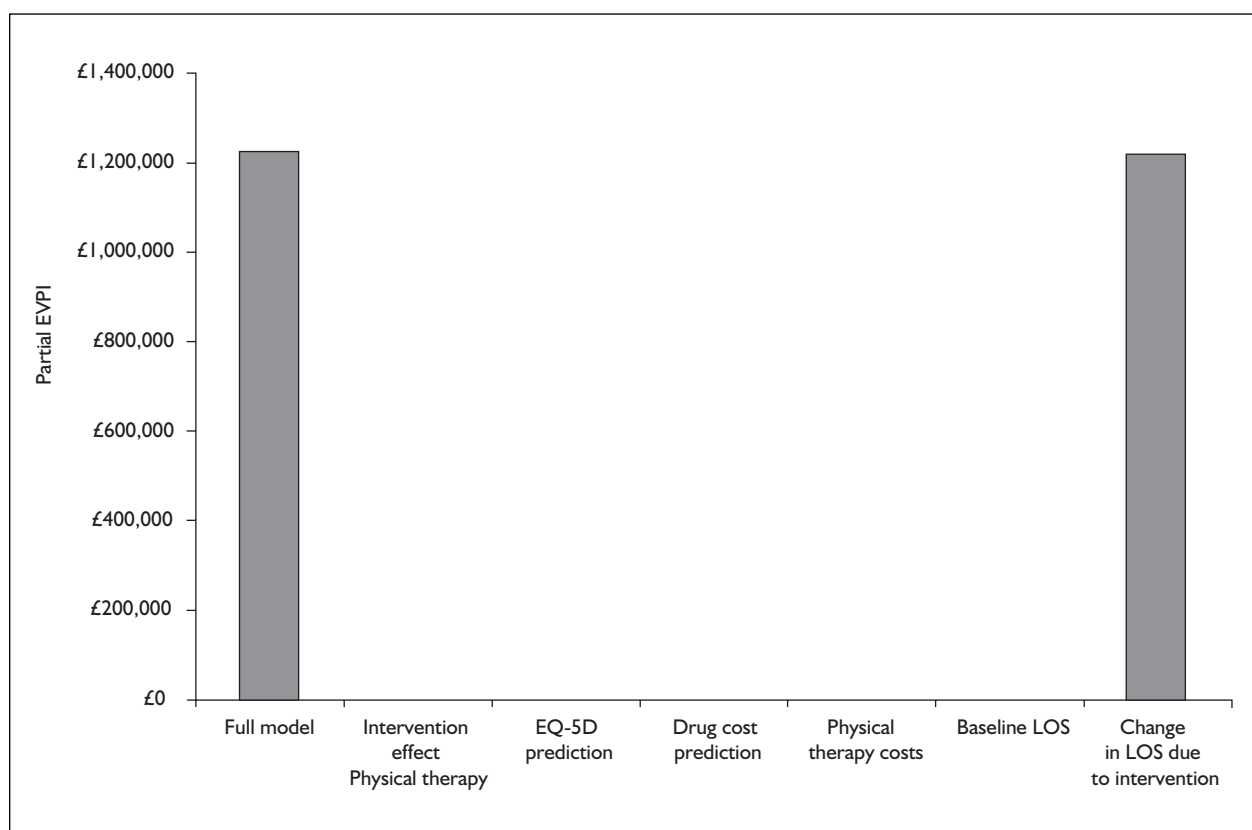


FIGURE 5 Partial EVPI (children treated in hospital)

A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme

Assessing the cost-effectiveness of manual chest physiotherapy techniques for adults with chronic obstructive pulmonary disease

Background

Policy background

Manual chest physiotherapy is used for a range of respiratory disorders including asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis. The techniques used include postural drainage, chest percussion, vibration, chest shaking, directed coughing and autogenic drainage. A recent Cochrane review has concluded that there is insufficient evidence to either support or refute the use of manual chest physiotherapy techniques in COPD patients.

Decision problem

We have assessed the cost-effectiveness of, and potential value of future research for, manual chest physiotherapy interventions compared with no such intervention in adults with COPD. The specific interventions under investigation are autogenic drainage, active breathing, the use of a heat lamp and chest percussion with drainage.

Methods

Description of model

The structure of the decision model is illustrated in *Figure 1*. The effect of the interventions is modelled as change in lung function measured by FEV₁ (forced expiratory volume in one second). The proportional change from the baseline FEV₁ (FEV₁ with no intervention) is based on reported trial results. EQ-5D quality of life scores (in terms of 0 to 1 'utilities'), daily medication cost and hospitalisations are predicted contingent on FEV₁ values using a series of equations derived from the 1996 Health Survey for England (HSE). Predicted quality of life scores are used to calculate expected QALYs for each intervention and baseline. Hospital costs are based on predicted

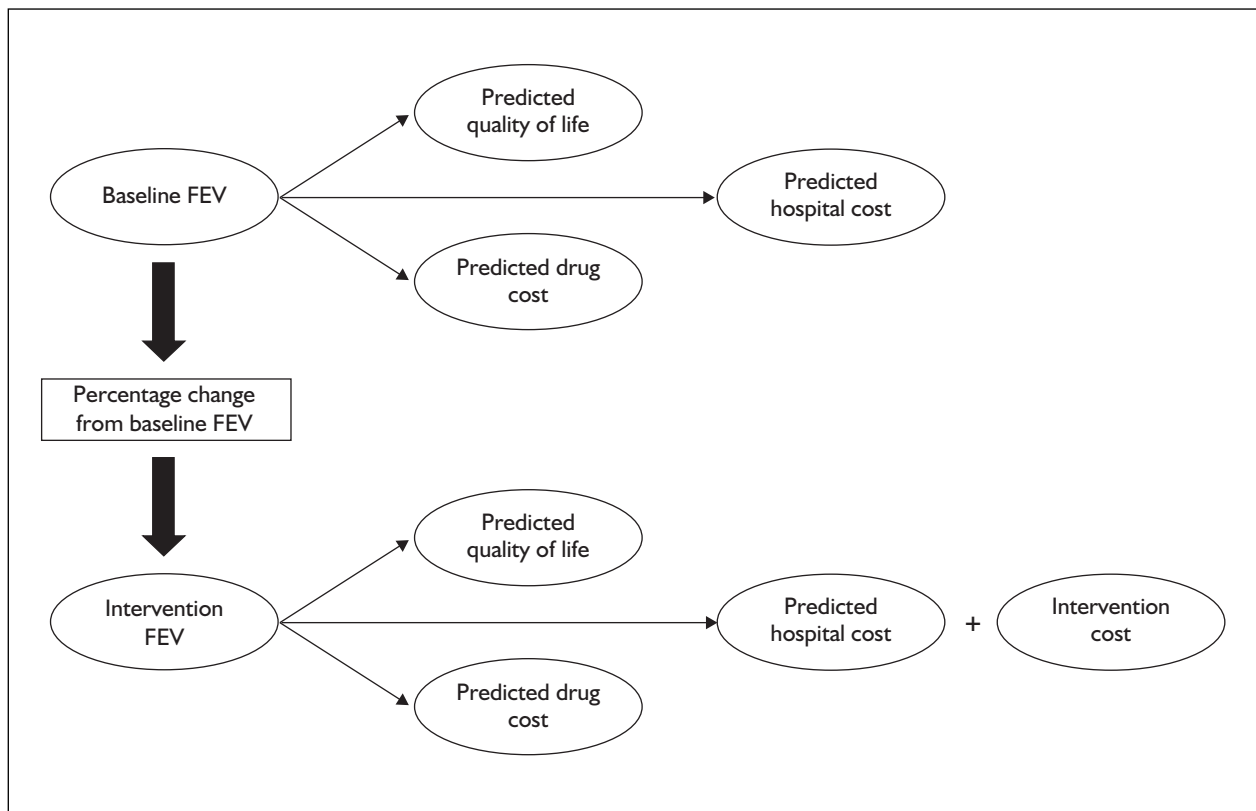


FIGURE 1 Model structure

hospitalisations and average length of stay for COPD patients. Total expected costs include the cost of medications, hospitalisations and intervention costs. Treatment effect and costs are only sustained while treatment continues. The time horizon of the model is 30 days and the perspective is the NHS.

Evidence

The Cochrane review and an updated search identified eight trials that have evaluated the use of chest physiotherapy in patients with COPD. The outcomes used in the trials were varied and include sputum weight, sputum production, radioaerosol clearance from the lung and peripheral lung, radioaerosol retention in the lung, arterial oxygen partial pressure (PaO_2) and lung function measures such as FEV_1 , peak expiratory flow rate (PEFR) and forced vital capacity (FVC). Beneficial effects have been confined to sputum production and radioaerosol clearance outcomes, but there is no evidence to relate these outcomes to quality of life. The only end-point that could be related to quality of life was FEV_1 by using the 1996 HSE. Without patient-level data, it was not possible to link FEV_1 with other outcomes, such as sputum production. Two

trials report FEV_1 as an outcome. Savci *et al.* compared autogenic drainage and the active cycle of breathing in adult male patients with stable clinical COPD. May and Munt compared the physiological effects of chest percussion and drainage with heat lamp therapy in adults with stable chronic bronchitis. Baseline FEV_1 was based on a pooled estimate from Savci *et al.* with a distribution based on the 95% confidence interval of the pooled data. The proportional change from baseline, as reported in both trials, is used to obtain the treatment effect of each intervention, and distributions were assigned based on the standard errors reported in the trials. Distributions were also assigned to the coefficients of the equations (derived from the 1996 HSE), which predict quality of life scores, daily medication costs and hospitalisations, based on estimated standard errors; the correlations between the coefficients of the prediction equation were also accounted for. Each intervention was assigned a fixed cost, which was derived from a standard NHS cost estimate for a hospital-based physiotherapist. Advice about the model structure and sources of evidence was taken from Dr Mike Pearson (Royal College of Physicians, London).

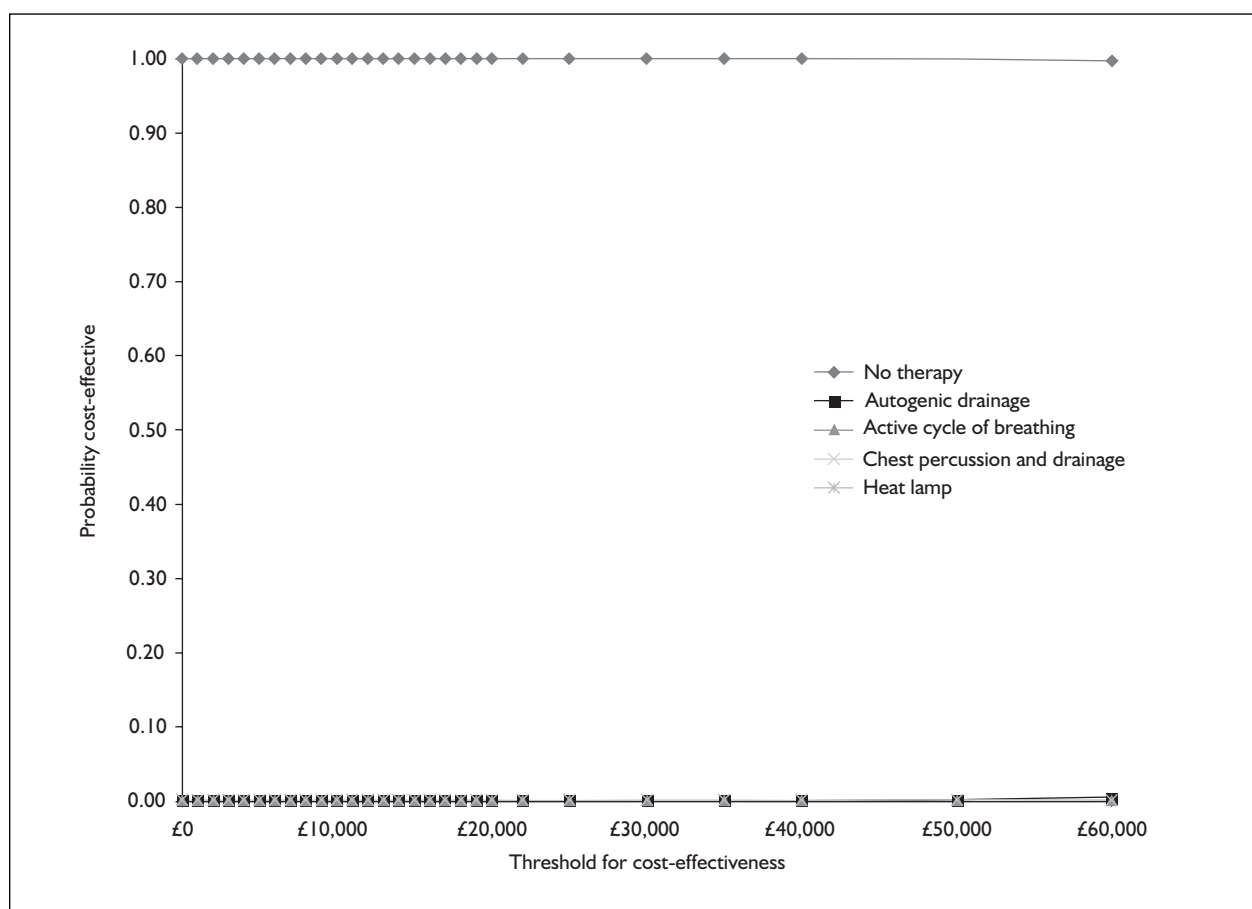


FIGURE 2 Cost-effectiveness acceptability curve

Analysis

Monte Carlo simulation was used to run the model and to generate cost-effectiveness acceptability curves for adults with COPD. The output of this simulation was used to estimate the expected value of perfect information (EVPI) for individual patients. Population EVPIs were based on the estimated incidence and prevalence of COPD, and alternative lifetimes of the technology of 5, 10 and 15 years.

Results

Cost-effectiveness

Manual chest physiotherapy techniques cannot be regarded as cost-effective when compared with no physiotherapy (incremental cost per additional QALY for autogenic drainage compared with no therapy = £232,673; all other interventions are dominated by autogenic drainage). Moreover, this decision is not uncertain (probability that no chest physiotherapy is cost-effective at a threshold of £30,000 is 1, falling to 0.9963 at a threshold of

£60,000). The decision uncertainty over a range of threshold values is illustrated in *Figure 2*.

Expected value of perfect information

The population EVPI for adults with COPD is illustrated in *Figure 3*. At a cost-effectiveness threshold of £30,000, the population EVPI is zero for a 5-, 10- and 15-year lifetime for the technology. At cost-effectiveness thresholds greater than £40,000 per QALY, the population EVPI becomes positive (£205,556 at a threshold of £60,000 per QALY and a 10-year lifetime for the technology).

Partial EVPI

As the population EVPI for the decision is zero at a threshold of £30,000, the partial EVPIs for each of the model inputs are also zero. It is only at very high cost-effectiveness thresholds that a small degree of decision uncertainty results in substantial population EVPI (£6.1 million at a threshold of £100,000 per QALY, with a 10-year lifetime for the technology). In this case, there are also positive partial EVPIs associated with the

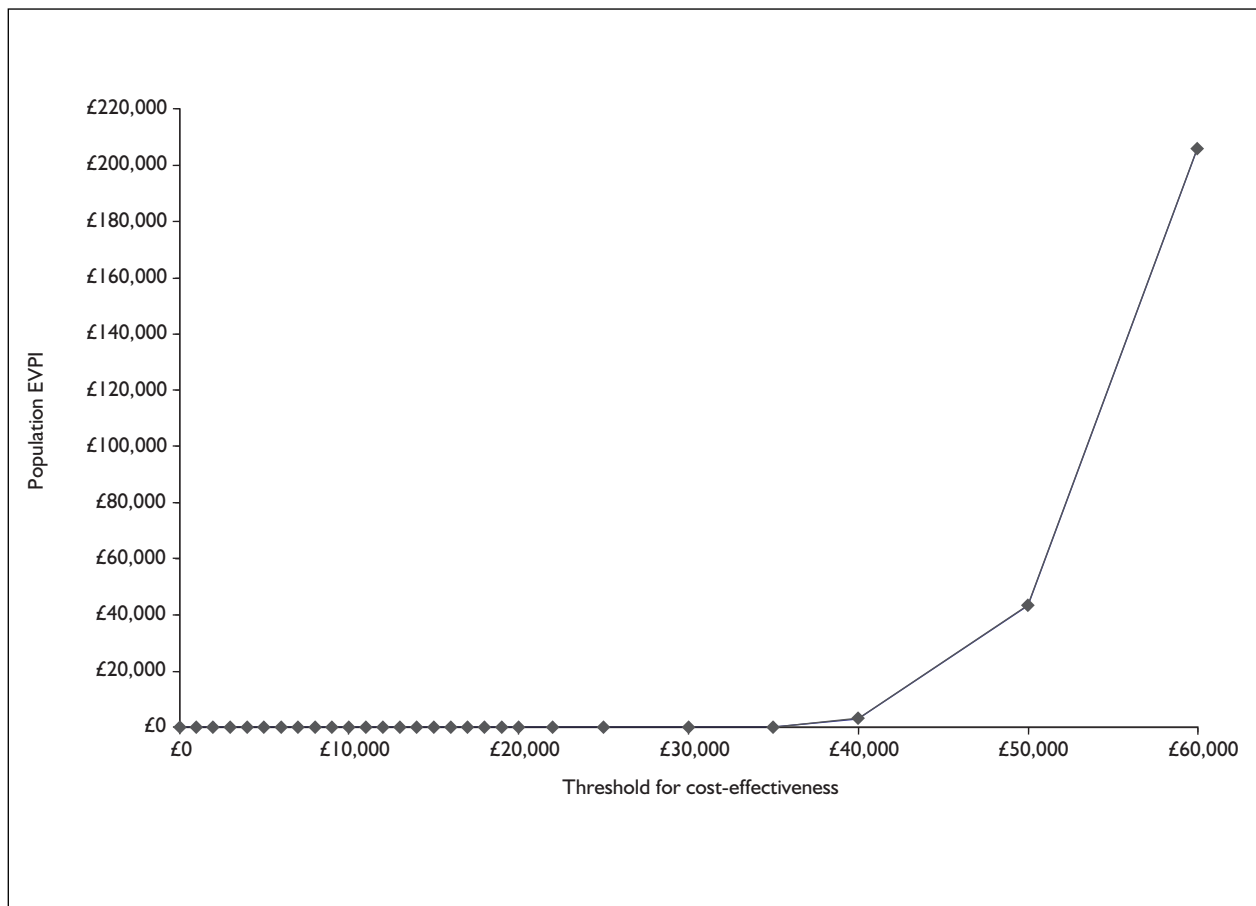


FIGURE 3 Population EVPI

proportional change in FEV₁ from autogenic drainage, breathing, the use of a heat lamp and chest percussion with drainage. However, the highest partial EVPI is associated with the equation predicting quality of life from FEV₁ (£5.2 million). Other inputs, such as the equations predicting hospitalisations and medications from FEV₁, also have positive EVPIs.

Conclusion

Manual chest physiotherapy for adults with COPD is not cost-effective. Furthermore, there is very little decision uncertainty, and the value of additional information is negligible. The costs of

proposed research are likely to exceed the population EVPI over a range of plausible cost-effectiveness thresholds and additional research is unlikely to be cost-effective.

In addition, there are some reasons why the model may overestimate the cost-effectiveness of the interventions and the population EVPI: (i) FEV₁ outcomes may be overestimated (uncontrolled placebo effects in the trials); (ii) the costs associated with physiotherapy equipment have been excluded; and (iii) the calculations of population EVPIs are based on all-age average incidence applied to the total England and Wales population (this may overestimate the population of current and future adult COPD patients).

Appendix 2

Document presented to Diagnostic Technologies and Screening Panel

A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme

Is there an effective method for screening for age-related macular degeneration?

Background

Policy background

Photodynamic therapy (PDT) for age-related macular degeneration (AMD) has recently been appraised by the National Institute for Clinical Excellence (NICE). The evidence from the Assessment Report, and the provisional guidance issued by NICE, indicate that PDT will only be potentially cost-effective for the treatment of AMD in the better seeing eye (after first eye involvement) and only for certain types of AMD (neovascular, predominantly classic, subfoveal). AMD can progress rapidly (declining visual acuity) and is a significant cause of blindness. Early PDT can halt or slow the decline in visual acuity. Earlier treatment with PDT at better starting visual acuities is more cost-effective. PDT is unlikely to be cost-effective and is not recommended for starting visual acuities lower than 20/100. A self-screening test of central vision distortion (Amsler grid) is available. Earlier treatment with PDT is beneficial, so it is possible that repeat self-screening would be cost-effective by identifying patients with AMD before their visual acuity declines.

Decision problem

AMD is a bilateral disease and, following consultation with clinical experts and the authors of the NICE Assessment Report, we have focused on the use of weekly self-screening following first eye involvement with neovascular AMD. This self-screening strategy is compared to two alternatives: no screen but diagnosis and treatment of eligible

AMD following self-referral (due to declining visual acuity) to an ophthalmologist (this strategy is consistent with provisional NICE guidance); and a strategy of no screening and no PDT. The analysis reported here has assessed the cost-effectiveness of, and potential value of future research for, these alternative strategies.

Methods

Description of the model

The structure of the decision model is illustrated in *Figure 1*. A Markov process is used to model the incidence of second eye neovascular AMD over 10 years and the decline in visual acuity following undiagnosed second eye involvement. Each week patients with positive screen results will be referred for a full eye exam by an ophthalmologist (patients may also self-refer due to declining visual acuity). The eye examination identifies patients with neovascular AMD (i.e. false positives are identified), and angiography is conducted to identify the type of disease which is eligible for PDT. Patients with diagnosed AMD which is eligible for PDT experience an expected quality of life (and costs) taken from the output of a model of PDT developed as part of the NICE appraisal of PDT. Expected quality of life with PDT depends on the visual acuity at diagnosis, where patients with better visual acuities will experience better quality of life.

The evidence

The incidence of second eye neovascular AMD, the eligibility for PDT (subtypes of AMD), the sensitivity and specificity of the Amsler grid screen and compliance with self-screening were all based on a number of observational studies. Beta distributions were assigned to reflect the amount of evidence available for each of these parameters. The decline in visual acuity for undiagnosed second eye involvement was based on the 2-year results of the control arm of the TAP trial of PDT, with beta distributions assigned to these transition probabilities. Two trials of PDT for AMD are available; however, only the TAP trial included predominantly classic AMD. The effectiveness (in

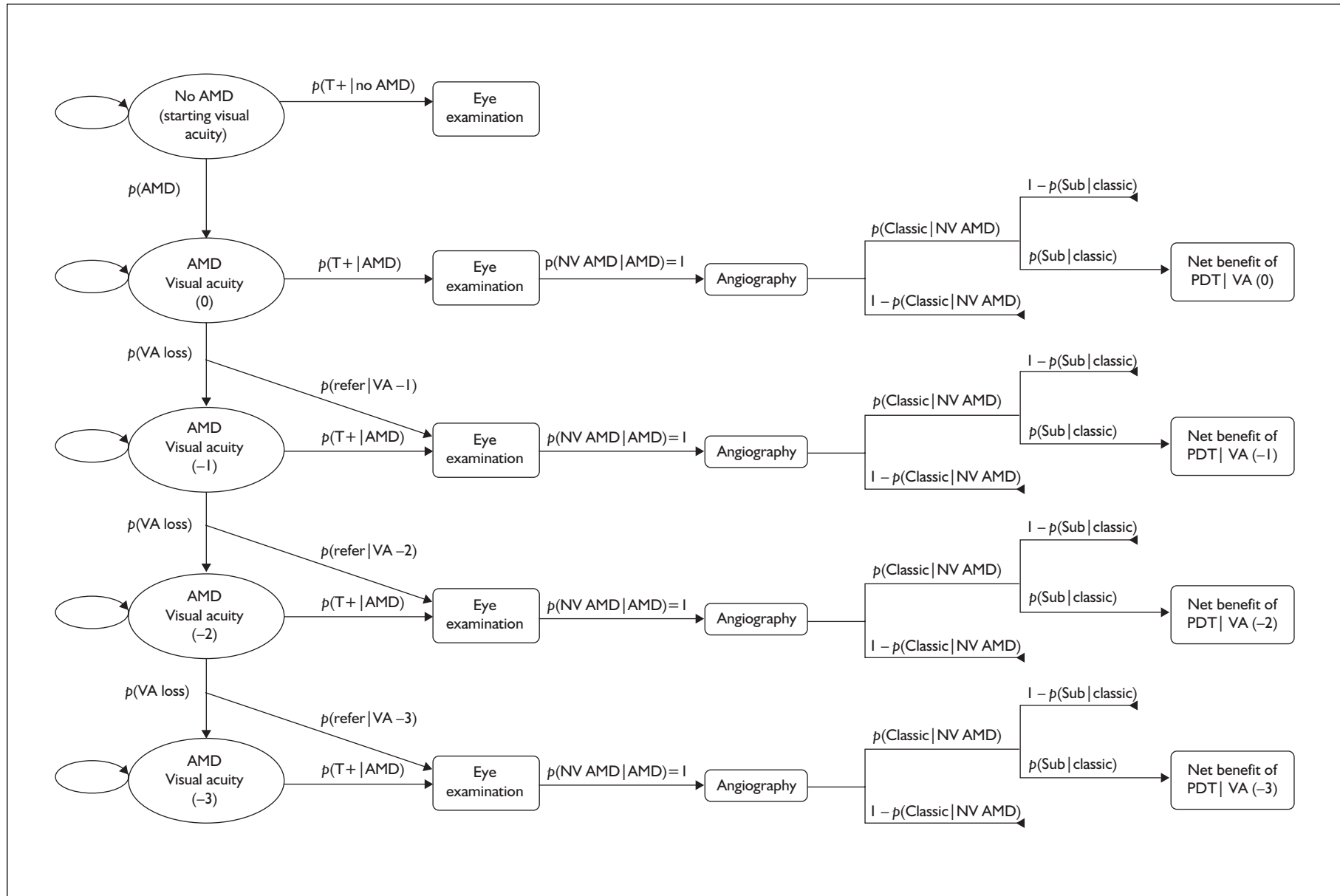


FIGURE I Model structure for AMD screening

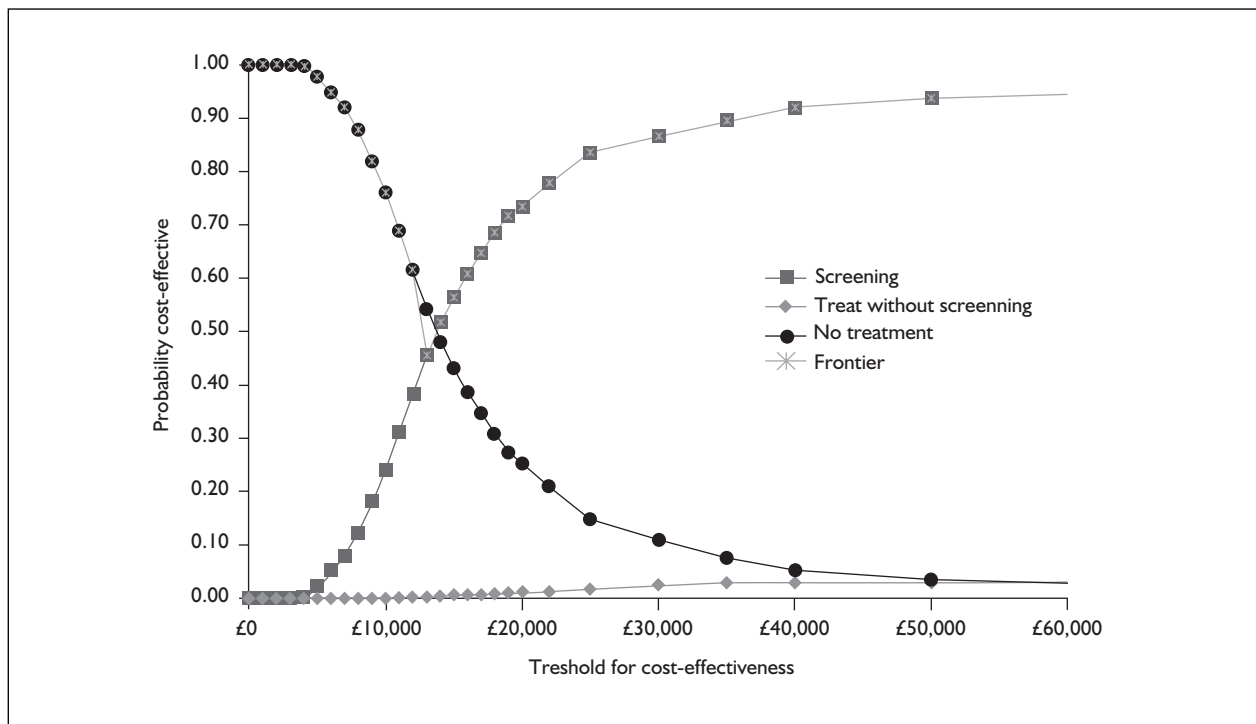


FIGURE 2 Cost-effectiveness acceptability curve (male with a starting visual acuity of 20/40)

terms of QALYs) and cost of PDT for diagnosed eligible patients were based on a probabilistic model, which used patient level data from the classic, subfoveal subgroup of the TAP trial. Expected QALYs over 5 years for PDT and for control were available for eight starting visual acuities. Gamma distributions were assigned using the reported means and variances. No evidence was available regarding the probability that patients will self-refer following each decline in visual acuity. Therefore, clinical judgements were used with beta distributions reflecting the range of possible values. The costs of PDT were based on the earlier model and the costs of screening and diagnosis were based on the NICE Assessment Report. All-cause mortality was also incorporated in the model (for a male and female population aged 55–64) based on UK life tables. Advice about model structure and sources of evidence was taken from Mr Richard Wormald (Moorfields Eye Hospital) and Dr Liam Smeeth (London School of Hygiene).

Analysis

Monte Carlo simulation was used to run the model and to generate cost-effectiveness acceptability curves for starting visual acuities of 20/40 and 20/80, and for male and female populations aged 55–64. The output of these simulations was used to estimate the expected value of perfect information (EVPI) for individual patients. Estimates of the current and future

patient population were based on the incidence of first eye AMD (NICE Assessment Report) and a lifetime for the technology of 5, 10 and 15 years. An analysis of the partial EVPIs associated with groups of model inputs was also conducted.

Results

Cost-effectiveness

For patients with a starting visual acuity of 20/40, screening can be regarded as cost-effective when compared to no treatment (incremental cost per additional QALY = £12,740). The strategy of no screen but treatment on diagnosis is not cost-effective when compared to no treatment (incremental cost per additional QALY = £54,670) and is extendedly dominated. However, the cost-effectiveness of screening is uncertain (probability that screening is cost-effective with a threshold for cost-effectiveness of £30,000 is 0.866), and this decision uncertainty is illustrated in *Figure 2*.

Screening is less cost-effective when compared to no treatment (incremental cost per additional QALY = £17,881) and is more uncertain (probability that screening is cost-effective with a threshold for cost-effectiveness of £30,000 is 0.7) for patients with a lower starting visual acuity of 20/80. Cost-effectiveness and decision uncertainty are very similar for both males and females.

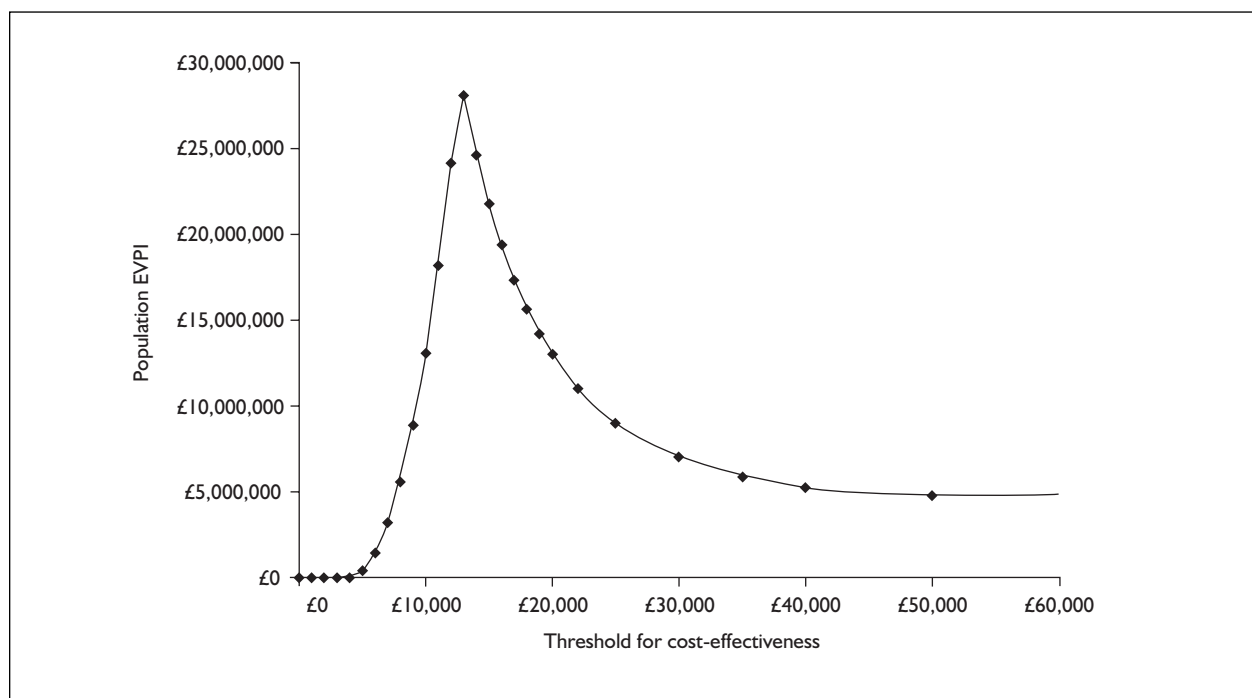


FIGURE 3 Population EVPI (male with a starting visual acuity of 20/40)

Expected value of perfect information

The population EVPI for a starting visual acuity of 20/40 is illustrated in *Figure 3*. At a threshold for cost-effectiveness of £30,000 the population EVPI is £6.95 million assuming a 10-year lifetime for the technology (£178 for individual patients) or £3.91 and £9.18 million assuming a lifetime of 5 and 15 years, respectively. The population EVPI with starting visual acuity of 20/80 is higher: £18.26 million assuming a 10-year lifetime of the technology (£468 for individual patients) or £3.91 and £9.18 million assuming a lifetime of 5 and 15 years, respectively. Estimates of EVPI for male and female populations are very similar.

Partial EVPIs

The partial EVPI for groups of model inputs is illustrated in *Figure 4* for a threshold for cost-effectiveness of £30,000 and a 10-year lifetime for the technology. For patients with a starting visual acuity of 20/40, the value of information associated with the expected QALYs from PDT is £1.35 million. The other groups of model inputs, such as screening accuracy, have no value of information associated with them. At a starting visual acuity of 20/80, the value of information associated with the expected QALY from PDT is £2.83 million and the value associated with the expected QALYs with no treatment is £1.05 million. The other groups of model inputs have no value of information associated with them.

In general, partial EVPIs will not sum to the EVPI for the decision as a whole. In this case many of the groups of model inputs have no value associated with them. This does not mean that the uncertainty surrounding their values is unimportant (together, they generate the EVPI for the decision) but it does mean that more information about these inputs individually may not be valuable.

Conclusions

Self-screening first eye neovascular AMD appears to be a potentially cost-effective intervention for patients with initial visual acuities ranging from 20/40 to 20/80. However, the cost-effectiveness of self-screening is uncertain and, at a threshold for cost-effectiveness of £30,000 per additional QALY, the value of information surrounding the decision problem is significant, particularly when patients have lower initial visual acuities. The EVPI may exceed the cost of further investigation, which suggests that further research will be potentially cost-effective. The EVPI associated with model inputs indicates that more evidence about the impact of PDT on expected quality of life and the quality of life for those not treated with PDT would be most valuable. It also suggests that additional evidence about other inputs individually (such as screening accuracy) is of little

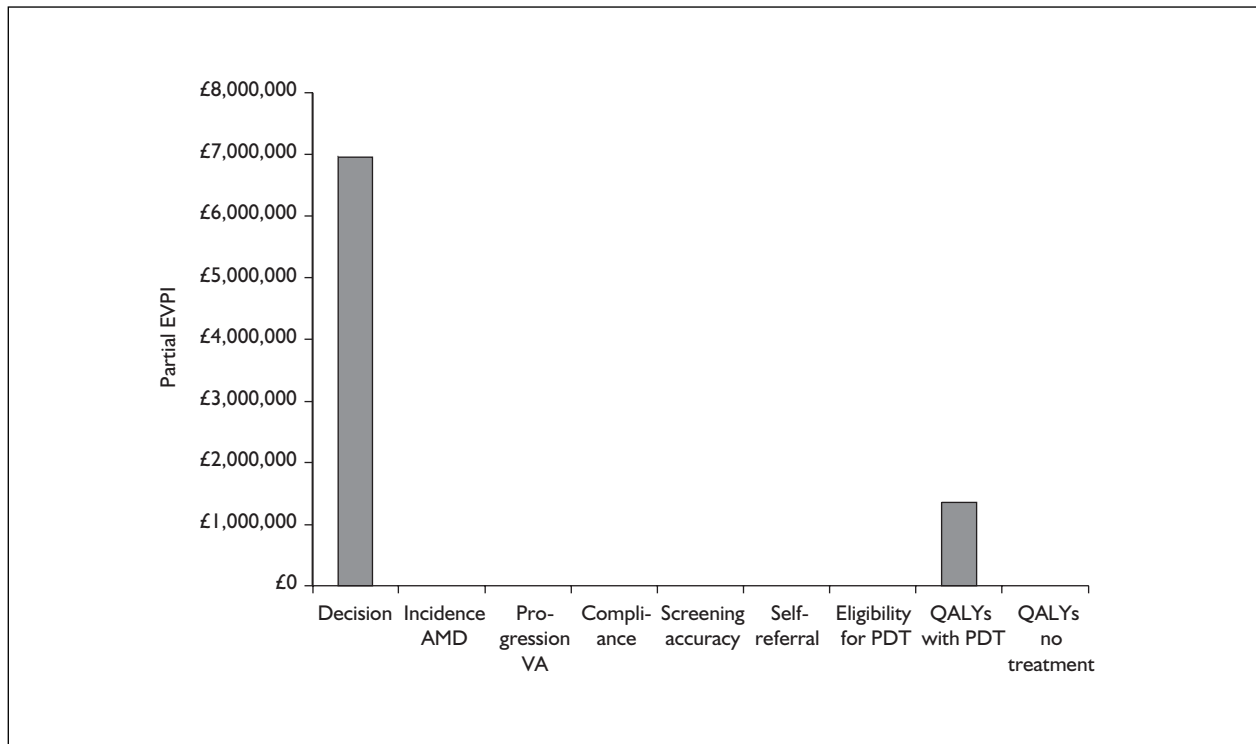


FIGURE 4 Partial EVPI (male with a starting visual acuity of 20/40)

value. However, this does not mean that additional information about all the model inputs combined would not be valuable.

This model has focused on self-screening patients with first eye neovascular AMD. A policy of self-screening for AMD before first eye involvement

would not be cost-effective because treatment will not be cost-effective in the better seeing eye and this screening strategy would generate a very large number of false-positive results and unnecessary eye examinations. Similarly, the decision uncertainty and EVPI surrounding this policy would also be very low.

Appendix 3

Document presented to the PSG

A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme

What is the cost-effectiveness of long-term antibiotic treatment for preventing recurrent urinary tract infections (UTI) in children?

Background

Policy background

Acute urinary tract infection (UTI) is common in children. Recurrent UTIs, and pyelonephritis in particular, can cause progressive renal scarring (PRS), which can lead to renal failure in later life. Long-term antibiotic treatment may be required in children and infants with recurrent UTI and normal urinary tracts, as well as for children with urinary tract abnormalities who are a greater risk of renal scarring. A recent Cochrane review found evidence that three long-term antibiotics – trimethoprim, nitrofurantoin and cotrimoxazole – may reduce the risk of recurrent UTI in children. However, the evidence for the widespread use of long-term antibiotics was regarded as “weak”.

Decision problem

The analysis reported here has assessed the cost-effectiveness of, and potential value of future research for, long-term (3-year) treatment with either trimethoprim, nitrofurantoin or cotrimoxazole compared with intermittent antibiotic treatment of infections when they occur. The analysis considers the cost-effectiveness of these interventions for children with confirmed diagnosis of recurrent UTI but no urinary tract abnormality, and for those with confirmed mild (grade I and II) vesicoureteral reflux (VUR). Severe VUR was excluded because interventions for this group are well established, and additional primary research would not be regarded as ethical. Analysis for recurrent UTI and mild VUR was conducted for boys and girls aged either 1 year or 3 years (i.e. four alternative treatments for eight patient groups).

Methods

Description of the model

The structure of the decision model is illustrated in *Figure 1*. The frequency of recurrent UTI over 3 years is modelled as a Markov process for each of the patient groups, with the impact on quality of life and resource use recorded. Each time a recurrent UTI occurs there is a chance that this will be a pyelonephritic attack, which will also have an impact on quality of life and costs. VUR status and the cumulative number of pyelonephritic attacks are important determinants of the risk of developing progressive renal scarring. Those children who develop progressive renal scarring face a risk that this will lead to end-stage renal disease (ESRD) at some time in the future. The consequences of ESRD (transplant and dialysis) include a reduction in quality-adjusted life expectancy as well as resource costs. The effect of long-term antibiotics is, therefore, established through a series of links of evidence: a reduction in the frequency of recurrent UTIs may reduce the number of pyelonephritic attacks, which may reduce the risk of PRS and the development of ESRD in later life. In this way the model uses RCT evidence of effect on frequency of UTI, combined with natural history evidence, to estimate the short-run and longer term impacts on quality-adjusted life expectancy and resource use.

The evidence

The structure of the model was used to define a number of systematic searches, which were conducted by the information service at York. In addition, a model of UTI in children and an associated systematic review were identified (1999). The effect of each of the interventions on the frequency of UTI was based on evidence from a Cochrane review (2002), which identified four trials that have evaluated the use of long-term antibiotics (trimethoprim, nitrofurantoin and cotrimoxazole) for recurrent UTI. Three trials compared intervention to intermittent antibiotic treatment, and one trial compared alternative long-term antibiotics. In order to use all the RCT evidence, multiple parameter synthesis (a generalisation of Bayesian meta-analysis) was conducted to estimate log odds ratios for each of the interventions (the posterior distributions and

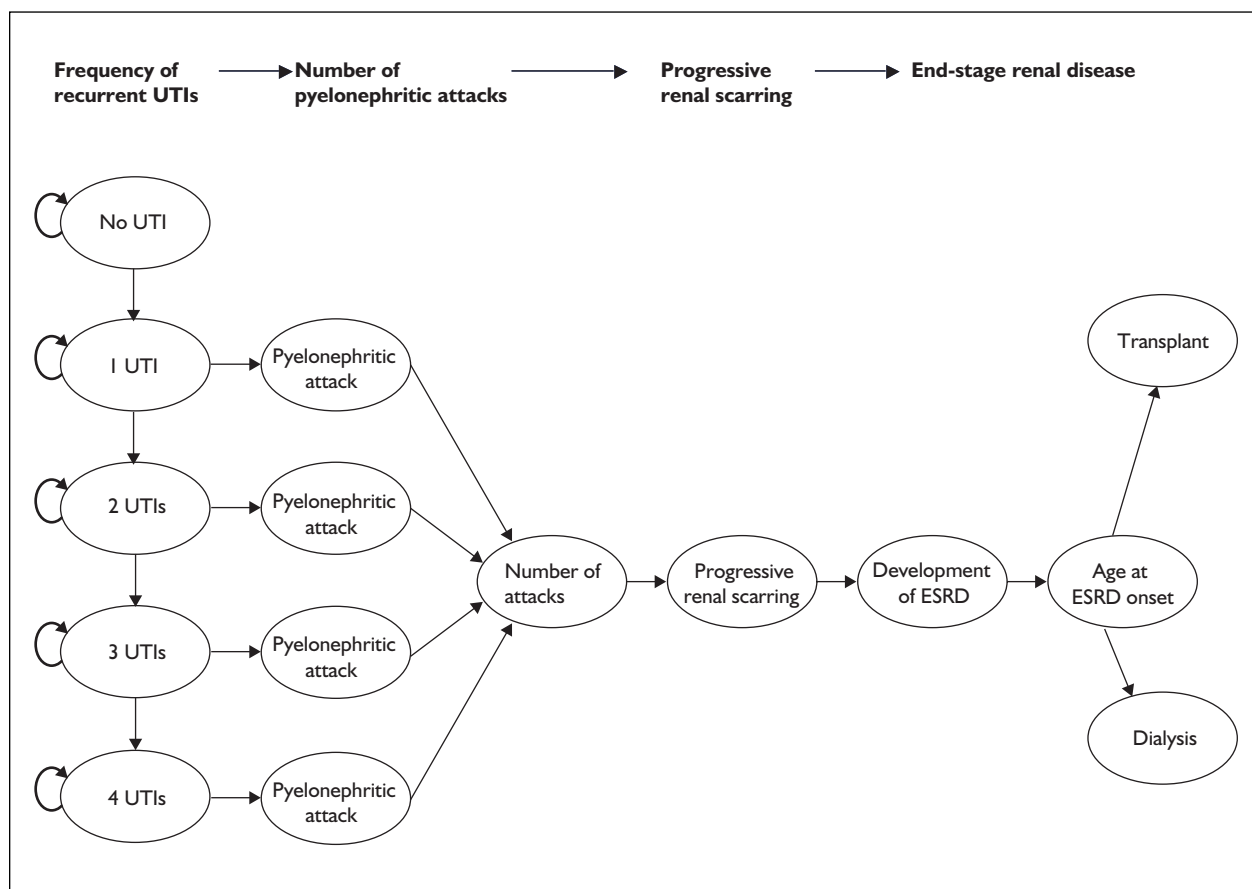


FIGURE 1 Model structure

the correlations between them were used directly in the analysis). The frequency of subsequent recurrent UTI without intervention was based on the pooled control arms of three trials. The probability of a UTI being pyelonephritic (by age and gender) and the probability of PRS given the cumulated number of pyelonephritic attacks (by VUR status) was based on natural history evidence, with beta distributions assigned reflecting the number of observations in each case. The probability of developing ESRD for children who experienced PRS was based on registry data. The age at onset of ESRD for this group of patients was based on limited evidence from two observational studies with a triangular distribution assigned to reported ranges. The impact of ESRD on quality-adjusted life expectancy was established by combining estimates of survival and quality of life following transplant and dialysis from a number of published studies (distributions were assigned based on reported standard errors or the number of observations). The impact of UTI and pyelonephritis on quality of life was also based on published sources with distributions assigned to reflect the reported ranges. The costs of intermittent treatment of UTI and pyelonephritis

were based on dosage, duration of treatment and primary/secondary care visits. The costs of ESRD were taken from the CIPFA database and estimates from a published NICE assessment report. The possibility of resistance to long-term antibiotics was not included due to a lack of suitable evidence on which to base such a model. Advice about the model structure and sources of evidence was taken from Professor Ian Watt (Department of Health Sciences, University of York) and Dr Stephen Downs (Riley Hospital for Children, University of Indiana, USA).

Analysis

Monte Carlo simulation was used to run the model and to generate cost-effectiveness acceptability curves for the eight patient groups. The output of these simulations was used to estimate the expected value of perfect information (EVPI) for individual patients. Population EVPIs were based on the incidence of recurrent UTI and mild VUR for boys and girls aged 1 and 3 years, and alternative assumptions about the expected lifetime of the technology of 5, 10 and 15 years. An analysis of the partial EVPIs associated with groups of model inputs was also conducted.

Results

Cost-effectiveness

The cost-effectiveness results are summarised in *Table 1* at the end of the document. Some form of long-term antibiotic treatment can be regarded as cost-effective for all eight patient groups (intermittent treatment is less effective and more costly in every case). There is very little uncertainty surrounding this result and the probability that intermittent treatment will be cost-effective remains very close to zero over a range of cost-effectiveness thresholds, with the highest probability being for boys aged 3 with no VUR ($p = 0.02$). There is, however, substantial uncertainty in the choice of which long-term antibiotic treatment will be cost-effective. In most cases, this choice is between trimethoprim and cotrimoxazole (at a cost-effectiveness threshold of £30,000 nitrofurantoin is never cost-effective). As expected, long-term treatment with the more effective but more costly antibiotic (cotrimoxazole) is more cost-effective for those with VUR, for younger children and in girls.

Girls aged 3 with no VUR

Long-term treatment with cotrimoxazole may be

regarded as cost-effective (incremental cost per QALY gained of £16,739). However, this is uncertain, and the probability that it is cost-effective at a threshold of £30,000 per QALY is only 0.46. This decision uncertainty is illustrated in *Figure 2* and shows that the probability that nitrofurantoin will be cost-effective is relatively low.

Girls aged 3 with VUR

Long-term treatment with cotrimoxazole is more cost-effective than in 3-year-old girls without VUR (incremental cost per QALY gained of £9157). However, this is still uncertain, and the probability that it is cost-effective at the threshold of £30,000 per QALY is 0.58.

Girls aged 1 with no VUR

Long-term treatment with cotrimoxazole may be regarded as cost-effective (incremental cost per QALY gained of £8333) and more cost-effective than in girls aged 3. However, this is uncertain, and the probability that it is cost-effective at the threshold of £30,000 per QALY is 0.50.

Girls aged 1 with VUR

Long-term treatment with cotrimoxazole is most cost-effective for this patient group (incremental

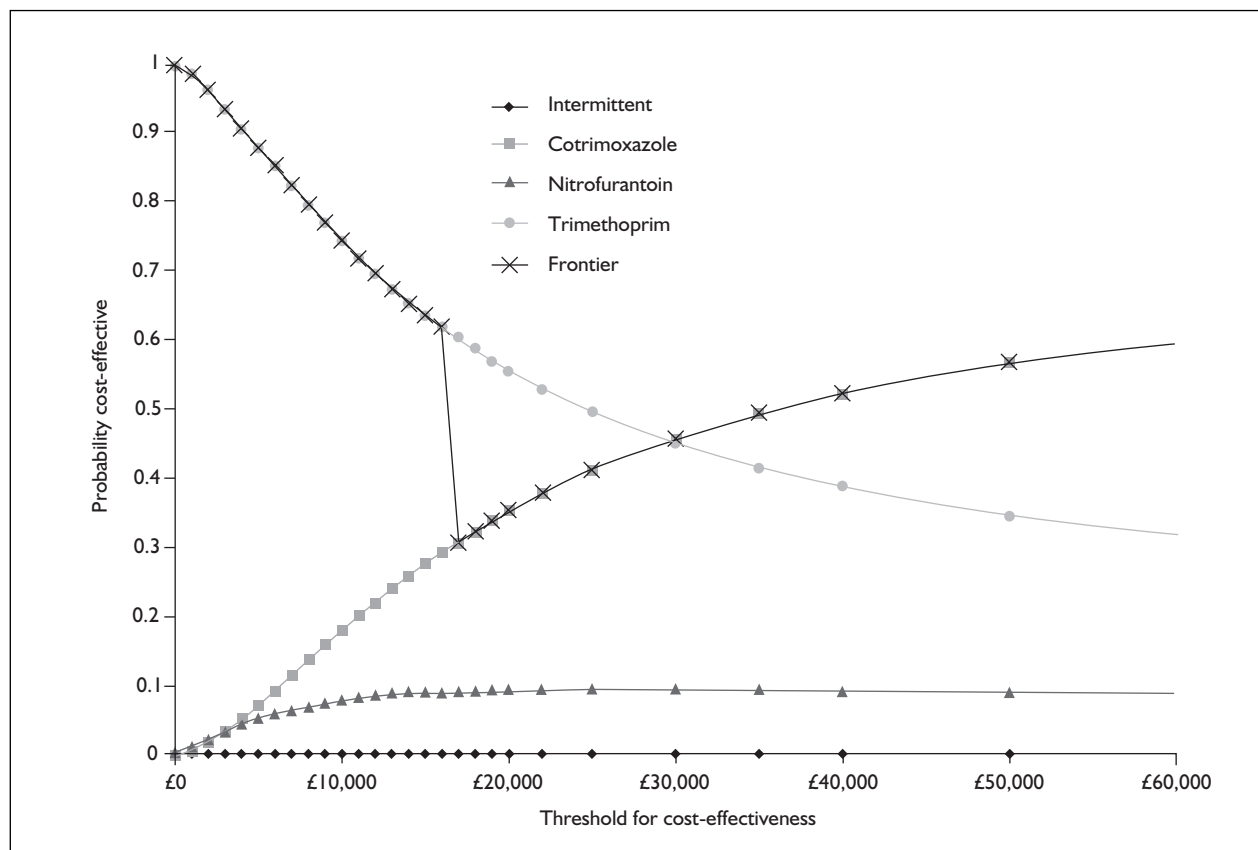


FIGURE 2 Cost-effectiveness acceptability curve (girls aged 3 with no VUR)

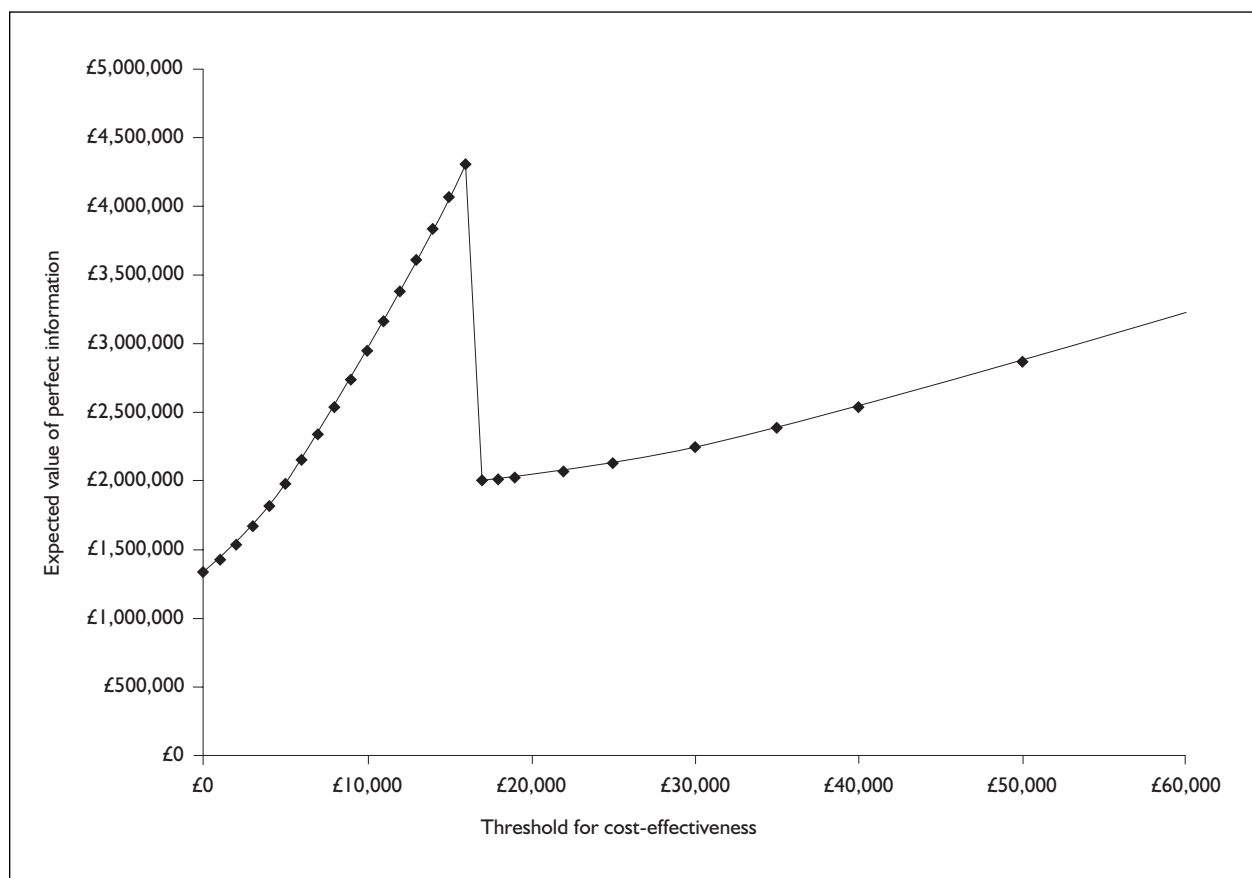


FIGURE 3 Population EVPI (girls aged 3 with no VUR)

cost per QALY gained of £2609). This choice is less uncertain than for other groups, and the probability that it is cost-effective at the threshold of £30,000 per QALY is 0.73. The probability that either nitrofurantoin or trimethoprim will be cost-effective is relatively low.

Boys aged 3 with no VUR

Long-term treatment with trimethoprim may be regarded as cost-effective, and the probability that it is cost-effective at the threshold of £30,000 per QALY is 0.77. In this case, nitrofurantoin and cotrimoxazole may not be regarded as cost-effective (incremental cost per QALY gained of £51,428 and £86,000, respectively). The probability that they will be cost-effective at a threshold of £30,000 per QALY is 0.16 and 0.05, respectively.

Boys aged 3 with VUR

Long-term treatment with cotrimoxazole is more cost-effective than in boys aged 3 with no VUR (incremental cost per QALY gained of £20,476). However, this choice is very uncertain, and the probability that it is cost-effective at the threshold of £30,000 per QALY is only 0.29.

Boys aged 1 with no VUR

Long-term treatment with cotrimoxazole is more cost-effective than in boys aged 3 (incremental cost per QALY gained of £11,111), but this choice remains uncertain and the probability that it is cost-effective at the threshold of £30,000 per QALY is 0.45.

Boys aged 1 with VUR

Long-term treatment with cotrimoxazole is most cost-effective for this group of boys (incremental cost per QALY gained of £3246). This choice is less uncertain, and the probability that it is cost-effective at a threshold of £30,000 per QALY is 0.72.

Expected value of perfect information

The population EVPIs for all eight patient groups at a threshold for cost-effectiveness of £30,000 per QALY and assuming a 10-year lifetime for the technology are reported in *Table 1* at the end of the document.

Girls aged 3 with no VUR

Population EVPI is illustrated in *Figure 3* and is highest for this patient group. This is due to

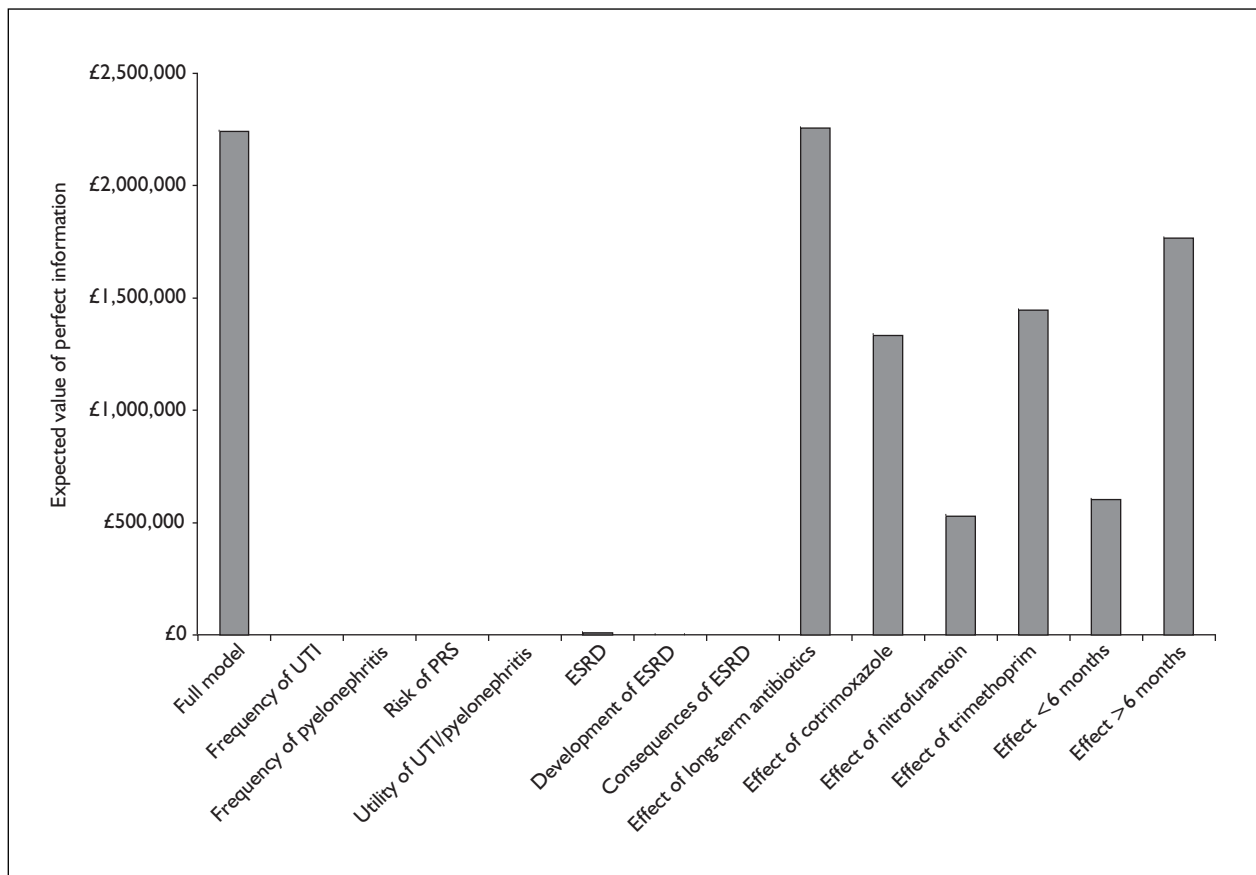


FIGURE 4 Partial EVPIs (girls aged 3 with no VUR)

substantial decision uncertainty and the relatively high incidence. At a threshold for cost-effectiveness of £30,000 per QALY, the population EVPI is above £2.24 million, assuming a 10-year lifetime for the technology (£1.28 and £2.95 million assuming a lifetime of 5 and 15 years, respectively).

Girls aged 3 with VUR and girls aged 1 with and with no VUR

The population EVPIs for these patient groups, at a threshold for cost-effectiveness of £30,000 per QALY, are similar: £612,499 for girls aged 3 with VUR, £689,977 for girls aged 1 with no VUR and £543,529 for girls aged 1 with VUR assuming a 10-year lifetime for the technology.

Boys aged 3

Population EVPI is low for these patient groups due to relatively little decision uncertainty for those with no VUR and low incidence for those with VUR. At a threshold for cost-effectiveness of £30,000 per QALY, the population EVPI is £22,546 with VUR and £40,931 with no VUR assuming a 10-year lifetime for the technology.

Boys aged 1

Population EVPI is higher than for boys aged 3, but remains relatively low. At a threshold for cost-effectiveness of £30,000 per QALY, the population EVPI is £267,109 for those with VUR and £172,611 for those with no VUR.

Partial EVPIs

Girls aged 3 with no VUR

The partial EVPIs for model inputs are illustrated in *Figure 4* for a cost-effectiveness threshold of £30,000 per QALY and a 10-year lifetime for the technology. The value of information associated with the effectiveness of long-term antibiotics is £2.25 million, which is substantially higher than for any other model input. This is broken down into the EVPI associated with the effectiveness of each of the three antibiotics separately (it should be noted that this breaks the correlation generated in the multiple parameter synthesis and will tend to overestimate partial EVPIs), and shows that additional evidence about cotrimoxazole and trimethoprim (partial EVPIs of £1.33 and £1.45 million, respectively) are higher than for nitrofurantoin (£0.53 million). The partial EVPI

associated with effectiveness can also be broken down into effectiveness within 6 months (existing trial evidence) and longer follow-up from 6 months to 3 years. This suggests that evidence about the longer run effectiveness of these antibiotics is more valuable than additional evidence of effect within 6 months (partial EVPIs of £1.77 million and £0.6 million, respectively). Model inputs associated with the development and the impact of ESRD also have positive but low

partial EVPI (£8500). The partial EVPIs associated with other model inputs are negligible for this patient group.

Other patient groups

The pattern of partial EVPIs for other patient groups is very similar to that illustrated in *Figure 4*, with relatively high values associated with effectiveness, particularly for the longer run effectiveness of cotrimoxazole and trimethoprim.

TABLE 1 Summary of results by patient group

Strategy	ICER	Probability cost effective ^a	Population EVPI ^{ab}
<i>Girls aged 3 with no VUR</i>			
Cotrimoxazole	£16,739	0.46	£2,241,627.00
Nitrofurantoin	E dominated	0.09	
Trimethoprim		0.45	
Intermittent	Dominated	0.00	
<i>Girls aged 3 with VUR</i>			
Cotrimoxazole	£9,157	0.58	£612,499.90
Nitrofurantoin	E dominated	0.09	
Trimethoprim		0.33	
Intermittent	Dominated	0.00	
<i>Girls aged 1 with no VUR</i>			
Cotrimoxazole	£8,333	0.50	£689,977.70
Nitrofurantoin	£7,209	0.20	
Trimethoprim		0.30	
Intermittent	Dominated	0.00	
<i>Girls aged 1 with VUR</i>			
Cotrimoxazole	£2,609	0.73	£543,529.60
Nitrofurantoin	£2,171	0.15	
Trimethoprim		0.12	
Intermittent	Dominated	0.00	
<i>Boys aged 3 with no VUR</i>			
Cotrimoxazole	£86,000	0.05	£40,931.96
Nitrofurantoin	£51,428	0.16	
Trimethoprim		0.77	
Intermittent	Dominated	0.02	
<i>Boys aged 3 with VUR</i>			
Cotrimoxazole	£20,476	0.30	£22,546.97
Nitrofurantoin	£18,947	0.23	
Trimethoprim		0.47	
Intermittent	Dominated	0.00	
<i>Boys aged 1 with no VUR</i>			
Cotrimoxazole	£11,111	0.45	£267,106.00
Nitrofurantoin	£6,596	0.24	
Trimethoprim		0.31	
Intermittent	Dominated	0.00	
<i>Boys aged 1 with VUR</i>			
Cotrimoxazole	£3,246	0.72	£172,611.30
Nitrofurantoin	£2,154	0.16	
Trimethoprim		0.12	
Intermittent	Dominated	0.00	

^a At threshold for cost-effectiveness of £30,000 per QALY.
^b Assuming 10-year lifetime for the technology.
 E dominated = subject to extended dominance.

Of the other model inputs, those associated with ESRD have the highest partial EVPI (up to £32,000 in girls aged 3 with VUR). Also, in girls aged 3 with VUR, the probabilities of renal scarring and the disutility of UTI/pyelonephritis have small EVPIs associated with them (£13,000 and £2000, respectively).

Conclusions

Some form of long-term antibiotic treatment can be regarded as cost-effective for all eight patient groups (intermittent treatment is more costly and less effective). There is also very little decision uncertainty surrounding this result, and the probability that intermittent treatment will be cost-effective remains close to zero over a range of cost-effectiveness thresholds. This suggests that the question for further research is which of the antibiotics should be used rather than whether long-term antibiotics are worthwhile.

At a cost-effectiveness threshold of £30,000 per QALY, cotrimoxazole is cost-effective for every patient group with the exception of boys aged 3 with no VUR, where long-term treatment with trimethoprim is cost-effective. However, there is substantial decision uncertainty about which of the three long-term antibiotic treatments will be the most cost-effective. In many cases, this is a choice between trimethoprim and cotrimoxazole. However, there is also a chance that nitrofurantoin will be cost-effective. For patients with mild VUR, for younger children and for girls, long-term treatment with cotrimoxazole (which is more effective and more costly) is more cost-effective, with less decision uncertainty.

In general, the population EVPI in this area is substantial (£4.6 million across all eight patient groups) but differs by patient group. The population EVPI is highest for girls aged 3 with no VUR (£2.24 million at a threshold of £30,000) and suggests that further research in this patient group could be potentially worthwhile. The population EVPI for some other patient groups, such as girls aged 3 with VUR and girls aged 1 (with and without VUR), is still substantial (£612,499, £689,977 and £543,529, respectively, at a threshold of £30,000), although this may not exceed the costs of primary research. In boys, the population EVPI is lower, particularly for boys aged 3, and additional research may not be cost-effective for this group.

The partial EVPIs associated with the model inputs suggest that, if further research is commissioned, it should focus on the relative effectiveness of alternative long term antibiotics in reducing the frequency of UTI, particularly their longer run effectiveness. Although additional evidence about all three interventions will be valuable, it seems that evidence about cotrimoxazole and trimethoprim would be most important.

In summary, the analysis suggests that additional primary research may be required for selected patient groups (particularly girls with no VUR). If additional trials are conducted, they should include head-to-head comparisons of either cotrimoxazole and trimethoprim or all three antibiotics. In addition, longer follow-up (6 months to 3 years) would be worthwhile as additional trials with 6-month follow-up are unlikely to be cost-effective.

Appendix 4

Search strategies

Update process

Dates

The Cochrane review states that an update search was carried out in November 2001 and did not identify any new studies for inclusion. The interfaces and resources searched are not listed, so to minimise the risk of missing studies publications dated 2000 onwards were searched for.

Strategies

From the review it seems that the Cochrane Airways Review Group (CARG) register was searched using four key terms:

- postural drainage
- physical therapy
- percussion
- physiotherapy.

The CARG register is built up by searching MEDLINE, EMBASE and CCTR with the search strategies listed in the Airways Group protocol. An attempt was made to replicate the process that the CARG trials searchers may have used by using the strategies that they list for asthma, COPD and bronchiectasis and running them on MEDLINE, EMBASE and Cochrane Controlled Trials Register (CCTR). The results were then combined with the four key terms listed above and an RCT filter (in the case of MEDLINE and EMBASE only). The documentation of the Airways Group specifies that the Cochrane RCT filter be used; as this is appropriate for MEDLINE it was used with the MEDLINE search. The version of the RCT filter used with EMBASE was not presented, so the Cochrane filter was adapted for use with EMBASE by replacing MeSH with relevant Emtree terms. The strategies used are listed below.

Reference processing

Records were loaded into Endnote and deduplicated. Cochrane reviews were removed. Other reviews have been retained to allow comparison with Cochrane findings if required. The next step would be to compare the Endnote references with the Cochrane review to remove references already assessed by the reviewers. Unfortunately, there was no time for an

information officer to do this, so it was done by the Centre for Health Economics researcher this time.

Strategies

MEDLINE

MEDLINE was searched using the Ovid Internet interface on 11 December 2002; 57 records were downloaded.

MEDLINE (1996 to October week 5 2002)

- 1 exp asthma/ or bronchial hyperreactivity/ (19196)
- 2 asthma\$.mp. (24006)
- 3 exp respiratory sounds/ (2016)
- 4 wheez\$.mp. (1935)
- 5 exp respiratory hypersensitivity/ (21751)
- 6 exp pulmonary emphysema/ (1293)
- 7 lung diseases, obstructive/ (4840)
- 8 bronchitis/ or emphysema/ or mediastinal emphysema/ or subcutaneous emphysema/ (2807)
- 9 bronchit\$.mp. (3215)
- 10 emphysema.mp. (2758)
- 11 (chronic adj4 obstructive).mp. (4482)
- 12 (pulmonary or lung\$ or airway\$).mp. (136576)
- 13 11 and 12 (4285)
- 14 (copd or coad).mp. (3386)
- 15 bronchiectasis/ or bronchiectasis.mp. (1053)
- 16 or/1-10,13-15 (39937)
- 17 randomized controlled trial.pt. or randomized controlled trials/ (85586)
- 18 random allocation/ or double blind method/ or single blind method/ (40497)
- 19 clinical trial.pt. (137491)
- 20 exp clinical trials/ or placebos/ (45990)
- 21 (clin\$ adj3 trial\$).ti,ab. (34140)
- 22 (singl\$ adj3 (blind\$ or mask\$)).ti,ab. (2406)
- 23 (doubl\$ adj3 (blind\$ or mask\$)).ti,ab. (21980)
- 24 (trebl\$ adj3 (blind\$ or mask\$)).ti,ab. (0)
- 25 (tripl\$ adj3 (blind\$ or mask\$)).ti,ab. (75)
- 26 (placebo or random).ti,ab. (56984)
- 27 research design/ (19620)
- 28 or/17-27 (251228)
- 29 16 and 28 (6767)
- 30 animal/ not (human/ and animal/) (556787)
- 31 29 not 30 (6694)

- 32 postural drainage.mp. or exp Drainage, Postural/ (77)
- 33 exp Physical Therapy Techniques/ or physical therapy.mp. or exp "Physical Therapy (Specialty)"/ (24991)
- 34 percussion.mp. or exp PERCUSSION/ (614)
- 35 physiotherapy.ti,ab. (1418)
- 36 or/32-35 (26284)
- 37 31 and 36 (121)
- 38 from 37 keep 1-121 (121)
- 39 limit 38 to yr=2000-2002 (57)

EMBASE

EMBASE was searched using the Ovid Internet interface on 11 December 2002; 51 records were downloaded.

EMBASE (1996 to week 49 2002)

- 1 asthma/ or allergic asthma/ or wheezing/ or exercise induced asthma/ or occupational asthma/ (25811)
- 2 asthma\$.mp. (27582)
- 3 asthmatic state/ (217)
- 4 wheez\$.mp. (2717)
- 5 exp chronic obstructive lung disease/ or exp chronic bronchitis/ (8345)
- 6 exp lung emphysema/ (1863)
- 7 exp obstructive airway disease/ (40551)
- 8 exp bronchitis/ (5194)
- 9 bronchitis.ti,ab,hw,tn,mf. or (lung adj4 emphysema).mp. (4431)
- 10 (pulmonary adj4 emphysema).mp. (604)
- 11 (chronic adj4 obstructive).mp. (4512)
- 12 (pulmonary or lung\$ or airway\$).mp. (147704)
- 13 11 and 12 (4334)
- 14 (copd or coad).mp. (3509)
- 15 bronchiectasis/ or bronchiectasis.mp. (1331)
- 16 or/1-10,13-15 (45737)
- 17 major clinical study/ or controlled study/ or clinical trial/ (1166554)
- 18 controlled study/ or double blind procedure/ or placebo/ (926117)
- 19 follow-up/ or prospective study/ or clinical study/ or longitudinal study/ (87454)
- 20 random\$.ti,ab. (115732)
- 21 (clin\$ adj3 trial\$).ti,ab. (36285)
- 22 (singl\$ adj3 (blind\$ or mask\$)).ti,ab. (2525)
- 23 (doubl\$ adj3 (blind\$ or mask\$)).ti,ab. (23976)
- 24 (trebl\$ adj3 (blind\$ or mask\$)).ti,ab. (0)
- 25 (tripl\$ adj3 (blind\$ or mask\$)).ti,ab. (76)

- 26 placebo.ti,ab. (31549)
- 27 comparison/ (22629)
- 28 or/17-27 (1245828)
- 29 16 and 28 (22251)
- 30 animal/ not (human/ and animal/) (329)
- 31 29 not 30 (22251)
- 32 postural drainage.mp. or exp Postural drainage/ (91)
- 33 exp Physiotherapy/ or physical therapy.mp. or exp "Physical Therapy (Specialty)"/ (0)
- 34 percussion.mp. or exp PERCUSSION/ (517)
- 35 physiotherapy.ti,ab. (1888)
- 36 or/32-35 (2455)
- 37 31 and 36 (55)
- 38 physiotherapy/ (5743)
- 39 or/36,38 (6778)
- 40 31 and 39 (95)
- 41 limit 40 to yr=2000-2004 (51)

Cochrane Controlled Trials Register

CCTR was searched on 11 December 2002 using the 2002/4 CD-ROM version; 29 records were downloaded.

- 1. (ASTHMA*:ME or BRONCHIAL-HYPERREACTIVITY*:ME)
- 2. RESPIRATORY-SOUNDS*:ME
- 3. RESPIRATORY-SOUNDS*:ME
- 4. (ASTHMA* or WHEEZ*)
- 5. LUNG-DISEASES-OBSTRUCTIVE:ME
- 6. BRONCHITIS*:ME
- 7. PULMONARY-EMPHYSEMA*:ME
- 8. (BRONCHITIS or (PULMONARY and EMPHYSEMA))
- 9. (OBSTRUCTIVE and ((LUNG* or AIRWAY* or PULMONARY))
- 10. (COPD or COAD)
- 11. BRONCHIECTASIS*:ME
- 12. BRONCHIECTASIS
- 13. ((((((((((#1 or #2) or #3) or #4) or #5) or #6) or #7) or #8) or #9) or #10) or #11) or #12)
- 14. (((POSTURAL next DRAINAGE) or (PHYSICAL next THERAPY)) OR PERCUSSION) OR PHYSIOTHERAPY)
- 15. DRAINAGE-POSTURAL*:ME
- 16. PHYSICAL-THERAPY*:ME
- 17. PERCUSSION*:ME
- 18. (((#14 or #15) or #16) or #17)
- 19. (#13 and #18)
- 20. (#13 and #18)

Appendix 5

Summary of trial data

Summary of trials included in the asthma model

	Balon et al., 1998³⁷	Field et al., 1998³⁹	Neilson et al., 1995⁴⁰	Asher et al., 1990³⁸
Study design	RCT	RCT	Single-site cross-over RCT	RCT
Participants	80 children, aged 7–16 years, with asthma requiring the use of an inhaler at least three times per week	32 children, aged 4–14 years, with asthma	31 adults, aged 18–44 years, with chronic asthma controlled by bronchodilators and/or inhaled steroids	38 children, aged 6–13 years, with acute severe asthma
Interventions	CSM or simulated (sham) CSM	Massage therapy or relaxation therapy	CSM or simulated (sham) CSM	Physical therapy or placebo treatment (tender loving care)
Outcomes	Peak expiratory flow, FEV ₁ , use of medications and symptom score	Peak expiratory flow, FEV ₁ , FVC, children and parents' attitudes towards asthma	Self-rated asthma, asthma severity, FEV ₁ , FVC, use of medications	FVC, FEV ₁ , peak expiratory flow, days in hospital, expiratory reserve volume, functional residual capacity, total lung capacity
Follow-up	2 months and 4 months	30 days	4 weeks + 2 week washout period + 4 weeks	Treatments received over 2 days

Summary of the trials included in the COPD model

	May and Munt, 1979⁵⁷	Savci et al., 2000⁵⁸
Study design	Cross-over trial with random order of interventions	RCT
Participants	35 adults, aged 37–83 years, with chronic bronchitis	30 adults, males, with clinically stable COPD
Interventions	Chest percussion + postural drainage or heat lamp (sham procedure)	Autogenic drainage or active cycle of breathing techniques
Outcomes	Peak expiratory flow, FVC, FEV ₁ , alveolar–arterial oxygen pressure gradients	Peak expiratory flow, FVC, FEV ₁ , alveolar–arterial oxygen pressure gradients, exercise performance
Follow-up	30 minutes	20 days

Appendix 6

Details of urinary tract infection parameter-specific searches

Searchable questions

Natural history

In infant girls less than 1 year:

1. What is the frequency of acute UTIs with recurrent UTI but no VUR?
2. What is the frequency of acute UTIs with mild VUR?
3. What is the frequency of acute UTIs with severe VUR?
4. What is the incidence and prevalence of: recurrent UTI (no VUR), mild VUR, severe VUR?

In infant boys less than 1 year:

5. What is the frequency of acute UTIs with recurrent UTI but no VUR?
6. What is the frequency of acute UTIs with mild VUR?
7. What is the frequency of acute UTIs with severe VUR?
8. What is the incidence and prevalence of: recurrent UTI (no VUR), mild VUR, severe VUR?

In girls aged between 1 and 10 years:

9. What is the frequency of acute UTIs with recurrent UTI but no VUR?
10. What is the frequency of acute UTIs with mild VUR?
11. What is the frequency of acute UTIs with severe VUR?
12. What is the incidence and prevalence of: recurrent UTI (no VUR), mild VUR, severe VUR?

In boys aged between 1 and 10 years:

13. What is the frequency of acute UTIs with recurrent UTI but no VUR?
14. What is the frequency of acute UTIs with mild VUR?
15. What is the frequency of acute UTIs with severe VUR?
16. What is the incidence and prevalence of: recurrent UTI (no VUR), mild VUR, severe VUR?

In infant girls less than 1 year:

17. What proportion of acute UTIs are pyelonephritic attacks in those with recurrent UTI (no VUR)?
18. What proportion of acute UTIs are pyelonephritic attacks in those with mild VUR?
19. What proportion of acute UTIs are pyelonephritic attacks in those with severe VUR?

In infant boys less than 1 year:

20. What proportion of acute UTIs are pyelonephritic attacks in those with recurrent UTI (no VUR)?
21. What proportion of acute UTIs are pyelonephritic attacks in those with mild VUR?
22. What proportion of acute UTIs are pyelonephritic attacks in those with severe VUR?

In girls aged between 1 and 10 years:

23. What proportion of acute UTIs are pyelonephritic attacks in those with recurrent UTI (no VUR)?
24. What proportion of acute UTIs are pyelonephritic attacks in those with mild VUR?
25. What proportion of acute UTIs are pyelonephritic attacks in those with severe VUR?

In boys aged between 1 and 10 years:

26. What proportion of acute UTIs are pyelonephritic attacks in those with recurrent UTI (no VUR)?
27. What proportion of acute UTIs are pyelonephritic attacks in those with mild VUR?
28. What proportion of acute UTIs are pyelonephritic attacks in those with severe VUR?
29. What is the relationship between the number of pyelonephritic attacks and the risk of progressive renal scarring (most importantly by VUR no VUR, as well as age and maybe gender)?
30. What is the relationship between developing progressive renal scarring and developing end-stage renal disease?

31. Are there any other significant consequences of progressive renal scarring (severe hypertension)?
32. What are the consequences (and their likelihood) of end-stage renal disease?

Quality of life

33. What is the impact on quality of life of acute UTIs and pyelonephritic attacks in infants and children (duration of symptoms would be good too)?
34. What is the reduction in quality-adjusted life expectancy (or failing that of life expectancy) of the consequences of end-stage renal disease?
35. What is the reduction in quality-adjusted life expectancy (or failing that of life expectancy) of any other consequences of progressive renal scarring?

Resource use

36. What are the costs of treating acute UTIs and pyelonephritic attacks in infants and children (duration, drugs/doses, hospitalisations, primary care visits)?
37. What are the costs of the consequences of end-stage renal disease?
38. What are the costs of any other consequences of progressive renal scarring?

Effectiveness of interventions

39. We have a Cochrane review 2001 (four trials some very old) and it would be useful to search for any other trials of long-term low-dose antibiotics for these patient groups and indications.
40. We are told that surgery is used to treat VUR but we have no evidence about the effectiveness (on any outcome) of this procedure for these patient groups.

Antibiotics resistance

41. We don't believe we will be able to model resistance due to lack of long-term evidence, but a search for studies which have looked at resistance to these antibiotics (first in these patient groups and then more broadly) might be worthwhile to confirm this view.

Search strategies

Natural history

MEDLINE (1966 to 2002/03 week 2–40)
(includes questions 1, 4, 5 and 8)

1. *"Urinary Tract Infections"/di, ep [Diagnosis, Epidemiology]

2. *bacteriuria/di, ep [Diagnosis, Epidemiology]
3. (uti or utis).ti.
4. (urinary tract adj3 infection\$).ti.
5. bacteriuria.ti.
6. or/1-5
7. (recurren\$ or recrudescense\$ or remission\$ or relapse\$ or reinfection\$ or re-infection\$).ti,ab.
8. Recurrence/
9. 7 or 8
10. 6 and 9
11. exp infants/
12. (frequency or frequencies or occurrence\$ or incidence\$ or prevalence\$ or number\$ or times or rate or rates or episode\$ or natural history).ti,ab.
13. exp data collection/
14. 12 or 13
15. 10 and 11 and 14
16. male/
17. (boy or boys or male or males).ti,ab.
18. 16 or 17
19. 15 and 18
20. female/
21. (girl or girls or female or females).ti,ab.
22. 20 or 21
23. 15 and 22
24. 19 or 23

MEDLINE (1966 to 2002/03 week 2–40)
(includes questions 2–4 and 6–8)

1. *"Urinary Tract Infections"/di, ep [Diagnosis, Epidemiology]
2. *bacteriuria/di, ep [Diagnosis, Epidemiology]
3. (uti or utis).ti.
4. (urinary tract adj3 infection\$).ti.
5. bacteriuria.ti.
6. or/1-5
7. exp infants/
8. (frequency or frequencies or occurrence\$ or incidence\$ or prevalence\$ or number\$ or times or rate or rates or episode\$ or natural history).ti,ab.
9. exp data collection/
10. 8 or 9
11. 6 and 7 and 10
12. Vesico-Ureteral Reflux/
13. vesicoureteral reflux.ti,ab.
14. Vesico-Ureteral Reflux.ti,ab.
15. vur.ti,ab.
16. or/12-15
17. 11 and 16
18. limit 17 to male
19. limit 17 to female
20. 18 or 19
21. 20 and (mild or severe or grade\$).af.

**MEDLINE (1966 to 2002/03 week 2–40)
(includes questions 9, 12, 13 and 16)**

1. *"Urinary Tract Infections"/di, ep [Diagnosis, Epidemiology]
2. *bacteriuria/di, ep [Diagnosis, Epidemiology]
3. (uti or utis).ti.
4. (urinary tract adj3 infection\$).ti.
5. bacteriuria.ti.
6. or/1-5
7. (recurren\$ or recrudescence\$ or remission\$ or relapse\$ or reinfection\$ or re-infection\$).ti,ab.
8. Recurrence/
9. 7 or 8
10. 6 and 9
11. exp child/
12. (frequency or frequencies or occurrence\$ or incidence\$ or prevalence\$ or number\$ or times or rate or rates or episode\$ or natural history).ti,ab.
13. exp data collection/
14. 12 or 13
15. 10 and 11 and 14
16. male/
17. (boy or boys or male or males).ti,ab.
18. 16 or 17
19. 15 and 18
20. female/
21. (girl or girls or female or females).ti,ab.
22. 20 or 21
23. 15 and 22
24. 19 or 23

**MEDLINE (1966 to 2002/03 week 2–40)
(includes questions 10–12 and 14–16)**

1. *"Urinary Tract Infections"/di, ep [Diagnosis, Epidemiology]
2. *bacteriuria/di, ep [Diagnosis, Epidemiology]
3. (uti or utis).ti.
4. (urinary tract adj3 infection\$).ti.
5. bacteriuria.ti.
6. or/1-5
7. exp child/
8. (frequency or frequencies or occurrence\$ or incidence\$ or prevalence\$ or number\$ or times or rate or rates or episode\$ or natural history).ti,ab.
9. exp data collection/
10. 8 or 9
11. 6 and 7 and 10
12. Vesico-Ureteral Reflux/
13. vesicoureteral reflux.ti,ab.
14. Vesico-Ureteral Reflux.ti,ab.
15. vur.ti,ab.
16. or/12-15
17. 11 and 16

18. 17 and (mild or severe or grade\$).af.
19. from 18 keep 1-30

**MEDLINE (1966 to 2002/03 week 2–40)
(includes questions 17 and 20)**

1. *"Urinary Tract Infections"/di, ep [Diagnosis, Epidemiology]
2. *bacteriuria/di, ep [Diagnosis, Epidemiology]
3. (uti or utis).ti.
4. (urinary tract adj3 infection\$).ti.
5. bacteriuria.ti.
6. or/1-5
7. (recurren\$ or recrudescence\$ or remission\$ or relapse\$ or reinfection\$ or re-infection\$).ti,ab.
8. Recurrence/
9. 7 or 8
10. 6 and 9
11. exp infants/
12. (proportion or proportions or rate or rates or percent\$ or per cent\$ or incidence or level).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
13. pyelonephriti\$.ti,ab.
14. exp pyelonephritis/
15. 13 or 14
16. 10 and 11 and 12 and 15
17. from 16 keep 1-25

**MEDLINE (1966 to 2002/03 week 2–13)
(includes questions 18, 19, 21 and 22)**

1. pyelonephriti\$.ti,ab.
2. exp pyelonephritis/
3. 1 or 2
4. *"Urinary Tract Infections"/di, ep [Diagnosis, Epidemiology]
5. *bacteriuria/di, ep [Diagnosis, Epidemiology]
6. (uti or utis).ti.
7. (urinary tract adj3 infection\$).ti.
8. bacteriuria.ti.
9. or/4-8
10. exp infants/
11. Vesico-Ureteral Reflux/
12. vesicoureteral reflux.ti,ab.
13. Vesico-Ureteral Reflux.ti,ab.
14. vur.ti,ab.
15. or/11-14
16. (proportion or proportions or rate or rates or percent\$ or per cent\$ or incidence or level).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
17. 3 and 9 and 15 and 16
18. (mild or severe or grade\$).af.
19. 17 and 18
20. from 19 keep 1-10
21. from 19 keep 1-13

**MEDLINE (1966 to 2002/03 week 2–40)
(includes questions 23 and 26)**

1. *"Urinary Tract Infections"/di, ep [Diagnosis, Epidemiology]
2. *bacteriuria/di, ep [Diagnosis, Epidemiology]
3. (uti or utis).ti.
4. (urinary tract adj3 infection\$.ti.
5. bacteriuria.ti.
6. or/1-5
7. (recurren\$ or recrudescense\$ or remission\$ or relapse\$ or reinfection\$ or re-infection\$.ti,ab.
8. Recurrence/
9. 7 or 8
10. 6 and 9
11. exp child/
12. (proportion or proportions or rate or rates or percent\$ or per cent\$ or incidence or level).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
13. pyelonephriti\$.ti,ab.
14. exp pyelonephritis/
15. 13 or 14
16. 10 and 11 and 12 and 15
17. [from 16 keep 1-25]

**MEDLINE (1966 to 2002/03 week 2–13)
(includes questions 24, 25, 27 and 28)**

1. pyelonephriti\$.ti,ab.
2. exp pyelonephritis/
3. 1 or 2
4. *"Urinary Tract Infections"/di, ep [Diagnosis, Epidemiology]
5. *bacteriuria/di, ep [Diagnosis, Epidemiology]
6. (uti or utis).ti.
7. (urinary tract adj3 infection\$.ti.
8. bacteriuria.ti.
9. or/4-8
10. exp child/
11. Vesico-Ureteral Reflux/
12. vesicoureteral reflux.ti,ab.
13. Vesico-Ureteral Reflux.ti,ab.
14. vur.ti,ab.
15. or/11-14
16. (proportion or proportions or rate or rates or percent\$ or per cent\$ or incidence or level).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
17. 3 and 9 and 15 and 16
18. (mild or severe or grade\$.af.
19. 17 and 18
20. [from 19 keep 1-10]
21. [from 19 keep 1-13]

**MEDLINE (1966 to 2002/03 week 2–40)
(question 29)**

1. pyelonephriti\$.ti,ab.
2. pyonephrosis.ti,ab.
3. *PYELONEPHRITIS/
4. or/1-3
5. renal scar\$.mp.
6. kidney scar\$.mp.
7. exp Kidney Diseases/
8. exp kidney/
9. *Cicatrix/
10. (7 or 8) and 9
11. renal lesion\$.mp.
12. kidney lesion\$.mp.
13. renal damage.mp.
14. (cause or causes or causative or relations or relationship\$ or link or effect or etiology).ti,ab.
15. (subsequent or lead or leads or leading or correlated or related or complications).ti,ab.
16. 14 or 15
17. 5 or 6 or 10 or 11 or 12 or 13
18. 4 and 17 and 16
19. animal/ not (animal/ and human/)
20. 18 not 19

**MEDLINE (1966 to 2002/03 week 2–40)
(question 30)**

1. renal scar\$.mp.
2. kidney scar\$.mp.
3. exp Kidney Diseases/
4. exp kidney/
5. *Cicatrix/
6. (3 or 4) and 5
7. renal lesion\$.mp.
8. kidney lesion\$.mp.
9. renal damage.mp.
10. (cause or causes or causative or relations or relationship\$ or link or effect or etiology).ti,ab.
11. (subsequent or lead or leads or leading or correlated or related or complications).ti,ab.
12. 10 or 11
13. 1 or 2 or 6 or 7 or 8 or 9
14. animal/ not (animal/ and human/)
15. Kidney Failure, Chronic/
16. esrd.ti,ab.
17. end-stage renal disease\$.ti,ab.
18. end-stage kidney disease\$.ti,ab.
19. renal insufficiency.ti,ab.
20. kidney insufficiency.ti,ab.
21. renal failure.ti,ab.
22. or/15-21
23. 12 and 13 and 22
24. 1 or 2 or 6

25. 12 and 24 and 22
26. 25 not 14
27. from 26 keep 1-64

**MEDLINE (1966 to 2002/03 week 2–40)
(question 31)**

1. pyelonephriti\$.ti,ab.
2. pyonephrosis.ti,ab.
3. *PYELONEPHRITIS/
4. or/1-3
5. renal scar\$.mp.
6. kidney scar\$.mp.
7. exp Kidney Diseases/
8. exp kidney/
9. *Cicatrix/
10. (7 or 8) and 9
11. renal lesion\$.mp.
12. kidney lesion\$.mp.
13. renal damage.mp.
14. (cause or causes or causative or relations or relationship\$ or link or effect or etiology).ti,ab.
15. (subsequent or lead or leads or leading or correlated or related or complications).ti,ab.
16. 14 or 15
17. 5 or 6 or 10 or 11 or 12 or 13
18. 4 and 17 and 16
19. animal/ not (animal/ and human/)
20. 18 not 19
21. Kidney Failure, Chronic/
22. esrd.ti,ab.
23. end-stage renal disease\$.ti,ab.
24. end-stage kidney disease\$.ti,ab.
25. renal insufficiency.ti,ab.
26. kidney insufficiency.ti,ab.
27. renal failure.ti,ab.
28. or/21-27
29. 4 and 16 and 28
30. 29 not 19
31. ((consequence\$ or complication\$ or outcome\$ or sequelae or long-term effects or long-term effect or impact or impacts) adj3 (renal or kidney)).mp.
32. 17 and 31
33. 28 and 31

**MEDLINE (1966 to 2002/03 week 2–40)
(question 32)**

1. ((consequence\$ or complication\$ or outcome\$ or sequelae or long-term effects or long-term effect or impact or impacts) and (renal scar\$ or kidney scar\$ or kidney lesion\$ or renal lesion\$ or renal damage or kidney damage)).ti.

2. ((consequence\$ or complication\$ or outcome\$ or sequelae or long-term effects or long-term effect or impact or impacts) adj (esrd or renal insufficiency or kidney insufficiency or end-stage kidney disease or end-stage renal disease or end-stage renal failure or end-stage kidney failure)).ti.

Quality of life

**MEDLINE (1966 to 2002/03 week 2–40)
(question 33)**

1. *"Urinary Tract Infections"/
2. *bacteriuria/
3. (uti or utis).ti.
4. (urinary tract adj3 infection\$.ti).
5. bacteriuria.ti.
6. pyelonephriti\$.ti,ab.
7. exp pyelonephritis/
8. pyonephrosis.ti,ab.
9. or/1-8
10. "health status indicators"/
11. "outcome and process assessment (health care)"/
12. "outcome assessment (health care)"/
13. quality of life/
14. health status/
15. severity of illness index/
16. "Self Assessment (Psychology)"/
17. outcome measure\$.tw.
18. health status.tw.
19. quality of life.tw.
20. (endpoint\$ or end point\$ or end-point\$.tw).
21. (self-report\$ or self report\$.tw).
22. functional outcome\$.tw.
23. outcome\$.ti.
24. outcome\$.tw.
25. measure\$.tw.
26. assess\$.tw.
27. (score\$ or scoring).tw.
28. index.tw.
29. indices.tw.
30. scale\$.tw.
31. monitor\$.tw.
32. or/10-23
33. or/25-31
34. 24 and 33
35. 32 or 34
36. 35 and 9
37. exp child/ or exp infant/
38. 36 and 37
39. ((duration or length or time or period) adj2 symptoms).tw.
40. 9 and 37 and 39
41. 38 or 40

Resistance**MEDLINE (1966 to 2002/03 week 2–40)
(question 41)**

1. *"Urinary Tract Infections"/
2. *bacteriuria/
3. (uti or utis).ti.
4. (urinary tract adj3 infection\$).ti.
5. bacteriuria.ti.
6. pyelonephriti\$.ti,ab.
7. exp pyelonephritis/
8. pyonephrosis.ti,ab.
9. or/1-8
10. *"Trimethoprim Resistance"/
11. *"Nitrofurantoin"/
12. (proloprim or trimethoprim).ti.
13. (trimpex or monotrim or trimopan).ti.
14. (macrodantin or furadantin or macrobid).ti.
15. furadoine.ti.
16. furadonine.ti.
17. furantoin.ti.
18. Nitrofurantoin.ti.
19. (Cephalexin or ceporex or keflex).ti.
20. (ceporexine or cefalexin).ti.
21. palitrex.ti.
22. *"cephalexin"/ or *"cefaclor"/ or *"cefadroxil"/ or *"cefatrizine"/ or *"cephaloglycin"/ or *"cephradine"/
23. *"trimethoprim"/ or *"trimethoprim-sulfamethoxazole combination"/
24. *"drug resistance"/ or *"drug resistance, microbial"/ or *"drug resistance, bacterial"/ or *"drug resistance, multiple"/ or *"drug resistance, multiple, bacterial"/ or *"drug tolerance"/ or *"tachyphylaxis"/
25. (resistance or resistant).ti.
26. or/10-23
27. 24 or 25
28. 9 and 26 and 27
29. exp child/ or exp infant/
30. 28 and 29

EMBASE**EMBASE (1980 to 2003 week 6–19) (question 1)**

1. *"Urinary Tract Infections"/di, ep [Diagnosis, Epidemiology]
2. *bacteriuria/di, ep [Diagnosis, Epidemiology]
3. (uti or utis).ti.
4. (urinary tract adj3 infection\$).ti.
5. bacteriuria.ti.
6. or/1-5
7. (recurren\$ or recrudescense\$ or remission\$ or relapse\$ or reinfection\$ or re-infection\$).ti,ab.
8. Recurrence/
9. 7 or 8
10. 6 and 9

11. (frequency or frequencies or occurrence\$ or incidence\$ or prevalence\$ or number\$ or times or rate or rates or episode\$ or natural history).ti,ab.
12. exp data collection/
13. 11 or 12
14. male/
15. (boy or boys or male or males).ti,ab.
16. 14 or 15
17. female/
18. (girl or girls or female or females).ti,ab.
19. 17 or 18
20. 10 and 13
21. exp infant/
22. 20 and 21
23. 22 and 16
24. 22 and 19
25. 23 or 24

EMBASE (1980 to 2003 week 6–19) (question 2)

1. *"Urinary Tract Infections"/di, ep [Diagnosis, Epidemiology]
2. *bacteriuria/di, ep [Diagnosis, Epidemiology]
3. (uti or utis).ti.
4. (urinary tract adj3 infection\$).ti.
5. bacteriuria.ti.
6. or/1-5
7. (recurren\$ or recrudescense\$ or remission\$ or relapse\$ or reinfection\$ or re-infection\$).ti,ab.
8. Recurrence/
9. 7 or 8
10. 6 and 9
11. (frequency or frequencies or occurrence\$ or incidence\$ or prevalence\$ or number\$ or times or rate or rates or episode\$ or natural history).ti,ab.
12. exp data collection/
13. 11 or 12
14. male/
15. (boy or boys or male or males).ti,ab.
16. 14 or 15
17. female/
18. (girl or girls or female or females).ti,ab.
19. 17 or 18
20. 10 and 13
21. exp infant/
22. 20 and 21
23. 22 and 16
24. 22 and 19
25. 23 or 24

EMBASE (1980 to 2003 week 6–19) (question 10)

1. *"Urinary Tract Infections"/di, ep [Diagnosis, Epidemiology]
2. *bacteriuria/di, ep [Diagnosis, Epidemiology]

3. (uti or utis).ti.
4. (urinary tract adj3 infection\$.ti.
5. bacteriuria.ti.
6. or/1-5
7. exp child/
8. (frequency or frequencies or occurrence\$ or incidence\$ or prevalence\$ or number\$ or times or rate or rates or episode\$ or natural history).ti,ab.
9. exp data collection/
10. 8 or 9
11. 6 and 7 and 10
12. Vesico-Ureteral Reflux/
13. vesicoureteral reflux.ti,ab.
14. Vesico-Ureteral Reflux.ti,ab.
15. vur.ti,ab.
16. or/12-15
17. 11 and 16
18. 17 and (mild or severe or grade\$.af.
19. from 18 keep 1-38
20. exp INFORMATION PROCESSING/
21. Vesicoureteral Reflux/

EMBASE (1980 to 2003 week 6–19) (question 17)

1. *"Urinary Tract Infections"/di, ep [Diagnosis, Epidemiology]
2. *bacteriuria/di, ep [Diagnosis, Epidemiology]
3. (uti or utis).ti.
4. (urinary tract adj3 infection\$.ti.
5. bacteriuria.ti.
6. or/1-5
7. (recurren\$ or recrudescence\$ or remission\$ or relapse\$ or reinfection\$ or re-infection\$.ti,ab.
8. Recurrence/
9. 7 or 8
10. 6 and 9
11. (proportion or proportions or rate or rates or percent\$ or per cent\$ or incidence or level).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
12. pyelonephriti\$.ti,ab.
13. exp pyelonephritis/
14. 12 or 13
15. Recurrent Disease/
16. exp infant/
17. 16 and 14 and 10
18. 17 and 11

EMBASE (1980 to 2003 week 6–19) (question 29)

1. Pyelonephritis/
2. pyelonephriti\$.ti,ab.
3. pyonephrosis.ti,ab.
4. *PYELONEPHRITIS/

5. or/2-4
6. renal scar\$.mp.
7. kidney scar\$.mp.
8. Kidney Scar/
9. renal lesion\$.mp.
10. kidney lesion\$.mp.
11. renal damage.mp.
12. (cause or causes or causative or relations or relationship\$ or link or effect or etiology).ti,ab.
13. (subsequent or lead or leads or leading or correlated or related or complications).ti,ab.
14. 12 or 13
15. (animal/ or nonhuman/) not ((animal/ or nonhuman/) and human/)
16. or/6-11
17. 5 and 16 and 14
18. 17 not 15

EMBASE (1980 to 2003 week 6–19) (question 30)

1. Kidney Failure, Chronic/
2. esrd.ti,ab.
3. end-stage renal disease\$.ti,ab.
4. end-stage kidney disease\$.ti,ab.
5. renal insufficiency.ti,ab.
6. kidney insufficiency.ti,ab.
7. renal failure.ti,ab.
8. or/1-7
9. renal scar\$.mp.
10. kidney scar\$.mp.
11. Kidney Scar/
12. renal lesion\$.mp.
13. kidney lesion\$.mp.
14. renal damage.mp.
15. (cause or causes or causative or relations or relationship\$ or link or effect or etiology).ti,ab.
16. (subsequent or lead or leads or leading or correlated or related or complications).ti,ab.
17. 15 or 16
18. (animal/ or nonhuman/) not ((animal/ or nonhuman/) and human/)
19. or/9-11
20. 19 and 8 and 17
21. 20 not 18

EMBASE (1980 to 2003 week 6–19) (question 41)

1. *"Urinary Tract Infections"/
2. *bacteriuria/
3. (uti or utis).ti.
4. (urinary tract adj3 infection\$.ti.
5. bacteriuria.ti.
6. pyelonephriti\$.ti,ab.
7. exp pyelonephritis/
8. pyonephrosis.ti,ab.

9. or/1-8
10. *"Nitrofurantoin"/
11. (proloprim or trimethoprim).ti.
12. (trimpex or monotrim or trimopan).ti.
13. (macrodantin or furadantin or macrobid).ti.
14. furadoine.ti.
15. furadonine.ti.
16. furantoin.ti.
17. Nitrofurantoin.ti.
18. (Cephalexin or ceporex or keflex).ti.
19. (ceporexine or cefalexin).ti.
20. palitrex.ti.
21. *"cefalexin"/ or *"cefactor"/ or *"cefadroxil"/
or *"cefatrizine"/ or *"cefaloglycin"/ or
*"cephradine"/
22. *"trimethoprim"/ or *"TRIMETHOPRIM
SULFATE"/ or *"SULFADOXINE PLUS
TRIMETHOPRIM"/ or *"TRIMETHOPRIM
DERIVATIVE"/
23. *"drug resistance"/ or *"antibiotic resistance"/
or *"cross resistance"/ or *"multidrug
resistance"/ or *"drug tolerance"/ or *"drug
cross tolerance"/
24. (resistance or resistant).ti.
25. 23 or 24
26. exp child/ or exp infant/
27. or/10-22
28. 25 and 26 and 27 and 9
29. 25 and 27 and 9

**Incidence and Prevalence Database (IPD)
(1994 to 1 February 2003)**

s urinary tract(3w)infection?
s bacteriuria
s uti or utis
s s1:s3
s recurren?
s recrudescense?
s remission?
s relapse?
s reinfection?
s re(w)infection?
s s5:s10
s infant?
s s4 and s11 and s12
s child?
s s4 and s11 and s14
s pyelonephriti?
s pyonephrosis
s s16:s17
s s4 and s11 and s18
s vesico(w)ureteral(w)reflux
s vesicoureteral(w)reflux
s vur
s s20:s22
s severe or mild or grade?

s s24 and s4 and s23 and s12
s s24 and s4 and s23 and s14
s s4 and s23 and s18 and s24
s renal(w)scar?
s kidney(w)scar?
s renal(w)lesion?
s kidney(w)lesion?
s renal(w)damage
s cicatrix
s s28:s33
s kidney(w)failure
s esrd
s end(w)stage(w)renal(w)disease?
s end(w)stage(w)kidney(w)disease?
s renal(w)insufficiency
s kidney(w)insufficiency
s renal(w)failure
s s35:s41
s consequence?
s complication?
s outcome?
s sequelae
s long(w)term(w)effects
s long(w)term(w)effect
s impact
s impacts
s s43:s50
s s34 and s51
s s42 and s51
s cause
s causes
s causative
s relations
s relationship?
s link
s effect
s etiology
s subsequent
s lead
s leads
s leading
s correlated
s related
s complications
s s54:s68
s s69 and s34 and s42
s s69 and s34 and s18
s13 or s15 or s25 or s26 or s27 or s52 or s53 or
s70 or s71

This yielded 947 hits, 25 of which were selected by the information officer as of potential relevance.

**Centre for Reviews and Dissemination (CRD)
Administration Database NHS Economic
Evaluation Database (EED) (question 36)**
Searched 17 February 2003

S (uti OR utis OR urinary(w)tract(3w)infection\$
OR pyonephrosis OR pyelonephritis OR
bacteriuria)/ttl

This yielded 58 hits.

Health Economics Evaluation (HEED) (Issue February 2003) (question 36)

Searched 26 February 2003

TI=uti
TI=utis
TI='urinary tract infection'
TI='urinary tract infections'
TI=pyonephrosis
TI=pyelonephritis
TI=bacteriuria
CS=1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7

This yielded 64 hits, 42 of which were unique.

Hospital episode statistics

Day cases and hospital admissions for kidney or urinary tract infections and main operations

BNF

Costs of Drugs

Morbidity Statistics from General Practice

UTI prevalence rates broken down by gender and age (0–4 years, 5–15, etc.)

New and first ever episodes/Patients consulting and Consultations with doctor broken down by age

Reference costs

Costs of kidney or urinary tract infections for Primary Care Trusts?

Costs for dialysis

Question 40

Cochrane Database of Systematic Reviews/CENTRAL (2003 Issue 1)

- #1. VESICO-URETERAL REFLUX explode all trees (MeSH) 60
- #2. vur 17
- #3. (vesico next ureteral next reflux) 66
- #4. (vesicoureteral next reflux) 43
- #5. (#1 or #2 or #3 or #4) 86

This yielded six reviews and two protocols, which were sifted by the information officer; one protocol was sent to the health economists. There were 72 hits in CENTRAL, 32 of which were sent to the health economist.

Database of Abstracts of Reviews of Effects (DARE)/HTA

Searched 31 January 2003

S vesico(w)ureteral(w)reflux or
vesicoureteral(w)reflux

This yielded no hits.

Question 39

Cochrane Database of Systematic Reviews (2003 Issue 1)

- #1. BACTERIURIA single term (MeSH) 372
- #2. URINARY TRACT INFECTIONS single term (MeSH) 1254
- #3. (uti:ti or utis:ti) 23
- #4. ((urinary:ti next tract:ti) and infection*:ti) 964
- #5. bacteriuria:ti 173
- #6. (#1 or #2 or #3 or #4 or #5)

This yielded ten reviews and four protocols, which were sifted by the information officer; two reviews and one protocol were sent to the health economists.

CRD Public Administration Database, DARE/HTA

Searched 31 January 2003

S (uti OR utis OR urinary(w)tract(3w)infection\$
OR pyonephrosis OR pyelonephritis OR
bacteriuria)/ttl
S (urinary-tract-infection\$ OR bacteriuria)/kwo
S s1 OR s2

This yielded 30 hits, which were sifted by the information officer; six were sent to health economists.

HTA

Searched 31 January 2003

S (uti OR utis OR urinary(w)tract(3w)infection\$
OR pyonephrosis OR pyelonephritis OR
bacteriuria)/ttl
S (urinary-tract-infection\$ OR bacteriuria)/kwo
S s1 OR s2

This yielded four hits, which were sifted by the information officer; none was sent to the health economists.

CENTRAL

- #1. URINARY TRACT INFECTIONS explode all trees (MeSH) 1527

- #2. BACTERIURIA single term (MeSH) 372
- #3. URINARY TRACT INFECTIONS single term (MeSH) 1254
- #4. (uti:ti or utis:ti) 23
- #5. ((urinary:ti next tract:ti) and infection*:ti) 964
- #6. bacteriuria:ti 173
- #7. (#2 or #3 or #4 or #5 or #6) 1803
- #8. CHILD explode all trees (MeSH) 55840
- #9. child* 36019
- #10. (#8 or #9) 66898
- #11. (#7 and #10) 523
- #12. ANTIBIOTICS explode all trees (MeSH) 15132
- #13. antibiotic* 11263
- #14. (#12 or #13) 19381
- #15. (#11 and #14) 317

Revised quality of life searches

MEDLINE (1966 to April week 3 2003)

Searched: 1 May 2003

1. (sf36 or sf 36).tw.
2. (EQ-5D or eq 5d or euroqol or euro qol).tw.
3. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
4. (hrql or hrqol or h qol or hql or hqol).tw.
5. (hye or hyes or health\$ year\$ equivalent\$ or health utilit\$).tw.
6. health related quality of life.tw.
7. rosser.tw.
8. (standard gamble\$ or time trade off or time tradeoff or tto or willingness to pay).tw.
9. (disutilities or disutility or daly or disability adjusted life).tw.
10. "Quality of Life"/
11. health status indicators/
12. quality adjusted life year/
13. (qaly\$ or quality adjusted life or quality of life or life quality).tw.
14. qwb\$.tw.
15. (quality of wellbeing or quality of well being).tw.
16. factor analysis.tw.
17. preference based.tw.
18. health status.tw.
19. (state adj2 (value or values or valuing or valued)).tw.
20. hspv.tw.
21. *"Urinary Tract Infections"/
22. *bacteriuria/
23. (uti or utis).ti.
24. (urinary tract adj3 infection\$).ti.
25. bacteriuria.ti.
26. pyelonephriti\$.ti,ab.

27. exp pyelonephritis/
28. pyonephrosis.ti,ab.
29. or/21-28
30. or/1-20
31. 29 and 30
32. from 31 keep 1-51
33. life expectancy/
34. life expectancy.tw.
35. 33 or 34
36. 29 and 35
37. ((duration or length or period of time or lasting or last or lasted) adj4 symptom\$).ti,ab.
38. 29 and 37

This yielded 51 papers from the quality of life filter, 13 from life expectancy and 35 from duration of symptoms.

EMBASE (1980 to week 17 2003)

Searched: 1 May 2003

1. (sf36 or sf 36).tw.
2. (EQ-5D or eq 5d or euroqol or euro qol).tw.
3. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
4. (hrql or hrqol or h qol or hql or hqol).tw.
5. (hye or hyes or health\$ year\$ equivalent\$ or health utilit\$).tw.
6. health related quality of life.tw.
7. rosser.tw.
8. (standard gamble\$ or time trade off or time tradeoff or tto or willingness to pay).tw.
9. (disutilities or disutility or daly or disability adjusted life).tw.
10. "Quality of Life"/
11. health status indicators/
12. quality adjusted life year/
13. (qaly\$ or quality adjusted life or quality of life or life quality).tw.
14. qwb\$.tw.
15. (quality of wellbeing or quality of well being).tw.
16. factor analysis.tw.
17. preference based.tw.
18. health status.tw.
19. (state adj2 (value or values or valuing or valued)).tw.
20. hspv.tw.
21. *"Urinary Tract Infections"/
22. *bacteriuria/
23. (uti or utis).ti.
24. (urinary tract adj3 infection\$).ti.
25. bacteriuria.ti.
26. pyelonephriti\$.ti,ab.
27. exp pyelonephritis/

28. pyonephrosis.ti,ab.
29. or/21-28
30. or/1-20
31. 29 and 30
32. from 31 keep 1-85
33. life expectancy/

34. life expectancy.tw.
35. 33 or 34
36. 29 and 35
37. ((duration or length or period of time or
lasting or last or lasted) adj4 symptom\$).ti,ab.
38. 29 and 37

Appendix 7

Feedback from senior lecturers at the PSG meeting in March 2003

Asthma and COPD models: feedback from Therapeutic Procedures Panel

Tentative conclusions from a very small sample are as follows.

Application of resources

The vignettes take 2 person-days each, versus 6 person-weeks of more senior time for the VOI work. If we want to spend more resources on the panels, where should it go? The Therapeutic Procedures Panel would want more on the A list and more/better vignettes.

Chronology

Process of vignette production takes time. They move from a crude 'area of enquiry' into a 'more tightly developed research question' over about 10 weeks, through reading literature, discussion with advisors and thinking time. VOI would add the risk of delay, especially for models that are more sophisticated or iterated. We experienced the problems arising from not tying together vignette production and VOI modelling.

Volume

There are 45 vignettes a year. What should the selection criteria be for VOI work? VOI seemed to be especially difficult where a systematic review recommends primary research, because of inadequate evidence, as is common for the Therapeutic Procedures Panel.

Panel buy-in

The Therapeutic Procedures and Diagnostic Technologies and Screening Panels did not seem to be influenced by the case studies. This raised questions about the extent to which VOI work will have traction on panel decision-making.

Conclusion

We are not convinced of a clear role of VOI in the panels. Possibly, it may be more appropriate for PSG and/or panels sometimes to be able to identify a need for VOI analysis in special cases.

AMD model: feedback from Diagnostic Technologies and Screening Panel

- Are the asthma results implausible? "You're damned if you do and you're damned if you don't". (That is, if the model confirms what you knew intuitively, it wasn't worth doing; and if it suggests what is counter-intuitive, you don't believe it.)
- Way it is presented – liked histogram presenting components, will inform debate. Mental discipline in putting the model together – looking at criteria/parameters is helpful.
- Is this way of presenting the model the best one? It is relevant but heavy. Could it be presented in a way more digestible to clinicians or managers? Perhaps use a more structured/logical approach, considering effectiveness and then cost-effectiveness.
- The panels found histograms helpful, as also setting out the decision problem in a diagram and being clear about the parameters.
- The models are very complex. UTIs have eight patient groups, multiple parameter inputs, lengthy and branching structure and use multiple synthesis methods.
- Problems with opacity, told where evidence is coming from and given result. Needs something for people to get greater understanding of what results are based on. Make it acceptable.
- Should you take a British or a world perspective on research?
- How far is all this about changing clinical practice? Large studies are very compelling and VOI on its own may not drive clinical practice. Surely it's not worth spending money on research which won't change practice.
- We can't expect routine VOI analyses to be as rigorous or as thoughtful as those done in this project (effectiveness–efficacy distinction).
- Important to keep the two issues of the value of research and changing clinical practice separate. Mega-trials are not the only way to change practice and they may not be very efficient in doing so.

- How about structuring the partial EVPs around incidence, natural history, effectiveness and costs?
- How far are trimethoprim and cotrimoxazole real alternatives, in the real world? Does it make sense to plan a head-to-head trial of these?
- There needs to be adequate clinical and clinical epidemiological input.
- This methodology is claimed to be used in industry – how is it communicated in that setting? What have the successes and failures in industry been? Presenting complexity with transparency.
- Panel often wants piece of work and indicate systematic review/health economic modelling. How many people are doing particular practice in technologies will affect cost-effectiveness generally. Calculating cost-effectiveness ratios is not enough. Identifying technologies below ceiling value will present problems in cost of implementing these decisions. Primary research has to take into account current clinical practice and epidemiological treatment pathways.
- How is bias handled? The RCTs that built the UTI model have low internal and external validity. Response: one can treat bias as inflating the variance (possibly not symmetrically).
- The team have assumed uninformative priors, but could formally adopt ones. That would focus attention on the marginal value of information that would shift your prior. Could go further and impose more subjective approach on the models, down-weighting evidence, etc. Survey information of current practice would help inform priors.
- The relationship between intuition and the models. Intuition may be criticised but it is often right.
- 6 person weeks to get the question right isn't of itself unaffordable or poor value for money, especially if the VOI is added onto the margin of a systematic review rather than on a vignette.
- Incorporating VOI into systematic reviews:
 - This should be integral.
 - Often difficult to integrate in practice, with NICE demanding both a model and lots of other information.
 - It requires careful management of the teams.
 - Is there adequate capacity in the system? What happened to operational research?
 - Needs to be combined with surveys of current practice.
 - There may be value also in knowing about baseline practice and expected changes.

Additional comments from PSG minutes

The vignette suggested secondary research,

although the York team's model, based on a very tightly defined research question, assumed an RCT. PSG decided to commission through open advertisement. Any group would need strong subspecialty input from ophthalmologists.

From memory, PSG was clearly impressed by both the rigour of the AMD model and its conclusions. My impression was that, however, the lack of systematic review(s) to feed into the model meant that PSG was not convinced that the research question assumed by the model was the right one; and that therefore they felt that there might in the future be a case for examining other models of AMD screening in primary research.

Hence the focus of the commissioning brief on a SR-based examination of the issue against the National Screening Committee criteria, together with economic modelling (possibly VOI) of research questions that emerged from that work.

Overall impact of the VOI AMD model therefore:

- it didn't lead to primary research being commissioned
- it did open PSG's mind (and more broadly the mind of the HTA programme) to the possible value of VOI analyses in this area.

UTI model: feedback from Pharmaceuticals Panel

Recurrent UTI in children

The panel senior lecturer explained that the decision had been made on this topic at the last meeting but if, in the light of the VOI the commissioning brief and research question were seen in a different light, then they could be changed. VUR was being diagnosed more frequently and was showing up antenatally. The topic had come from a Cochrane review which said that the evidence base was weak. The panel senior lecturer had worked closely with the York team on the VOI and their work was based on the NCCHTA vignette which was already finalised.

The panel senior lecturer had concerns with the difference between the result of DA-VOI, suggesting that there was little uncertainty whether long-term antibiotics were cost-effective, and the Cochrane review, which said that the evidence of effectiveness was limited and poor. The VOI had not addressed the question of whether the trials had been susceptible to bias (they were). In addition, the sample size was small (three trials with a total 150 patients in the 1970s).

The senior lecturer's concerns were: (1) whether the trials were well done, and (2) since the environment for prescribing antibiotics was different now, results from the 1970s may not be generalisable to the present day.

The important question of bacterial resistance could not be built into the VOI model.

Despite these observations about the findings of the VOI, the panel senior lecturer felt that raised the possibility that methods other than an RCT might be useful in tackling this topic. For example, an investigation into the risk of resistance with long-term treatment might be very helpful. Further work could be worthwhile to establish current prescribing practice for recurrent UTIs and to investigate the sensitivity, specificity and positive predictive value of ultrasonic detection of renal scarring in predicting end stage renal failure.

It was agreed the commissioning brief should be redrafted by the senior lecturer involving an informed group of people. This draft would be considered at the next PSG meeting.

Decision:

- Redraft commissioning brief, to be a review of bacterial resistance with long-term treatment, a survey of current clinical practice and a review of the association between renal scarring and end-stage renal failure.
- Involve experts/informed people.
- Consider at September PSG meeting.

In conclusion, the VOI process had been useful and had changed the decision of the PSG. However, that may have been the result of the careful further examination of the research question by the York team and the panel senior lecturer, rather than because of the use of the VOI method specifically.



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Pharmaceuticals Panel

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Feedback

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We look forward to hearing from you.