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Title **Methods for Expected Value of Information Analysis in Complex Health Economic Models: Developments on the Health Economics of Beta Interferon and Glatiramer Acetate for Multiple Sclerosis**

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Aim

To develop methods to perform expected value of perfect information (EVPI) analysis in computationally expensive models and to report on the health economics of interferon-β and glatiramer acetate in managing multiple sclerosis (MS) using this methodological framework.

Conclusions and results

A review of metamodeling approaches suggested that the simpler techniques, eg, linear regression, may be easier to implement, but their predictive accuracy may be limited. More complex methods, eg, Gaussian process (GP) metamodeling and neural networks, tend to use less-restrictive assumptions about the relationship between model inputs and net benefits, and may be more accurate in estimating EVPIs. Assuming independent treatment efficacy, the *per patient* EVPI for all uncertainty parameters in the ScHARR MS model is GBP 8855. This leads to a population EVPI of GBP 86 208 936 (the upper estimate for the overall EVPI over 10 years). Assuming all treatment efficacies are perfectly correlated, the overall per patient EVPI is GBP 4271. This leads to a population EVPI of GBP 41 581 273 (the lower estimate for the overall EVPI over 10 years). The partial EVPI analysis, using both the linear regression metamodel and GP metamodel, suggests the need for further research on the long-term impact of these therapies on disease progression, the proportion of patients dropping off therapy, and the relationship between the expanded disability status scale (EDSS), quality of life, and cost of care.

Recommendations

The applied methodology points toward using more sophisticated metamodeling approaches to obtain greater accuracy in estimating EVPI. Programming requirements, software availability, and statistical accuracy should be considered when choosing metamodeling techniques. Simpler, more accessible techniques are open to greater predictive error. Sophisticated methodologies may enhance accuracy within non-linear models, but are more difficult to implement and may require specialist expertise. Only a few metamodeling techniques, including GP modeling, have been applied, their suitability for use in EVPI analysis is yet to be demonstrated.

Methods

A methodological framework was developed for undertaking EVPI analysis for complex models. The framework identifies conditions for calculating EVPI numerically, where the one-level algorithm sufficiently approximates the two-level algorithm, and whereby metamodeling techniques may accurately approximate the original simulation model. Metamodeling techniques, eg, linear regression, neural networks, and GP, were systematically reviewed and critically appraised. Linear regression metamodeling, GP metamodeling, and the one-level EVPI approximation were used to estimate partial EVPIs using the ScHARR MS cost-effectiveness model.

Further research/reviews required

Further clinical research is required on the relationship between the EDSS, costs of care and health outcomes, the rates at which patients drop off therapy, and the impact of disease-modifying therapies on MS progression. Further methodological research is indicated concerning inclusion of epidemiological population parameters in EVPI analyses, development of criteria for selecting a metamodeling approach, application of metamodeling techniques in EVSI information, and expected net benefit of sampling (ENBS) analyses.

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