

available at www.sciencedirect.comjournal homepage: www.ejconline.com

Current perspective

Health economics in drug development: Efficient research to inform healthcare funding decisions

Peter S. Hall ^{a,*}, Christopher McCabe ^a, Julia M. Brown ^a, David A. Cameron ^b

^a University of Leeds, Charles Thackrah Building, 101 Clarendon Road, Leeds LS2 9LJ, UK

^b Edinburgh Cancer Research Centre, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU, UK

ARTICLE INFO

Article history:

Received 14 June 2010

Accepted 22 June 2010

Available online 23 July 2010

Keywords:

Drug development

Health economics

Decision theory

ABSTRACT

In order to decide whether a new treatment should be used in patients, a robust estimate of efficacy and toxicity is no longer sufficient. As a result of increasing healthcare costs across the globe healthcare payers and providers now seek estimates of cost-effectiveness as well. Most trials currently being designed still only consider the need for prospective efficacy and toxicity data during the development life-cycle of a new intervention. Hence the cost-effectiveness estimates are inevitably less precise than the clinical data on which they are based. Methods based on decision theory are being developed by health economists that can contribute to the design of clinical trials in such a way that they can more effectively lead to better informed drug funding decisions on the basis of cost-effectiveness in addition to clinical outcomes. There is an opportunity to apply these techniques prospectively in the design of future clinical trials. This article describes the problems encountered by those responsible for drug reimbursement decisions as a consequence of the current drug development pathway. The potential for decision theoretic methods to help overcome these problems is introduced and potential obstacles in implementation are highlighted.

© 2010 Elsevier Ltd. All rights reserved.

1. Introduction

For a drug license to be granted, a manufacturer will generally be required to prove the safety and efficacy of a drug for a given indication. The increasing costs of healthcare around the world have led to healthcare providers and payers requiring further evidence relating to value for money. Almost all developed healthcare systems have now established reimbursement processes to formally assess this evidence and make recommendations on how new drugs should be paid for (reimbursed).¹ Economic evaluation provides a means to assess whether new treatments represent value for money. The need to demonstrate cost-effectiveness has been

described as the ‘fourth hurdle’ after quality of manufacture, safety and efficacy.²

Overcoming the fourth hurdle is problematic for all concerned. Clinical trials of new cancer drugs are designed primarily to meet the requirements of licensing authorities such as the European Medicines Agency in Europe or the US Food and Drug Administration. Despite attention from the academic community separating the design characteristics of pragmatic and explanatory trials,³ it is rare for such trials to collect the information required for a robust economic evaluation. The ability of reimbursement authorities to make a fully informed adoption decision is, therefore, often compromised by uncertainty in the evidence for cost-effectiveness.

* Corresponding author. Tel.: +44 1133430814.

E-mail address: p.s.hall@leeds.ac.uk (P.S. Hall).

0959-8049/\$ - see front matter © 2010 Elsevier Ltd. All rights reserved.

doi:10.1016/j.ejca.2010.06.122

A landmark example demonstrating the difficulties this type of decision making can face was seen with the introduction of trastuzumab (Herceptin®) for early breast cancer which gained a license as adjuvant treatment in 2006. Clinical efficacy was proven beyond reasonable doubt but estimates of cost-effectiveness accepted by the UK reimbursement authority the National Institute for Health and Clinical Excellence (NICE) were highly uncertain due to the necessary extrapolation and assumptions beyond trial-based evidence.⁴ This led to delays in approval with consequent public outcry and also a formal appeal by a local healthcare provider against the final positive decision.^{5,6}

Despite difficulties in assessing cost-effectiveness, when faced with the challenge of maximising the health of the population within the constraints of a fixed public healthcare budget, it is a vital consideration. Therefore, if patients are to access new drugs through a publicly funded system, cost-effectiveness must be considered along with other social and political factors prior to a positive reimbursement decision.⁷

2. Cost-effectiveness modelling and the drug development pathway

While trial-derived data on all aspects of clinical and economic evidence might be considered optimal, it is frequently unavailable. This necessitates the use of decision modelling to bring together evidence from other sources such as observational studies to inform a cost-effectiveness estimate.⁸ A modelling exercise can also facilitate estimation of cost-effectiveness in an actual patient population rather than a selected trial population. Fig. 1 illustrates a typical decision model for this purpose. Several countries use such a decision model at the time a reimbursement decision needs to be made, which is normally after a drug has received licensing approval (Fig. 2).

The ability of a reimbursement decision maker to make a fully informed adoption decision which considers cost-effectiveness or value may be compromised for a number of shortfalls in evidence. When considering clinical trial data, these

can include short follow-up, a highly selected patient population and a lack of prospectively collected real cost data. This could be rectifiable but for an often experienced inability to generate adequate evidence for cost-effectiveness assessment at this time point. This may be because once a drug is licensed and accepted as clinically efficacious further research becomes difficult. For example, randomised trials attempting to refine treatment regimens or collect additional data will often fail to recruit as patients are unwilling to risk randomisation that may deny them the drug as licensed. Furthermore, trials of newer agents tend to be more attractive to clinical investigators than studies designed to answer questions relating to population rather than individual patient benefit. In the case of trastuzumab for early breast cancer, these problems have hindered trials which are attempting to assess shorter treatment durations as well as collect in-depth quality of life and economic data after licensing approval has been granted.⁹

Despite this, a decision still has to be made. It is therefore accepted that an adoption decision should be made on the basis of the expected cost-effectiveness given existing information (i.e. choose the treatment strategy that is most likely to be cost-effective rather than require a *p*-value of 0.05 for cost-effectiveness). The greater the level of uncertainty in the evidence the more likely it becomes that a reimbursement authority will make an incorrect reimbursement decision. An incorrect decision wastes resources that could have been used for health gain elsewhere (opportunity cost). Further research aimed at reducing uncertainty consequently has value, meaning that there will be value in delaying the decision and conducting further research.¹⁰

There is thus a need to avoid delay in reimbursement decision making by generating sufficient evidence for a reimbursement decision alongside initial safety and efficacy data if patients are to have rapid access to new treatments. However, there is substantial uncertainty regarding how trials should be designed to provide such evidence, which will be unique to each drug, depending on other available information. It has therefore been suggested that the type of decision models used for economic evaluation could be used earlier in the drug development process to identify additional requirements for robust cost-effectiveness analysis (Fig. 3).^{11–13} Such models would synthesise all the available evidence prior to initiation of a pivotal trial and identify critical uncertainties in the evidence from the perspective of reimbursement. For example, there may be plenty of evidence about the costs of common toxicities from phase II studies or studies in different cancer types such that gathering further detailed evidence would be of little value. For a new anti-cancer drug there will undoubtedly be value in efficacy research, but there might also be a value in researching impact on quality of life and costs of care. As an alternative example, consider a study measuring the benefit of a new anti-emetic. The cost (and size) of a trial with a survival endpoint would be prohibitive and unnecessary, whereas measuring QoL and the reduction in costs of controlling emesis would be much more beneficial. This might seem obvious, but an explicit framework for identifying how much of each type of research would be useful for a given decision problem has much to offer when considering more subtle aspects of research design.

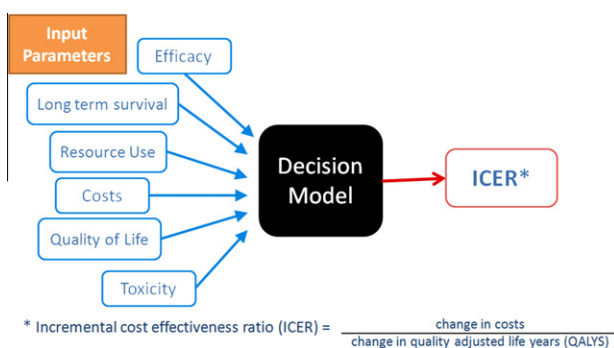


Fig. 1 – A decision-analytic model used for cost-effectiveness analysis. Multiple aspects of research contribute to the model as input parameters. The model produces an output as average life years or average quality-adjusted life years per patient as well as average cost per patient. These together form the measure of cost-effectiveness, the incremental cost-effectiveness ratio (ICER) between standard care and a new intervention.

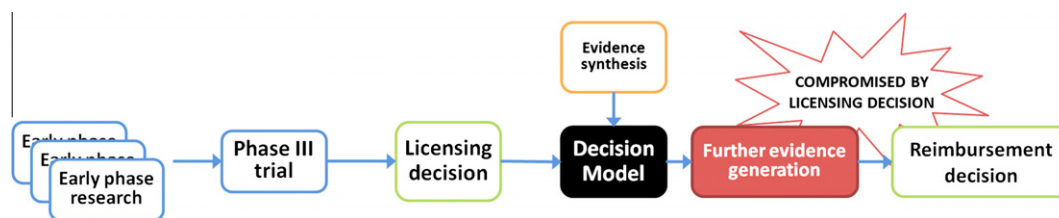


Fig. 2 – Current drug development and approval process for new pharmaceuticals. Further research is required to inform cost-effectiveness estimates after a licensing decision has been made. The result is a delay to the reimbursement decision and the act of licensing a drug can hinder further research.

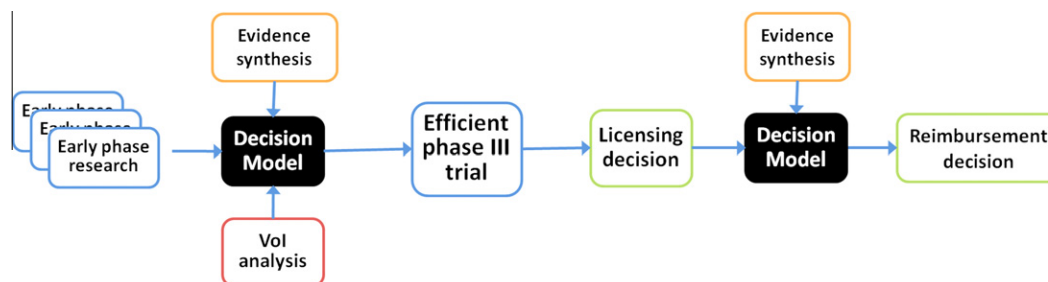


Fig. 3 – Suggested drug development process. By undertaking a decision modelling exercise prior to the phase III trial, research can be tailored to allow an adequately informed reimbursement decision without the need for further evidence generation.

3. Research prioritisation and efficient trial design

The overwhelming objective of medical research from a societal perspective should be population health gains from new interventions. This requires consideration of monetary expenditure on research in addition to expected clinical gains, given that similar expenditure elsewhere could potentially provide greater health gains. Current methods for public research prioritisation are far from transparent, but in general rely on pre-defined criteria which are open to interpretation within peer review and panel discussion procedures. An explicit and reproducible framework that complements this process is required to estimate the potential population-level benefit gained by specific research, including the benefits of reducing reimbursement decision uncertainty.

A number of potential solutions have been proposed.¹⁴ Most are a variant of the decision-analytic approach. During the last decade interest in research prioritisation within UK health economics has focussed on value of information (VoI) methods.¹⁵ These rely on decision theory and the Bayesian statistical paradigm. They were developed in the 1950s and 60s for business application and have subsequently been used within food standards, environmental and engineering fields.^{16–23} The last decade has seen them developed for health research prioritisation in the setting of health technology assessment.^{24–27}

A VoI analysis can be conducted using a decision model at any point in the drug development process. It has been likened to sensitivity analysis which, used alone, can indicate the magnitude of influence of different aspects of research on outcomes. VoI methods provide an advantage over sensitivity analysis by providing a quantifiable estimate of societal

payoff for aspects of research.²⁸ Theoretically, the VoI is the highest amount a decision maker would be willing to pay for information prior to making a decision. Within a health-care context this allows precise monetary value to be attributed to the information that can inform reimbursement decision making. This value reflects the opportunity cost to society (benefits foregone by patients) of making an incorrect reimbursement decision, multiplied by the probability of making that incorrect decision (derived from the uncertainty around current evidence). The decision uncertainty is the risk of making the wrong decision. The “expected value of perfect information” (EVPI) can be calculated for a given decision (e.g. the decision to fund a new drug) and represents an upper bound on the value of conducting research to inform this decision. VoI is a simple idea, but its conceptual origins are out-with classical medical statistics, thus requiring a cognitive shift for those who traditionally dictate methods in drug development research.

So how can a VoI analysis positively influence research design at the time of a phase III drug trial? Fig. 4 presents a hypothetical output from a VoI analysis on the basis of a decision model constructed at the pre-phase III time point. This shows the relative value of conducting research on different aspects of the evidence contributing to a cost-effectiveness endpoint. This can be used to tailor research designs to reduce uncertainty in the most valuable areas of evidence. The VoI approach can take into account the number of future patients likely to be affected by a disease, potential clinical benefits from treatment and costs to payers, with each of these parameters contributing to an overall estimate of the treatment's value.

While EVPI calculations are useful, they still have limitations. The EVPI should be the maximum a decision maker is

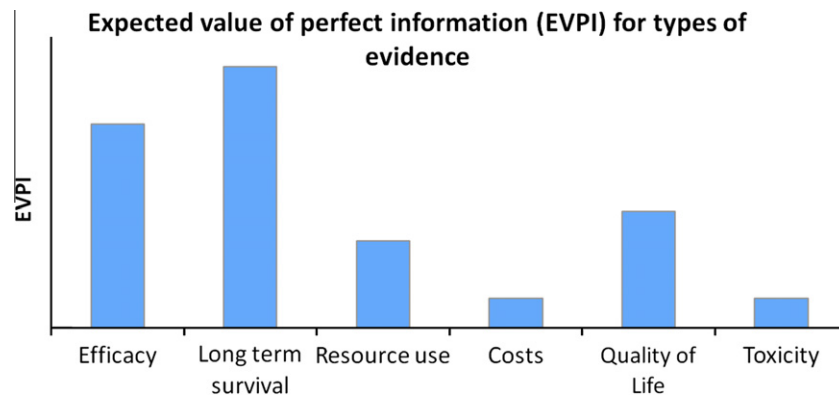


Fig. 4 – Value of Information analysis output. In this hypothetical example prior to a phase III trial there is value in research into efficacy, in particular long-term follow-up. A quality of life study is also worthwhile but research into costs or toxicity is less of a priority.

willing to pay to reduce uncertainty to zero. But this is an aspiration rather than a realistic goal. What is really needed is an estimate of payoff for a given research proposal. To meet this need, the same framework can be extended to calculate the expected value of sample information (EVSI). EVSI calculations are currently technically difficult as outlined below but in the future as methods advance they should have a lot to offer. The EVSI estimates the reduction in the cost of uncertainty induced by sampling (further research). By subtracting the cost of sampling from the EVSI the expected net gain (ENG) of the research can be calculated. By calculating the ENG for a variety of proposed trial designs (considering aspects such as sample size or length of follow-up) the preferred design can be selected.^{29,30} A hypothetical representation of an EVSI calculation for a trial sample size is shown in Fig. 5. An optimal sample size could be specified to inform a secondary cost-effectiveness endpoint, complementing the traditional sample size calculation based on the estimated effect size (and required *p*-value) of the primary endpoint. Such calculations might also indicate value in conducting a smaller additional sub-study such as a cost or quality of life sub-study on a portion of the total study sample.

4. Is decision theory ready to inform trial design?

Value of information methods based on decision modelling has recently been the focus of intense development by health economists and Bayesian statisticians in attempts to overcome a number of challenges their use poses:

4.1. Structuring a decision problem

It is important to adequately represent the clinical pathway upon which a decision model is based. All aspects of a problem need to be addressed without creating an over-complex model and resulting in analytical error. Adequately representing structural uncertainty remains difficult and omission of a key factor can lead to oversight in attributing priorities for research. This is a problem for any type of model-based eco-

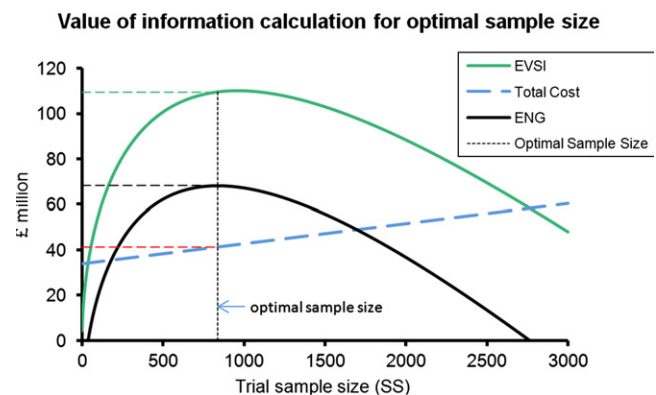


Fig. 5 – Hypothetical VoI calculation to determine the optimal sample size of a trial for a cost-effectiveness endpoint. The total cost of the research comprises an up-front cost and a per-patient cost. The expected value of sample information (EVSI) reaches an optimal level at a sample size of approximately 800 patients. At this point the expected net gain of sampling (ENG) is also at a maximum and is the EVSI minus the total cost of research. This represents the overall benefit (financial and health) of the research. Such a calculation might complement a traditional power calculation.

nomie evaluation, not just for research prioritisation.³¹ Sensitivity analysis around alternative model structures is the current best solution.

4.2. Evidence synthesis and model parameterisation

This includes, for example, the challenges of eliciting prior information from experts to inform model parameters where empirical research has not yet taken place. There is also a requirement to consider correlation between different parameters of a model and to accurately extrapolate short-term data over a relevant time horizon. Reliance on surrogate outcomes and transferability of data between healthcare settings also pose challenges.³²

4.3. Computational and statistical challenges

EVPI and EVSI can be calculated by a variety of methods depending on the validity of assumptions about model linearity and normality.^{33–35} A series of papers by Willan and Eckermann have developed purely parametric methods to a high theoretical level although their use with the complex models required for most health technology assessment may be limited.^{36,37} Non-parametric EVSI calculation poses a much higher computational burden and, although developments are ongoing, much more work is needed.^{38,39}

4.4. Adoption by regulatory organisations and reimbursement agencies

It is reimbursement authorities and other regulators who have the power to ensure these methods are implemented, perhaps with cooperation from licensing authorities. It will also be their responsibility to ensure that adequate analytic standards are adhered to. A number of challenges that must be overcome before they can do this have been pointed out. These include the problems associated with reversing a decision after the emergence of further information, problems with conducting further research after an intervention is adopted as routine care and the potential incentive for jurisdictions to wait for others to conduct research (free-rider problems).²⁵

4.5. Adoption by public research commissioners and clinical trialists

The framework for economic evaluation in healthcare that has emerged over the last 30 years is unfamiliar to much of the clinical research community. There remains mistrust of decision modelling which can seem opaque to those without technical expertise. Traditional methods for creating hypotheses and designing trials have developed over many decades. Clinicians and statisticians have learnt to work together to enhance the internal validity of clinical research: adoption of an alternative framework unsurprisingly faces some resistance. To be effective, clinicians, trialists and health economists must work together to deliver this alternative paradigm that acknowledges the reality of opportunity cost. Realistic and understandable applied examples in oncology are needed to demonstrate to a relevant audience how the methods described can improve the design of important drug trials.

4.6. Industrial drug development

Prioritising or designing research on the basis of societal benefit might seem irrelevant in the context of industry-funded drug research, when the objective is profit maximisation rather than societal health benefit. However, ensuring that pharmaceuticals research adequately informs public reimbursement decision makers is likely to work to the advantage of companies seeking to speed up market access. The provision of clear goal posts in this respect, as is likely to develop with the advent of value-based pricing mechanisms, gives the industrial research designer a clear incentive to generate

unambiguous cost-effectiveness-based outcomes. Indeed, as regulators move towards formally demanding cost-effectiveness evidence, there will be a need for companies to improve the efficiency of their research programmes in meeting these endpoints in addition to purely clinical outcomes.^{40,41}

5. Conclusion

The potential of VoI methods is clear from recent pilot studies.⁴² VoI analyses have been successfully conducted in non-cancer settings where they have presented priorities for further research as part of on-going public research programmes.^{43–49} Steps are being taken to introduce these methods into the decision-making process operated by NICE. In the UK the renegotiated Pharmaceuticals Pricing Regulation Scheme is likely to lead to greater requirements for economic outcome measures for new drugs. Future drug reimbursement decisions and drug pricing negotiations are likely to be conditional on the generation of further evidence.⁵⁰ Risk sharing schemes are being utilised in Europe as a stop-gap measure to address the problem of decision uncertainty. Their effectiveness remains unproven and they are not a solution.⁵¹ Value-based pricing is now being promoted as the future of pharmaceuticals pricing. Other countries, including the US, Australia and Canada, are exploring decision modelling and VoI analysis as a potential research prioritisation strategy in the light of this.⁵² Recent healthcare reform in the US places much emphasis on value for money, and countries across Europe are developing their own frameworks attempting to rationalise spiralling healthcare costs. It is clear that value not just efficacy will be a key requirement for the introduction of future drug innovations. Efficient research to determine value will therefore be vital.

An explicit framework for research priority setting is long overdue and decision theoretic methods show much promise as the foundation for a solution. They allow estimation of the value of conducting research and can help ensure that sufficient evidence is generated for adequately informed reimbursement decisions at, or close to, the time of licensing. In the coming years it should be possible for clinical trialists, working with health economists, to establish in advance how much and what type of evidence are required to inform a drug adoption decision, thereby improving the likelihood that effective therapies will be available for their patients.

Authors contributions

All authors contributed to the concepts and writing of the manuscript. The initial draft was produced by PH.

Conflict of interest statement

The authors have received no financial or non-financial considerations in relation to the work reported in the manuscript. PH receives a salary from the University of Leeds on a grant from Roche. He is also employed by the NHS. Between them, the authors have received research, consultancy and lecturing funding or honoraria from a number of global pharmaceutical companies and have also received research or salary funding

from various NHS organisations. All of these pharmaceutical companies and the NHS would be affected by the proposed changes in the methods of pharmaceutical research and development.

REFERENCES

1. ISPOR. International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Directory of health technology assessment organisations worldwide. <<http://www.ispor.org/HTADirectory/Index.aspx>> [accessed April 2010].
2. Taylor RS, Drummond MF, Salkeld G, Sullivan SD. Inclusion of cost effectiveness in licensing requirements of new drugs: the fourth hurdle. *BMJ* 2004;**329**(7472):972–5.
3. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol* 2009;**62**(5):464–75.
4. Editorial. Herceptin and early breast cancer: a moment for caution. *Lancet* 2005;**366**(9498):1673.
5. BBC. Herceptin: was patient power key? 2006. <<http://news.bbc.co.uk/1/hi/health/5063352.stm>> [accessed December 2009].
6. National Institute for Health and Clinical Excellence. Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. Decision of the Appeal panel. July 2006 <<http://www.nice.org.uk/nicemedia/live/11585/33457/33457.pdf>> [accessed April 2010].
7. Walker S, Palmer S, Sculpher M. The role of NICE technology appraisal in NHS rationing. *Br Med Bull* 2007;ldm007.
8. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddar G. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford University Press; 2005.
9. Earl H. PERSEPHONE – duration of trastuzumab study with chemotherapy in early breast cancer: six versus twelve months. Health Technology Assessment <<http://www.hta.ac.uk/1607>> [accessed March 2010].
10. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute for Clinical Excellence (NICE). *Lancet* 2002;**360**(9334):711–5.
11. Annemans L, Genesté B, Jolain B. Early modelling for assessing health and economic outcomes of drug therapy. *Value Health* 2000;**3**(6):427–34.
12. Fenwick E, Palmer S, Claxton K, et al. An iterative Bayesian approach to health technology assessment: application to a policy of preoperative optimization for patients undergoing major elective surgery. *Med Decis Making* 2006;**26**(5):480–96.
13. Hall P, Brown J, Cameron D, McCabe C. Efficient trial design for new cancer therapies. *National Cancer Research Institute (NCRI) Cancer Conference* 2009:Abstract C110.
14. Harper G, Townsend J, Buxton M. Preliminary economic evaluation of health technologies. In: Stevens A, Abrams K, Brazier J, Fitzpatrick R, Lilford R, editors. *The advanced handbook of methods in evidence based healthcare*. London: SAGE Publications; 2001.
15. Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. *Health Econ* 1996;**5**(6):513–24.
16. Howard R. Information value theory. *IEEE Trans Syst Sci Cyber* 1966(SSC-2):22–6.
17. Kuhn H. Extensive games and the problem of information. In: Kuhn HW, Tucker AW, editors. *Contributions to the theory of games II*. Princeton: Princeton University Press; 1953. p. 193–216.
18. Stratonovich R. On value of information. *Izv USSR Acad Sci, Tech Cyber* 1965;**5**:3–12 [in Russian].
19. Schlaifer R. *Probability and statistics for business decisions*. New York: McGraw-Hill; 1959.
20. Hammitt J, Cave J. *Research planning for food safety: a value-of-information approach*. Santa Monica, CA, USA: RAND Corporation; 1991.
21. Thompson K, Evans J. The value of improved national exposure information for perchloroethylene (perc): a case study for dry cleaners. *Risk Anal* 1997;**17**:253–71.
22. Thompson KM, Graham JD. Going beyond the single number: using probabilistic risk assessment to improve risk management. *Human Ecol Risk Assess: Int J* 1996;**2**(4):1008–34.
23. Yokota F, Thompson KM. Value of information analysis in environmental health risk management decisions: past, present, and future. *Risk Anal* 2004;**24**(3):635–50.
24. Briggs A, Claxton K, Sculpher M. *Decision modelling for health economic evaluation*. Oxford University Press; 2006.
25. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *J Health Econ* 1999;**18**(3):341–64.
26. Claxton K. Bayesian approaches to the value of information: implications for the regulation of new pharmaceuticals. *Health Econ* 1999;**8**(3):269–74.
27. Yokota F, Thompson KM. Value of information literature analysis: a review of applications in health risk management. *Med Decis Making* 2004;**24**(3):287–98.
28. Felli JC, Hazen GB. Sensitivity analysis and the expected value of perfect information. *Med Decis Making* 1998;**18**(1):95–109.
29. Claxton K, Thompson KM. A dynamic programming approach to the efficient design of clinical trials. *J Health Econ* 2001;**20**(5):797–822.
30. Claxton K, Lacey LF, Walker SG. Selecting treatments: a decision theoretic approach. *J Roy Statist Soc Ser A (Statist Soc)* 2000;**163**(2):211–25.
31. Sculpher M, Fenwick E, Claxton K. Assessing quality in decision analytic cost-effectiveness models. A suggested framework and example of application. *Pharmacoeconomics* 2000;**17**(5):461–77.
32. Ades AE, Claxton K, Sculpher M. Evidence synthesis, parameter correlation and probabilistic sensitivity analysis. *Health Econ* 2006;**15**(4):373–81.
33. Coyle D, Oakley J. Estimating the expected value of partial perfect information: a review of methods. *Eur J Health Econ* 2008;**9**(3):251–9.
34. Ades AE, Lu G, Claxton K. Expected value of sample information calculations in medical decision modeling. *Med Decis Making* 2004;**24**(2):207–27.
35. Groot Koerkamp B, Myriam Hunink MG, Stijnen T, Weinstein MC. Identifying key parameters in cost-effectiveness analysis using value of information: a comparison of methods. *Health Econ* 2006;**15**(4):383–92.
36. Willan AR, Pinto EM. The value of information and optimal clinical trial design. *Stat Med* 2005;**24**(12):1791–806.
37. Eckermann S, Willan AR. Expected value of information and decision making in HTA. *Health Econ* 2007;**16**(2):195–209.
38. Brennan A, Kharroubi SA. Efficient computation of partial expected value of sample information using Bayesian approximation. *J Health Econ* 2007;**26**(1):122–48.
39. Brennan A, Kharroubi SA. Expected value of sample information for Weibull survival data. *Health Econ* 2007;**16**(11):1205–25.
40. Backhouse ME. An investment appraisal approach to clinical trial design. *Health Econ* 1998;**7**(7):605–19.
41. Backhouse ME. Use of randomised controlled trials for producing cost-effectiveness evidence: potential impact of

- design choices on sample size and study duration [see comment]. *Pharmacoeconomics* 2002;20(15):1061–77.
42. Claxton KP, Sculpher MJ. Using value of information analysis to prioritise health research: some lessons from recent UK experience. *Pharmacoeconomics* 2006;24(11):1055–68.
43. Brennan A, Kharroubi S, O'Hagan A, Chilcott J. Calculating partial expected value of perfect information via Monte Carlo sampling algorithms. *Med Decis Making* 2007;27(4):448–70.
44. Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C. Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon-beta and glatiramer acetate for multiple sclerosis. *Health Technol Assess* 2004;8 (27).
45. Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J. The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation. *Health Technol Assess* 2008;12 (25).
46. Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S. A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme. *Health Technol Assess* 2004;8 (31).
47. Colbourn T, Asseburg C, Bojke L, et al. Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses. *Health Technol Assess* 2007;11(29).
48. Bojke L, Claxton K, Sculpher MJ, Palmer S. Identifying research priorities: the value of information associated with repeat screening for age-related macular degeneration. *Medical Decis Making* 2008;28(1):33–43.
49. McKenna C, McDaid C, Suekarran S, et al. Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis. *Health Technol Assess* 2009;13(24).
50. Claxton K, Briggs A, Buxton MJ, et al. Value based pricing for NHS drugs: an opportunity not to be missed? *BMJ* 2008;336(7638):251–4.
51. Stafinski T, McCabe CJ, Menon D. Funding the unfundable: mechanisms for managing uncertainty in decisions on the introduction of new and innovative technologies into healthcare systems. *Pharmacoeconomics* 2010;28(2):113–42.
52. Schmidt C. Researchers consider value-of-information theory for selecting trials. *J Natl Cancer Inst* 2010;102(3):144–6.