

# MRC PROGRAMME GRANT: METHODOLOGICAL ISSUES RELATING TO DECISION ANALYSIS FOR RESOURCE ALLOCATION IN HEALTH CARE

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## Background

A programme of methodological research is being undertaken relating to the methods of decision modeling and expected value of information analysis. This will provide a common and consistent framework within which the key policy questions listed above can be addressed. The specific focus will be on developing decision analytic methods in general and expected value of information analysis in particular. The benefits and practicality of adopting this approach will be assessed through its application to a number of case-studies relevant to NICE and NHS Health Technology Assessment (HTA) programme.

## *Links to the Bristol programme*

The proposed programme is closely linked to that of Ades *et al* (see [http://www.hsrc.ac.uk/Current\\_research/research\\_programmes/mpes.htm](http://www.hsrc.ac.uk/Current_research/research_programmes/mpes.htm)). The objectives of each programme are synergistic in that decision models require rigorous synthesis of all relevant evidence as parameter inputs, and multi-parameter evidence synthesis benefits from policy-relevant decision problems to demonstrate their potential and implications. It is proposed that the programmes will share two important resources. The first of these is the decision modelling case-studies which will be taken from CHE's applied work. These will provide a vehicle for exploring and illustrating methodological developments emerging from both programmes. The second shared resource will be staff. The core expertise in York will be decision modelling and health economics, while in Bristol it will be statistics. It is proposed that staff based in one of the two cities will also spend periods of time in the other as a way of making best possible use of scarce skills, and ensuring synergy between the two programmes.

## Methodological areas to be addressed

The framework described above has the potential to improve the consistency and efficiency of decision making in health care delivery, research prioritization and research design. However, it is necessary to build on work to date, and to address a number of methodological challenges, if these methods are to become routinely used. These can be categorized into four related areas.

### *Modelling clinical decision problems*

The first element of the iterative process of economic evaluation is to model the decision problem in a way that reflects the key features of the interventions being compared and the relevant health condition. This aspect of modelling is not without methodological challenges, particularly associated with the choice of pathways/states and the level of complexity required. However, it is the challenges associated with the second and third elements of this process which are the primary focus of this research. The second element is populating the models with estimates of input parameters and adequately reflecting the uncertainty surrounding these estimates. The latter is important because the key tasks of the model, in terms of research prioritization and optimal research design, are dependent on adequately characterising uncertainty. It is important to incorporate all available data into the model in a way that reflects the structure of the model and provides insight into the consistency between data sources, the topic for the Ades programme. The final element in this iterative process is updating the decision model as new evidence accumulates, and revising the estimates of cost-effectiveness and expected value of information. However, there are unresolved issues as to the most appropriate and feasible way to implement this process within complex decision models.<sup>1</sup>

### *Setting research priorities*

A number of methods for setting priorities in research and development of health care 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 and measures of the expected “payback” from research. However, each for these proposed methods has serious methodological problems. Most importantly, all of the currently proposed measures view research as simply a means of changing clinical practice rather than considering it as providing additional information which will reduce the uncertainty about what is appropriate clinical practice.

Expected value of information analysis has a firm foundation in statistical decision theory<sup>2</sup> and has been applied in other areas of research.<sup>3</sup> It provides an analytic framework, which can be used to establish the expected value of perfect information (EVPI) surrounding the decision to adopt a technology. This represents the maximum societal return to additional investigation, and can be used to identify those clinical decision problems which should be regarded as priorities for further research. To date, these methods have been demonstrated using stylised examples, often making assumptions of normality,<sup>4,5</sup> and there have only been a few published applications to more complex decision analytic models.<sup>1,6,7</sup> The value of information associated with particular uncertain parameters within the decision model can also be established (partial EVPI). In principle, this provides a useful means of focusing research priorities on those aspects of uncertainty where more information would be most valuable. However, there are a range of methodological and practical problems which must be surmounted before measures of EVPI can be used routinely to set research priorities in health care, and these will be addressed in the programme.

### *Identifying appropriate research designs*

It has been recognised for some time that it would be appropriate to base decisions about the design of research (optimal sample size, follow-up period and appropriate endpoints in a clinical trial) on explicit estimates of the additional benefits of the sample information and the additional costs, including both the resource and opportunity.<sup>8</sup> This approach offers a number of advantages over more traditional approaches which are based on the selection of an effect size which is worth detecting at traditional levels of statistical significance and power. Expected value of information theory offers a framework which can identify the expected value of sample information (EVSI) as the reduction in the expected cost of uncertainty surrounding the decision to adopt a technology as sample size increases. These expected benefits of sampling can be compared to expected costs to decide whether more sample information is worthwhile. This framework offers a means of ensuring that research designs are technically efficient in the sense that sample size, allocation of trial entrants, follow-up periods and the choice of endpoints are consistent with the objectives and the budget for the provision of health care.

Only recently has it been demonstrated that EVSI may have a useful application in the design of clinical research including sequential trial designs,<sup>9</sup> and in the selection of clinical strategies which should be included in proposed research.<sup>10</sup> These methods have been applied to simple stylised decision problems,<sup>4-6</sup> with limited application to a more complex decision model.<sup>11</sup> To date all applications have used parametric methods which rely on assumptions of normality. However, if this approach is to be used more widely and applied to more complex decision problems, then there are a number of methodological and practical problems which must be resolved.

### *Implementation and regulation*

If the objective of a collectively-funded health care system is to maximise health gains from available resources, then the adoption of a technology should be based on the expected (mean) 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 demand further research to support adoption (or rejection) is made.<sup>4,5</sup> This suggests that an efficient framework for the regulation and reimbursement of health technologies should regard the evidence to support the reimbursement or issuing of guidance for a technology to be sufficient when it is not cost-effective to demand further information. This has some key implications for an efficient regulatory framework: different amounts (and types) of evidence will be required for different technologies with different characteristics and different amounts of evidence should be demanded for the same technology in different circumstances.<sup>4,5</sup> The role of the regulatory authority would be to “police” the prior evidence used in the expected value of information analysis.

However, there are a number of issues, which must be addressed before this approach can be implemented. Firstly, technologies, which are considered cost-effective based on existing information and funded, may not be considered value for money when additional information subsequently emerges, but may be difficult to remove from routine clinical practice. This problem of ‘irreversibilities’ can be addressed analytically in a number of ways including option pricing, estimation of maximum sunk costs and risk sharing. Secondly, there may be an adverse impact of early adoption decisions on the feasibility and recruitment to ongoing and future clinical trials. Thirdly, there are potential disincentive effects (free rider problems) when companies which were first to market with a new product undertake the research necessary to achieve approval, and those companies following with products in the same class could “free-ride” on this prior evidence.<sup>12</sup> Fourthly, how the quality and the appropriateness of decision models and expected value of information analysis is to be “policed” by the regulatory authority.<sup>13</sup> Analytical approaches, as well as policy analysis, is needed to identify possible changes to the policy environment of regulating health care, which can ameliorate these potential problems.

### Objectives

- To develop and demonstrate appropriate decision analytic methods for setting priorities in the research and development of health care technologies.
- To resolve key methodological issues in developing decision analytic models and in applying Bayesian information value theory to complex decision models.
- To develop methods which can establish optimal sample size, appropriate endpoints and follow-up periods for future experimental research as well as value information from non-experimental designs.
- To demonstrate the practicality and utility of decision analysis and Bayesian methods through its application to a number of case studies relevant to the NHS HTA programme and NICE.
- To identify alternative policy approaches to implementing a framework for the efficient regulation of health care technologies

### **Research design and methods**

#### *Case studies*

It is an explicit objective of the proposed methodological work to develop a close relationship with the programme of applied decision analysis undertaken in York, primarily as technology assessments for NICE and NHS HTA. It is hoped that the methodological and applied work feed off each other, with methodological development facilitated by the testing of novel forms of analysis on policy-relevant and up-to-date decision questions; and applied work benefiting from new analytical approaches. Over a five-year period, it is expected that 3 to 5 decision analyses

will be undertaken which can be further developed for methodological work. These will be selected primarily according to whether they highlight the sorts of methodological problems that this programme is aimed at addressing. It is important to emphasise that HSRC Programme resources will only be used further to develop the models as methodological case studies. This will include making the models fully probabilistic, assessing the feasibility and utility of a range of alternative analytical approaches, and establishing whether (and in which circumstances) they generate differences in cost-effectiveness results and optimal decisions.

#### *General approach*

A series of methodological questions will be addressed during the programme using the careful selection of case studies as a vehicle to demonstrate and compare methods. The specific questions for each of the four areas defined above, and indications of the approaches which will be taken, are outlined below. The general approach to addressing these questions will involve three stages: (i) the identification of feasible alternative options based on literature review; (ii) the implementation of each option using one or more of the case-studies; and (iii) a comparison of the implications of each option both in terms practicality and ease of use, empirical results and the extent to which optimal decisions are altered.

#### *Methodological questions relating to decision modelling*

- The results of multiple parameter evidence synthesis (MPES) conducted by the Ades programme will be incorporated into the decision models for each of the common case studies. Initially, this will be done by modelling the correlation generated between inputs from MPES separately within the decision models. However, in collaboration with the Ades programme, we will also examine the feasibility of conducting evidence synthesis and complex decision modelling simultaneously within WinBUGS.
- Case-studies will be selected which have following characteristics: (i) require extrapolation beyond available data and from surrogate end-points to final outcomes; (ii) have parameter estimates which may suffer from publication and selection bias; (iii) require some assessment of exchangeability between different sources of data (e.g. between settings, dosage, time etc.). In each case, alternative approaches to characterising the additional uncertainty created by these issues will be applied and evaluated
- Case-studies will be selected where there is an accumulation of evidence over time. Initially, the retrospective process of updating the decision models with the accumulating evidence will be done for each parameter (using either analytic methods where priors are conjugate, or WinBUGS). However, in collaboration with the Ades programme, we will also examine the feasibility of building complex decision models within WinBUGS so that updating the evidence, and revising the estimates of cost-effectiveness and expected value of information can be conducted simultaneously

#### *Methodological questions relating to expected value of perfect information (EVPI)*

- Establish whether estimates of EVPI can be usefully compared over time as the evidence from research accumulates. This will be achieved by application to case-studies where an accumulation of evidence over time can be identified, and by retrospectively comparing the results of EVPI analysis to the subsequent accumulation of evidence.
- Identify the appropriate non-parametric methods of estimating partial EVPIs by comparing proposed alternatives using case-studies which exhibit different characteristics (i.e. linear and non linear models, and those with correlated and independent inputs).
- Identify solutions to the practical computation problems which emerge when model inputs are correlated by application of alternative approaches to specific case-studies with inputs exhibiting this feature.

- Identify methods for the estimation of the useful lifetime of a technology by comparing the impact on EVPI of using estimates based on historical evidence from other technologies, patent life times and judgement.
- Demonstrate the impact on research priorities by comparing the results of all the case- studies with the decisions about future research made by research funders (e.g. NHS HTA) and the suggestions for future research in NICE guidance.

*Methodological questions relating to expected value of sample information (EVSI):*

- Establish when EVSI, based on an assumption of a normal distribution, may be acceptable. This will be achieved by comparing the results to those generated with other conjugate priors or non-parametric methods for a range of case-studies with different characteristics.
- Implement EVSI with conjugate priors when the assumption of normality does not hold, including estimating EVSI from Markov Chain Monte Carlo models, by application to case-studies where priors on key parameters are unlikely to be normally distributed.
- Demonstrate whether non-parametric Bayesian methods, such as Bayesian Monte Carlo, can offer a more flexible way to estimate EVSI in the case of non-conjugate priors by application to case-studies where priors on key parameters are unlikely to be conjugate.
- Identify a computationally efficient way to estimate EVSI and establish which of a large number of possible clinical strategies should be included in a trial design by comparing alternative “search strategies” with dynamic programming. This will be investigated using case-studies of decision problems which offer a choice between many alternatives.
- Extend the framework of EVSI to include non-experimental designs by comparing the results of alternative approaches identified in a review of the methodological literature.

*Methodological questions relating to implementation and regulation*

- Explore alternative analytic solutions to the problem of ‘irreversibilities’ in each case- study by assessing the feasibility of option pricing, estimation of maximum sunk costs and developing alternative risk sharing models.
- The potential adverse impact of early adoption decisions on the feasibility of recruitment to ongoing and future clinical trials will be assessed for each case-study, and appropriate means to discount the value of information will be developed and applied.
- The existing guidance on assessing the quality and the appropriateness of decision models will be assessed, developed and extended to include expected value of information analysis so that regulatory authorities will have a means of “policing” this type of analysis.
- Proposals to overcome potential disincentive effects (free rider problems) of implementing a value of information framework will be examined. Analytical approaches (the economics of industrial organisation) ,as well as policy analysis, is needed to identify possible changes to the policy environment of regulating health care, which can ameliorate these potential problems. The general approach for these will be to review alternative policy options and consider their advantages and limitations, placing particular emphasis on literatures outside health care.

## **Implications**

The primary purpose of the methods research is to identify an analytical framework which supports decision making in maximising health gains from collectively-funded service delivery and research and development. The proposed policy analysis has the objective to exploring how this framework can be successfully implemented with health care systems such as the NHS.

## **Collaborations and links with other HSRC activities**

The proposed programme represents a collaboration between economists, decision modellers and

statisticians. We expect further to develop existing collaboration with Bayesian statisticians such as Keith Abrams and Alex Sutton (Leicester), Tony O'Hagan (Sheffield) and Max Parmar (MRC). We also expect close collaboration with the Health Technology Assessment Programme (through Ruairidh Milne) and NICE (through Carole Longson). As described above, the proposed programme is closely linked with the Ades *et al* HSRC programme.

## References

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