

Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon- β and glatiramer acetate for multiple sclerosis

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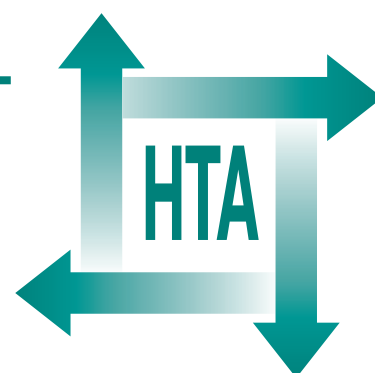
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Executive summary

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Executive summary

Aims and objectives

The aims of the report are: (1) to develop methods for performing expected value of perfect information (EVPI) analysis in computationally expensive models; these methodological advances will be reported and applied alongside a case study to form a clear and valuable reference source to health economists and analysts in other outcomes research organisations; (2) to report on the developments on the health economics of interferon- β (IFN- β) and glatiramer acetate in the management of multiple sclerosis (MS) using this methodological framework.

Background

The expected value of information (EVI) approach uses a decision analytic framework in order to prioritise further research through identifying those areas in which additional data collection, and hence the reduction of uncertainty, would be of most value. Value of information analysis describes the opportunity cost of uncertainty regarding a commissioning decision in terms of the probability that a suboptimal intervention is selected and the associated economic disbenefit. Further data collection is valuable if it reduces the likelihood of making the wrong decision. Step by step algorithms for performing EVPI analysis are described within the main body of the report.

Overview of case study model: the ScHARR MS model

MS is a demyelinating disease of the central nervous system. MS is the most frequent cause of neurological disability in young adults, and is typically characterised by chronic relapse and disease progression. There is no effective cure for MS; drugs known as disease-modifying therapies (the IFN- β s and glatiramer acetate) are aimed at reducing the number and severity of relapses experienced and slowing disease progression. These therapies were appraised by The National Institute for Clinical Excellence in 2001 and neither IFN- β nor glatiramer acetate was recommended for routine supply by the NHS in

England and Wales. The economic analysis identified several areas of key uncertainty; however, the computational expense of the ScHARR MS model precluded the formal quantification of undertaking further research in these areas. Owing to the commercial-in-confidence evidence on the relationship between the expanded disability status scale (EDSS), costs of care and health outcomes, we have converted the original ScHARR MS model into a public domain model to facilitate estimation of the value of conducting further research on IFN- β and glatiramer acetate.

Methodological framework for performing EVPI analysis on computationally expensive models

We report a methodological framework for undertaking a comprehensive analysis of the value of perfect information for computationally expensive health economic models. This proposed framework follows a sequential logic, and identifies conditions whereby EVPI may be calculated numerically, where a one-level sampling algorithm may sufficiently approximate the more computationally expensive two-level algorithm, in addition to identifying methods for metamodelling, that is, replacing the original economic model with a statistical approximation.

This review has resolved methods for defining the number of samples required to achieve stable and unbiased EVPI estimates from the two-level EVPI algorithm and for estimating confidence intervals for EVPI estimates.

A review of the current literature identified several metamodelling approaches; the following metamodelling techniques are reviewed:

- linear regression
- neural networks
- response surface methodology (using polynomial regression)
- multivariate adaptive regression splines
- Gaussian processes/Kriging (non-linear regression).



A critique of these metamodelling methods suggests that, in general, simpler techniques such as linear regression may be easier to implement, as they require little specialist expertise although they may provide limited predictive accuracy. Conversely, more sophisticated techniques such as Kriging/Gaussian process methodology and neural networks tend to require greater specialist expertise. These more complex methods, however, tend to use less restrictive assumptions concerning the relationship between the model inputs and net benefits, and may therefore permit greater accuracy in estimating EVPI.

Applied methodology

The methodological framework was applied to the SchHARR MS model in order to estimate the value of conducting further clinical research in this area. This analysis used three separate models:

1. the original SchHARR MS model
2. a linear regression metamodel used to approximate the SchHARR model
3. a Gaussian process metamodel used to approximate the SchHARR model.

Assuming independent treatment effects, the 'per patient' EVPI for all uncertain parameters within the case study model is £8855; this represents the upper estimate for the overall EVPI. Assuming that treatment efficacies are perfectly correlated, the global per patient EVPI is £4271; this represents a lower estimate for the overall EVPI.

Due to the computation time required, it was not possible to perform two-level partial EVPI analysis for parameters using the original SchHARR model. Linear regression analysis suggested a reasonable degree of linearity between the model inputs and net benefits. A linear regression metamodel and Gaussian process metamodel were constructed in order to approximate the relationship between model inputs and net benefits. The Gaussian process model is likely to be more reliable as it is a non-linear regression technique which incorporates all possible interactions between those variables included in the simulation model.

Case study results

We estimated the relevant population for the technology over a 10-year time horizon. Assuming independent treatment effects, the global population EVPI for all uncertain parameters

within the case study model is £86,208,936; this represents the upper estimate for the overall population EVPI. Assuming that treatment efficacies are perfectly correlated, the global population EVPI is £41,581,273; this represents a lower estimate for the overall EVPI. The partial EVPI analysis, calculated using both the linear regression model and Gaussian process model, clearly suggests that further research is indicated on the long-term impact of these therapies on disease progression, the proportion of patients dropping off therapy and the relationship between the EDSS, costs of care and health outcomes. Although further information on costs associated with particular EDSS states and the rates at which patients drop off therapy may be obtained through non-experimental designs such as observational studies, further useful information on the impact of disease-modifying therapies on disease progression and associated health outcomes would be most reliably obtained through a long-term randomised controlled trial which includes a direct assessment of quality of life.

Discussion

Linearity of the model

Regression analysis takes a central role in undertaking EVPI analysis via metamodelling. The main potential drawback concerns the degree of linearity between the model inputs and net benefits. If the relationship between net benefits and the parameter inputs is only weakly linear, multiple linear regression is unlikely to be useful in performing partial EVPI analysis. Conversely, if the relationship is strongly linear, it is likely that even if the expected net benefits for each treatment strategy are predicted with accuracy, the prediction error in the calculation of net benefits is likely to be magnified in the calculation of EVPI. The applied methodology clearly points towards using more sophisticated metamodelling approaches in order to obtain greater accuracy in EVPI estimation.

Where a reasonably strong linear relationship exists, the linear regression metamodel may be used in order to obtain one-level estimates of partial EVPI for all model parameters. This exercise may enable the modeller to ascertain which of the model parameters are likely to attain value and which are not, and potentially suggest an order of magnitude for this expected value. If the analyst is aware of the key parameters, it may be possible to revert

back to the original cost-effectiveness model and perform partial EVPI analysis using the correct two-level sampling algorithm for those identified parameters, and to ignore the remaining parameter set.

Although the question ‘how linear is linear enough?’ for use in EVPI analysis cannot be resolved using standard statistical tests, it is possible to explore the degree of approximation error resulting from a linear regression metamodel through comparing the global EVPI results calculated using the regression metamodel and the global EVPI results calculated using the original cost-effectiveness model. If the two global EVPI results are similar, this should enable the analyst to gauge the degree to which non-linearity may distort the partial EVPI estimates. If there is a considerable error between the global EVPI estimates, this should forewarn against the use of the one-level EVPI algorithm and highlight the need for non-linear methods such as Gaussian process metamodeling.

Use of metamodeling for undertaking value of information analysis

Although metamodels allow faster analysis of a problem, their use introduces an added element of uncertainty to the analysis; a metamodel can only ever approximate a system rather than fully replace it. Although many of the techniques appear similar in theory, the main difference relevant to the users of health economic models concerns the ease of use and availability of software. Many of these techniques have been applied in only a limited number of case studies, hence their suitability for use within EVPI analysis has not been demonstrated.

The suitability of these alternative metamodeling methods in performing EVPI analysis will essentially be determined by the expertise of the modeller, the time available for the project and the degree of accuracy required in the results. It is not unreasonable to postulate that when faced with a computationally expensive decision model, the general user of health economic models is primarily concerned with selecting the easiest and quickest metamodeling technique which provides reasonably accurate results. Indeed, in instances whereby the original cost-effectiveness model is approximately linear, regression metamodeling may be an adequate approach for identifying areas for investment in further research. This review has identified several classes of metamodeling technique. Although it has been possible to identify some of their more generic characteristics,

these are certainly insufficient to identify one generally preferred technique or to identify a set of criteria for selecting a specific technique given specific case study characteristics.

Limitations of this study

The information currently available in the public domain on the alternative metamodeling techniques is limited. Insufficient information was available on the practical application of several of the metamodeling methodologies reviewed, hence these methods could not be confidently applied to the case study model. Further, the complexity of the ScHARR MS model means that it is infeasible to generate the partial EVPI analysis using the two-level sampling algorithm. As a result, there is no direct means of validating fully the partial EVPIs calculated using either the one-level sampling algorithm, the linear regression metamodel or the Gaussian process metamodel. Direct tests of validity have only been possible on the estimate of overall EVPI. This analysis demonstrated a high degree of linearity between sampled parameters and net benefits generated by the ScHARR MS model; this means that the exploration of the impact of non-linearities on the predictive ability of the metamodels considered and of the impact on parameter selection via importance analysis has been limited.

Further research

A number of areas requiring further research have been highlighted.

Further research indicated by the case study

The partial EVPI estimates generated using both the linear regression metamodel and the Gaussian process metamodel suggest that further research concerning the relationship between the EDSS, costs of care and health outcomes, the rates at which patients drop off therapy and in particular the impact of disease-modifying therapies on the progression of MS is required.

Inclusion of the ‘relevant population’ within the sensitivity analysis

Previous value of information studies have calculated the population EVPI by simply multiplying the per patient EVPI by a fixed number of patients over the lifetime of the decision. However, as the population relevant to a particular decision is itself uncertain, there remains an unresolved methodological issue concerning whether the uncertainty in the epidemiological parameters should also be accounted for within the sensitivity analysis. ►

Development of criteria for selecting a metamodelling approach

There exist a number of metamodelling techniques which have not been presented in this review. Methodological and case study work would be of benefit in exploring the application of the metamodelling techniques within health economic models and in the specific application to EVI analyses.

The use of metamodelling for EVSI and expected net benefit of sampling (ENBS) analysis

Due to similarities in the algorithms used, it is reasonable to suggest that metamodelling could

have an instrumental role in performing EVSI and ENBS analysis for computationally expensive models.

Publication

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NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

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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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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