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DOI:
10.1177/0272989X15594369

Document Version
Peer reviewed version

Citation for published version (Harvard):
Andronis, L, Billingham, L, Bryan, S, James, N & Barton, P 2016, 'A practical application of value of information and prospective payback of research to prioritize evaluative research', *Medical Decision Making*, vol. 36, no. 3, pp. 321-334. https://doi.org/10.1177/0272989X15594369

A practical application of value of information and prospective payback of research to prioritise evaluative research.

Running head: Value of information and payback empirical application

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[1] Financial support for this study was provided by a grant made available from the National Institute for Health Research in the UK, through a NIHR Doctoral Researcher Fellowship award [NIHR DRF 2009-08]. LJB was supported by the Medical Research Council [grant number G0800808]. The funding agreement ensures the authors' independence in designing the study, interpreting the data, wording, and publishing the report.

Background: Efforts to ensure that funded research represents 'value for money' have led to increasing calls for the use of analytic methods in research prioritisation. A number of analytic approaches have been proposed to assist research funding decisions, the most prominent of which are 'value of information' (VOI) and 'prospective payback of research' (PPoR). Despite the increasing interest in the topic, there is paucity of VOI and PPoR applications on the same case study to contrast their methodologies and compare their outcomes.

Objectives: We undertook VOI and PPoR analyses to determine the value of conducting two proposed research programmes. The application served as a vehicle for identifying differences and similarities between the methodologies, gave an insight into the assumptions and practical requirements of undertaking prospective analyses for research prioritisation, and highlighted areas for future research.

Methods: VOI and PPoR were applied to case studies representing proposals for clinical trials in advanced non-small cell lung cancer and prostate cancer. Decision models were built to synthesise the evidence available prior to the funding decision. VOI (expected value of perfect and sample information) and PPoR (PATHS model) analyses were undertaken using the developed models.

Results and conclusions: VOI and PPoR results agreed in direction, suggesting that the proposed trials would be cost-effective investments. However, results differed in magnitude, largely due to the way each method conceptualises the possible outcomes of further research and the implementation of research results in practice. Compared to VOI, PPoR is less complex but requires more assumptions. Although the approaches are not free from limitations, they can provide useful input for research funding decisions.

Keywords: research prioritisation; value of information; prospective payback of research; expected value of sample information

Introduction

The advance of evidence-based decision-making in health care has highlighted the need for rigorous information on the effectiveness and 'value for money' of treatments, and has led to an increasing demand for clinical evaluative research. At the same time, public research resources are limited, and hard choices are often needed on how the available budget should be allocated across competing research activities.

A number of analytic models have been developed and put forward to identify the value of conducting research and to assist with prioritisation decisions [1-5]. On the basis of the principles underpinning them, two main analytic frameworks have been typically distinguished in the literature [6, 7]—'value of information' (VOI) and 'prospective payback of research' (PPoR). The approaches present similarities, but they differ in the way they conceptualise the value of research [7, 8]. VOI infers this value by looking at the expected benefits of making a decision in the light of improved information and reduced uncertainty [9, 10], while PPoR calculates the benefits that research may bring about by triggering a beneficial change in clinical practice [2, 3, 7].

While prospective analytic assessments are not currently part of the research prioritisation process, there have been increasing calls for their use and a growing interest in exploring their potential role [4, 11-14]. At the same time, there is a steady stream of academic research aiming to address methodological issues in analytic methods, particularly in VOI [15, 16]. Nonetheless, practical applications of PPoR and VOI on the same case study for the purpose of contrasting and comparing the approaches are scarce. The only study available in the literature [17] gives useful insights, but it reports only basic VOI calculations, which are unlikely to represent the full potential of the approach [18], or reveal the true level of complexity in its calculations [19, 20].

With this in mind, we set out to apply PPoR and VOI analyses to two case studies representing proposals for clinical trials. The application aimed to give prospective estimates of the expected value of undertaking the proposed trials as calculated by each of the methodologies. As well as adding to the existing literature of practical applications, this work provided a vehicle for exploring the similarities and differences between the frameworks, gave an insight into the practical requirements and use of assumptions associated with these analyses, and suggested areas for further research.

Methods

VOI and PPoR were applied to two stylized case studies representing proposals for clinical trials in non-small cell lung cancer (NSCLC) and advanced castrate-refractory prostate cancer (CRPC). The methodologies were applied retrospectively, to identify the expected benefits of the proposed trials at the point when funding was considered. The analyses were carried out in two stages. In the first, preliminary, stage, information existing up to the point when the research proposals were submitted for funding was synthesised through purpose-built decision models. In the second stage of the analyses, the developed models served as a basis for applying PPoR and VOI to determine the value of conducting the proposed trials. In this work, case studies aimed to serve as a platform for obtaining insights into the use of PPoR and VOI, rather than to inform actual treatment recommendations or research funding decisions.

Case study 1. Trial in non-small cell lung cancer

The standard of care for advanced NSCLC patients aims to prolong life or palliate symptoms and comprises a combination of a platinum analogue with third-generation chemotherapy, in which

gemcitabine is often used as the parent drug [21-23]. Two platinum agents have been traditionally used, cisplatin and carboplatin; however, the choice between them has been contentious, owing to uncertainty around their effectiveness, toxicity and cost effectiveness [24]. In view of this, a trial was proposed in 2004 to compare gemcitabine plus cisplatin (Gem+Cisp) and gemcitabine plus carboplatin (Gem+Carb) in patients with advanced (stage IIIB/IV) NSCLC. The proposal was submitted to Cancer Research UK and requested a grant of £336,700.

Case study 2. Trial in castrate-refractory prostate cancer

Advanced CRPC typically spreads to bones, which in turn results in severe skeletal pain. A number of agents have been developed for palliating the morbidity from bone metastases, including chemotherapy [25], radio-isotopes [26] and bisphosphonates [27, 28]. In the UK, these treatments are usually used singly in sequence. Two agents which have been proven beneficial in skeletal-related problems are zoledronic acid (ZA) and strontium-89 (Sr89)[29]. An early-stage trial, the Taxane Radioisotope Zoledronic Acid (TRAPEZE) phase II trial investigating these treatments in combination with standard chemotherapy had been successful in securing funding, and continuation of this study to a phase III RCT involving a larger sample was proposed in 2006. The proposal was submitted for funding to the NIHR Health Technology Assessment programme and requested a grant of £2.54 million.

Decision modelling and cost-effectiveness analysis

A decision model was developed for each case study. In the case of NSCLC, the model comprised three states: progression-free (PG-F), progression (PG) and death (D). Patients in the PG-F state

receive either Gem+Cisp or Gem+Carb and stay in this state until death or disease progression. Upon progression, patients move to PG and, eventually, to the death state D.

The CRPC model assessed the cost-effectiveness of four chemotherapy options: i) docetaxel and prednisolone (DP), ii) DP with zoledronic acid (DP+ZA), iii) DP with strontium-89 (DP+Sr89) and DP with zoledronic acid and strontium-89 (DP+ZA+Sr89). The model consisted of four health states: 'progression-free, on treatment' (PGF-OT), 'progression-free, not on treatment' (PGF), 'progression' (PG), and 'death' (D). CRPC patients with stable disease enter the model in the PGF-OT state, where they receive six cycles of chemotherapy, with each cycle lasting three weeks. Patients stay in this state for six cycles, unless they die or discontinue treatment. At the end of the treatment course, patients who have completed all six cycles move to the PGF state. Upon progression, patients move to the state PG and, eventually, to state D. Details on the structure of each model are given in Appendix A (web only).

Analyses were carried out from the perspective of the National Health Service in the UK. Inputs for the models were obtained from the literature available at the time each of the decisions was considered. In the CRPC model, key information on progression rates was available from phase II of the TRAPEZE trial. To account for uncertainty, key model parameters were represented as probability distributions [8] (Appendix A) (web only). As parameters were obtained from various sources, the correlation structure between them is usually not known, so the analysis effectively assumes that parameters are independent. Since this may not be the case, results need to be interpreted with caution. Monte Carlo methods were used to obtain 5000 simulated estimates of incremental costs and QALYs [30], which were subsequently converted into net monetary benefits (NMB) [31]. The latter measure translates health gains into monetary terms using as an exchange

rate a hypothetical value of the decision maker's (or society's) willingness to pay for a unit of benefit. A conventional willingness to pay value of £30,000 per QALY was used throughout; other values are equally applicable.

Value of information

'Value of information' analysis is part of statistical decision theory—a collection of analytic techniques aimed to assist decision making under conditions of uncertainty [32, 33]. The framework builds on the premise that choices between different options made under uncertainty about their true payoffs may turn out to be erroneous. Thus, uncertainty imposes an expected loss of benefits, which can be minimised if more information on the true payoffs becomes available. Measures of VOI seek to quantify the expected opportunity loss from decision making under uncertainty, with a view to inferring the value of obtaining additional information through research. Given this, VOI has been often advocated as a formal analytic framework to assist with topic prioritisation for clinical evaluative research [34, 35], as well as to guide funding decisions and determine efficient research design [19, 36, 37]. A first metric often calculated in VOI analysis is the expected value of perfect information (EVPI) [15, 38]. The EVPI for an individual patient is the difference between the expected benefits of making a decision with perfect and current information, and can be calculated from the simulated results of a probabilistic model as:

$$EVPI = E_\theta \, max_j \, NMB(j,\theta) - max_j \; E_\theta NMB(j,\theta)$$

where j represents the alternative options of interest, and θ represents all the uncertain parameters affecting the decisions [20]. Under current information, without knowing the true values of the uncertain parameters θ, the optimal decision is made by averaging over the NMBs

associated with all possible values of θ and selecting the intervention with the greatest expected (average) net benefits ($max_j E_\theta NMB(j,\theta)$). If perfect information was available, the decision maker would know which value θ would take, and would choose the intervention with the maximum NMBs for that particular value of θ. As the true value of θ is not known in advance, the expected net benefits from a decision under perfect information requires first obtaining the maximum NMBs for every possible value of θ and taking the mean across all the obtained maximum NMBs ($E_\theta max_j NMB(j,\theta)$). EVPI can be thought of as the maximum returns to conducting research around a decision problem and may be used as a 'first hurdle' in recommending further research: if the cost of a further study exceeds the maximum benefits expected from this study (i.e., the EVPI), conducting further research should be ruled out [4].

A more informative measure for research prioritisation is the expected value of sample information (EVSI). EVSI shows the expected benefit of making a recommendation in light of improved information drawn from research such as a clinical trial of a given sample size. EVSI represents the difference between the benefit expected from a decision with sample information and the benefit expected from the same decision made under current information. Owing to the complexity of EVSI calculations, the method is typically restricted to assessing the value of a clinical trial in informing one or a group of similar parameters [8]. Here, parameters of interest were the probabilities of disease progression and death for each case study. Assuming that a trial of sample size n is considered to provide evidence on the parameters of interest φ of all uncertain parameters θ, per-patient EVSI can be calculated as:

$$EVSI_n = E_D max_j \, E_{\varphi|D} \, NMB(j,\varphi) - \, max_j \, E_\theta \, NMB(j,\theta)$$

This formula is analogous to the formula for EVPI, but the expected net benefit after the proposed trial is dependent on the trial result, which is represented by a summary statistic *D*.

The process of calculating the expected benefit of a decision made under sample information requires simulating the possible results of a trial, taking into account any prior (i.e., existing) information, and combining this prior information and possible results into posterior information using Bayesian methods. The posterior information is, in turn, translated into a distribution of the expected NMB through the decision models. Subtracting the cost of research from the EVSI gives the Expected Net Benefit of Sampling (ENBS), a measure of the net value of the trial [20, 39]. The ENBS is seen as the net payoff to a proposed study and it represents the 'sufficient' condition for conducting this study: if ENBS is positive, further experimental research will be beneficial [39]. Detailed explanations of EVPI and EVSI calculations can be found in Ades et al. [20] and Briggs et al. [8]. The steps involved in calculating EVSI and ENBS can be seen in Appendix B (web only).

The EVPI (and similarly EVSI) values for the whole population of eligible patients can be calculated as:

$$EVPI_{pop} = \sum_{t=d,d+1,\ldots,d+T-1} I_t \frac{EVPI_{indiv}}{(1+r)^t}$$

Here, d is the time lag between a funding decision and dissemination of results, measured in relevant time periods, I_t represents the population of eligible patients at time t, and r is the discount rate applied to account for positive time preference. In this study, the discount rate employed is 3.5% per year and the time horizon T is set at 5 years for the NSCLC case study and 2 years for the CRPC study based on expert opinion. Given a yearly incidence of 3830 and 3330

chemotherapy eligible NSCLC and CRPC patients [40, 41], the total undiscounted number of patients who stand to benefit from research was estimated at 19150 and 6660 for NSCLC and CRPC, respectively. Assuming a time lag of 7 years from trial start to result dissemination, discounting at 3.5% per year effectively reduces these numbers to approximately 13,800 and 5100, respectively.

Prospective payback of research

PPoR is based on the concept that evidence generated through clinical evaluative research is valuable because it triggers changes in clinical practice, that is, the use of cost-effective treatments expands, and non-cost-effective treatments are contained or discontinued [3, 5]. Benefits accruing due to such changes in clinical practice are seen as a proxy for the value of the proposed research and can be calculated as the difference between two 'states of the world': a) a 'factual' state in which research takes place and triggers changes in clinical practice, and b) a 'counterfactual' state, in which research is not conducted and clinical practice remains largely as it is [2, 3, 42]. A number of models following the principles of the PPoR framework have been put forward over the last 30 years [2, 3, 11, 42, 43]; this study follows the methods in the most recent of them, the Preliminary Assessment of Technologies for Health Services (PATHS) model [11].

To estimate the population costs and benefits expected to accrue in the 'factual' and 'counterfactual' states, information is needed on: i) the per-patient costs and effectiveness of the treatments provided to patients, and ii) the use of these treatments in clinical practice, in terms of the proportion of patients receiving each treatment. In a prospective framework, the per-patient costs and benefits associated with each treatment are unknown (although some prior evidence may exist) and are expected to be revealed by research. As results cannot be known in advance,

the approach specifies a series of scenarios. These scenarios, taken one at a time, reflect the true underlying effectiveness and cost effectiveness of the compared treatments, which are assumed to hold true irrespective of whether research does take place and reveals them. Each scenario is associated with a particular research outcome and is expected to have an impact on clinical practice.

Three broad outcomes are usually hypothesised and specified in PPoR studies [11, 17]: i) a 'favourable' outcome, under which research results for a treatment of interest are hypothesised to be such that, when these are translated into cost-effectiveness estimates, the treatment appears cost-effective; ii) an 'inconclusive' outcome, under which results show the treatment to be of inconclusive cost-effectiveness; and iii) an 'unfavourable' outcome under which the hypothesised research results are such that the treatment is not cost-effective. To match the 'favourable', 'inconclusive' and 'unfavourable' outcomes above, hypothetical research results are typically specified in terms of key estimates of the treatments' effectiveness. In this study, estimates of the effectiveness were the probability of disease progression at 12 month follow-up for NSCLC and the probability of transition from progression-free to progression states for CRPC.

If research was conducted, observing each of these hypothetical outcomes would be expected to induce a change in treatments' prescription shares. Possible prescription patterns following the specified outcomes were determined after discussion with experts in cancer services commissioning. In both case studies it was assumed that, in the absence of research, prescription shares will largely remain at current levels. Specified scenarios and hypothesised results and change in clinical practice for the NSCLC and CRPC case studies are given in Appendix C. Given the

possible outcomes and the hypothesised change in clinical practice, a measure of the additional benefit of research is estimated as:

$$NMB_i = \lambda \times (E_{r,i} - E_{nr,i}) - (C_{st} + C_{r,i} - C_{nr,i})$$

Here, i is an indicator for the possible outcome, r and nr index the 'with research' and 'without research' situations, C_{st} represents the cost of the proposed research study, and $C_{r,i}$ and $C_{nr,i}$ are the costs associated with outcome i in the 'with research' and 'without research' situations, respectively. Last, $E_{r,i}$ and $E_{nr,i}$ are the effects (e.g., QALYs) associated with research and without research respectively, under outcome i, and λ stands for a decision maker's willingness to pay for a unit of effect. The above formula gives the benefit expected to accrue from each possible outcome, but only one of these outcomes would come true. Although it is not known in advance which of the outcomes will transpire, summary measures of the proposed study's payoff can be obtained by creating combinations where each possible outcome is weighted by a predetermined likelihood of occurrence [11]. Three combinations have been typically formed in the literature [11, 17]: i) an 'optimistic' combination, where the probability of observing a positive, inconclusive and negative outcome is 0.5, 0.25 and 0.25, respectively; ii) a 'neutral' combination, where each outcome has a one-third probability of being observed, and iii) a 'pessimistic' combination, where the probability of observing a positive, inconclusive and negative outcome is 0.25, 0.25 and 0.5, respectively. Following the previous notation, the weighted incremental NMB for a combination is given by:

$$NMB_k = \lambda \times \sum_i p_i \times (E_{r,i} - E_{nr,i}) - \sum_i p_i \times (C_{st} + C_{r,i} - C_{nr,i})$$

where k is an index for combinations and p_i is the probability of observing study outcome i. Similarly to the VOI analysis above, patient NMB in PPoR is extrapolated to the eligible population over a specified time horizon (5 and 2 years for NSCLC and CRPC, respectively), starting after research results are expected to be disseminated (7 years).

Results of Case Study 1: Trial in NSCLC

Cost-effectiveness results for the NSCLC case study

In light of evidence existing up to the point of the trial funding decision, results of the NSCLC model suggested that Gem+Cisp is less costly and more effective than Gem+Carb, resulting in mean cost savings of approximately £740 and a mean gain of 0.015 QALYs per patient. At a willingness to pay value of £30,000 per QALY, the results translate into £11,660 and £10,472 NMB for Gem+Cisp and Gem+Carb, respectively. At the particular threshold, the probability of Gem+Cisp being more cost-effective than Gem+Carb is approximately 0.64.

VOI analysis results for the NSCLC case study

The EVPI for the decision between Gem+Carb and Gem+Cisp was calculated at £950 and £13.08 million for the individual and the population, respectively. The results suggest that, at £30,000 per QALY, conducting research to provide further evidence around the NSCLC treatment adoption decision would be potentially—although not necessarily—worthwhile if the research programme costs less than £13.08 million. On this basis, funding and carrying out the proposed research, which required a grant of £336,700, would be a potentially worthwhile investment.

For the sample of 450 patients per treatment arm specified in the trial proposal, the EVSI was calculated at £677 for the individual patient and £9.33 million for the likely population of eligible patients over 5 years. Comparing EVSI with the cost of the trial gives the expected net benefit of sampling (ENBS), an estimate of the net value of the trial [39]. Given the cost of £336,700 for the proposed trial, the expected net benefit of the trial is £9 million. A graph of EVPI and EVSI at different willingness to pay values is given in Figure 1.

PPoR analysis results for the NSCLC case study

PPoR results for each specified outcome are presented in Table 1. Under the 'favourable' outcome for Gem+Carb, carrying out research is estimated to result in higher costs and more QALYs compared to a situation without research. Given that each additional QALY in this case would require an investment of less than £30,000, conducting research would result in a positive NMB of about £2.22 million. Under the 'inconclusive' outcome, conducting research is associated with no additional QALYs (as no change in uptake is expected to take place) for an extra cost due to conducting the trial. In this case, there will be a cost of about £336,700 for no additional benefits and negative NMB of -£336,700. Under the 'unfavourable' outcome for Gem+Carb, conducting research is associated with an increase in QALYs and cost-savings, due to limiting the use of the more costly and less effective Gem+Carb in the population. In this situation, carrying out research appears particularly appealing, as it is predicted to result in a NMB of £3.82 million.

Possible outcomes were assigned weights representing the likelihood of observing each outcome. Three different probability distributions of outcomes were compared (Table 2). In line with the PATHS methodology, such combinations aim to reflect the likelihood of observing the determined outcome, rather than the probability of obtaining definitive results which would resolve this

decision problem. Assuming a willingness to pay value of £30,000 per additional QALY, carrying out research would be a worthwhile investment, estimated to result in positive NMBs of £1.98 million, £1.88 million and £2.38 million under the 'optimistic', 'neutral' and 'pessimistic' combinations, respectively.

Results of Case Study 2: Trial in CRPC

Cost-effectiveness results for the CRPC case study

In relation to CRPC treatments, the cost-effectiveness analysis showed that two options (DP+ZA and DP+ZA+Sr89) were dominated. Of the remaining two, DP+Sr89 was associated with a greater cost, more QALYs and an ICER of about £8100 per additional QALY as compared to DP (the other non-dominated treatment). Probabilistic results showed DP+Sr89 to have the highest probability of being cost-effective, just over 0.53.

VOI analysis results for the CRPC case study

The per-patient EVPI for the decision related to CRPC was estimated at £1680 and the equivalent value for the population of eligible patients over a two-year time horizon was £8.55 million. On the basis of this estimate, and given a cost of £2.54 million for the proposed phase III trial, conducting the trial to provide evidence around the CRPC treatment adoption decision would be potentially worthwhile. Given a willingness to pay of £30,000 per QALY, the EVSI for 300 patients per arm was estimated at £605 and £3.09 million for the individual and the population, respectively. At a cost of £2.54 million, this trial would result in ENBS of about £550,000, suggesting that the trial is a worthwhile investment. The obtained EVPI and EVSI curves at different values of willingness to pay for a QALY can be seen in Figure 2.

PPoR analysis results for the CRPC case study

PPoR results for each of the specified research outcomes are given in Table 3. Under an outcome favourable for DP+Sr89, there would be costs due to conducting the trial and moving from DP towards the more costly DP+Sr89, but also gains in QALYs, resulting in overall NMB gains of £5.13 million. Under the 'inconclusive' scenario, there would be a loss of £2.54 million due to the expenditure for the 'inconclusive' trial. Under any outcome unfavourable for DP+Sr89, there would be cost savings from restricting the use of more expensive non-standard treatments, and additional QALYs, resulting in positive NMB ranging from £307,200 to £5.07 million.

Each outcome was assigned a weight representing its probability, to form combinations. In each of a series of alternative combinations, a weight of 0.5 was given to observing 'favourable' results for a specific treatment, with the likelihood weight for the rest of the results being 0.125. The analysis showed that funding and conducting the proposed phase III trial would be beneficial, and it is expected to lead to a NMB between £1.54 and £3.34 million (Table 4).

Comparison of PPoR and VOI

The applications revealed a number of similarities between VOI and PPoR. Essentially, both frameworks build on the idea that the value of research can be inferred from the additional benefits brought about by the availability of improved information. To estimate these benefits, both PPoR and VOI specify possible results of research and assess the returns from research using measures and techniques commonly seen in economic evaluation of health care technologies. In both frameworks, the value of research relates to quantifiable benefits in the population, while

none of the approaches aims to capture any wider economic and educational benefits from engaging in research.

Despite these similarities, there are notable differences in the rationales underpinning PPoR and VOI. To a large extent, VOI results depend on the degree of the existing uncertainty around the true payoffs of competing options (e.g., treatments), and the associated expected loss of benefits due to this uncertainty. On this basis, further research appears more desirable when uncertainty around the optimal treatment is high, the expected loss of benefits due to uncertainty is substantial, and the cost of further research is relatively low. On the other hand, PPoR results are driven by the hypothesised magnitude of change in clinical practice following research, rather than by the degree of uncertainty around the optimal treatment. Given this, PPoR estimates are expected to be favourable for research proposals on treatments which are used commonly in clinical practice, but for which further research may trigger a substantial change in their use. The fact that PPoR places prime importance on change in clinical practice has been criticised on the grounds that the approach sees research as a way of changing clinical practice, rather than as a means of reducing uncertainty [7, 34].

The results of the case studies showed that estimates produced by PPoR and EVSI agreed in direction, suggesting that the proposed trials in NSCLC and CRPC would be cost-effective investments. However, results differed in magnitude, owing to differences in the methods and calculations employed by each approach. In EVSI, possible research outcomes are obtained through formal Bayesian methods which combine existing information with simulated data. On the other hand, possible outcomes in PPoR are typically specified on the basis of expert opinion [11] or researchers' assumptions [17], bearing in mind that these should represent plausible

results, cover different eventualities and have an impact on clinical practice. While specification of possible outcomes in PPoR is relatively straightforward, the use of essentially arbitrary values adds a layer of subjectivity in the analysis. In general, a different conclusion would be drawn if the most likely outcome to occur were an 'inconclusive outcome', as this would result in costs due to undertaking the trial, but no change in clinical practice and thus no additional benefit.

Further, the approaches differ in the way they account for implementation of research results in clinical practice. VOI results are typically calculated on the premise that any decision informed by further research would be implemented perfectly, so that all, rather than a proportion, of the eligible patients would benefit from the availability of further evidence. As expected, the assumption of perfect implementation makes research appear more valuable, and is reflected in the higher EVSI results. Recent work has suggested ways of relaxing this assumption in the context of EVSI [44], but no applications of these calculations on EVSI values derived using non-parametric methods are available to date. In PPoR, assumptions around the implementation of research results are explicitly reflected in the hypothesised estimates of change in clinical practice and have a sizeable impact on the final results. In general, larger increases in the prescription shares of cost-effective treatments result in greater benefit. Indicatively, sensitivity analysis showed that the NSCLC and CRPC trials would be associated with negative NMB—thus, they would not be worth undertaking—if the use of treatments shown to be cost-effective increased by less than 3.8 percentage points in NSCLC (i.e., from 50% to 53.8%, rather than to 75% assumed in the base case), and less than 18.5 percentage points in CRPC (i.e., from 5% to 23.5% for each of the treatments currently not in wide use, rather than to more than 40% assumed in base case). The extent to which such changes in prescription shares are likely to be achieved will depend on different factors, including the effectiveness of result dissemination strategies and the existence of appropriate

infrastructure to support the change [5]. In the particular case studies considering the use of pharmaceuticals, it is thought that a change in implementation is unlikely to be hindered by significant barriers.

While no estimates of the likely change in clinical practice are typically used in VOI, results are greatly affected by assumptions used in the decision analytic model, especially when these assumptions relate to the degree of uncertainty around key parameters. Typically, greater uncertainty in parameters is associated with greater values of EVSI. In addition, it must be noted that the degree to which VOI results are unbiased depends largely on the validity of the decision model through which results are produced. Flaws in the model—for example incorrect structure and inappropriate representation of the joint distribution of uncertain parameters—may lead to inaccurate cost-effectiveness results, and, consequently, biased estimates of EVSI. Finally, it is currently not evident how other pertinent considerations, for example the fact that treatments of interest may become available as less costly generic products in the future, can be accounted for within the VOI and PPoR frameworks.

Evidently, both PPoR and VOI are sensitive to assumptions about the employed time horizon over which the produced evidence is expected to be useful. Long time horizons inflate the number of patients expected to benefit from the availability of improved information, increase the expected benefits in the population predicted by VOI and PPoR, and make further research appear more desirable. On the other hand, shorter time horizons reduce the estimated benefits of conducting the studies: at current annual incidence rates, sensitivity analysis on PPoR results showed that the proposed trials would not result in additional benefits if trial results were useful for less than 9 months for NSCLC and less than 1 year for CRPC. In VOI, the trials would not be worth conducting,

if the time horizon was less than 2 months for NSCLC and less than 20 months for CRPC. Such short time horizons are not unusual in situations where pharmaceuticals may be expected to be superseded by newer treatments. It is worth noting that the use of assumptions in processes evaluating the costs and effects of different activities is, to a large extent, inevitable, be it health care programmes or projects of public infrastructure [45, 46]. This would be expected to hold true for assessments of the value of future research, especially because such research is yet to take place and estimating its benefits requires 'guesses' and predictions.

Methodological challenges also arise when applying PPoR to case studies involving multiple comparisons, such as the CRPC study. The correct approach for dealing with such applications is unclear, while, at the same time, this task requires stronger assumptions when specifying possible outcomes. For instance, under the 'inconclusive' scenario, all four treatments are assumed to be of similar cost-effectiveness, which is an unlikely situation. In comparisons between multiple treatments, different possible outcomes need to be specified in a way that covers all the possible eventualities. As a result, the number of PPoR results increases, which poses additional difficulties for decision makers in selecting the results which are more likely to transpire.

An important consideration for potential users of these methods is the time and expertise requirements for undertaking VOI and PPoR [4, 11]. This application showed that preliminary tasks—literature reviews to identify the existing information and decision modelling—were the most time consuming elements of the analyses, taking approximately 6 months for each model. Once the decision models were constructed and their results became available, PPoR was carried out within two weeks of a researcher's full time equivalent, while VOI took about six weeks, mostly due to time required for setting up the programming codes for EVSI calculations and

running computations. While there was no difference in the computation needed for undertaking PPoR for the two-choice NSCLC and four-choice PPoR decision problems, considerably more computation was needed for undertaking EVSI for CRPC than for NSCLC, due to the complexity of the CRPC model and the greater number of choices involved. Both VOI and PPoR were undertaken using a widely available spreadsheet application.

Previous work has looked into the time frames within which VOI (EVPI for all or a subset of uncertain parameters) and PPoR (PATHS model) analysis can be carried out. Claxton and colleagues [4] found that modelling and VOI would take a team of researchers approximately 10 to 12 weeks to carry out, while Townsend et al. [11] suggested that PATHS analysis can be undertaken within 1 to 4 weeks, depending on the complexity of the project. These estimates are in broad agreement with observations from the present study. Evidently, if a systematic review and a decision model are already available for use, the analysis time required would be considerably shorter. It must be noted that, in a situation where research results are expressed as final outcomes (e.g., QALYs) which can be readily combined with costs to inform decisions, PPoR and VOI may be conducted with minimal, or no, modelling [11, 47]. In addition, there has been ongoing research on identifying situations where complex EVSI calculations can be substituted by simpler methods, as well as advances in identifying 'shortcuts' and efficient computation methods for estimating EVPI and EVSI [20, 48-50].

Discussion

While PPoR and VOI have been often advocated for use in priority-setting [2, 3, 9] practical applications on the same case studies for the purpose of contrasting and comparing the approaches are scarce. Only one such application was found in the literature: Fleurence [17]

applied VOI and PPoR to case studies of proposed clinical trials in the areas of osteoporosis and pressure ulcers. Both VOI and PPoR showed that further research would lead to additional benefits and suggested that the proposed trials in these areas would be cost-effective. This study offers useful insights into the strengths and limitations of PPoR and VOI; however, its scope and conclusions are constrained by the fact that VOI analysis comprised only EVPI calculations. By undertaking EVSI analysis, one can obtain a more complete view of the value and potential of VOI, and a more accurate picture of the complexity, computational requirements and feasibility of undertaking such analyses.

Importantly, EVPI and PPoR calculations have different purposes and aim to answer different questions. EVPI gives the maximum expected benefits from further research and, as such, it can only be used as a criterion for ruling out research which would not be worthwhile. EVPI results can be valuable in commissioned funding streams, which aim to identify and prioritise topics on which to commission further research [4]. On the other hand, PPoR aims to calculate the expected benefits from specific trials and, thus, its aims resemble more closely those of EVSI. Given this, EVSI and PPoR are better placed to help with funding decisions around specific trials and can be useful in researcher-led programmes, where decisions are needed on whether proposals submitted by researchers on topics of their choice should be funded.

The present study sought to extend the existing literature by undertaking a practical application of PPoR (PATHS model) and VOI, with the latter including both EVPI and EVSI analyses. Strengths of this study include the use of a decision model developed to facilitate the PPoR and VOI applications. EVPI and EVSI were calculated according to well-established non-parametric methods [8, 20]. The PPoR analysis was based on the most contemporary and comprehensive version

available in the literature [11]; however, it must be noted that other PPoR versions [2, 5] may have produced different results. A number of assumptions were required in this analysis; these are inherent to the assessed frameworks and aim to compensate for the lack of data. For example, empirical evidence on the time horizon over which information is expected to be useful, the likelihood of obtaining specific research results and the future uptake of treatments in light of different research outcomes is typically unobserved, and it was, necessarily, obtained from expert opinion.

The practical application highlighted methodological limitations in both PPoR and VOI. With regards to PPoR, the framework would benefit from more explicit and systematic ways of determining possible research outcomes, given the fact that such outcomes impact on the final results. Additional research would also be needed to look into appropriate ways of obtaining estimates of the likely uptake of treatments in clinical practice and the likelihood of a proposed trial showing the specified results. For the former, this may involve formal methods of eliciting expert opinion from adequately large groups of researchers, commissioners and decision makers. For the latter, there may be scope for obtaining likelihood weights by combining expert opinion with existing evidence (e.g., existing results of other studies, phase II data), possibly by using Bayesian processes [51, 52]. In relation to VOI, there is a need for further developments in the method to ensure that results are appropriately adjusted for the loss of benefits due to imperfect implementation. Both methods would benefit from methodological work around appropriate ways of predicting the length of time over which information will be useful, and establishing the relationship between availability of information and change in clinical practice.

Interestingly, ways of addressing the limitations of each approach may be identified by looking at their counterparts. EVSI may benefit from accounting for imperfect implementation in a way similar to that in PPoR, while PPoR would benefit from specification of possible research results which combines prior and possible new evidence in an analytic way. Existing limitations do not appear to be more substantial—or less likely to be resolved by research—than methodological limitations and debates seen in economic evaluations of health care technologies. While the approaches are not a panacea, it is thought that they can provide useful input for research funding decisions and offer greater assurance that research resources are spent prudently.

Acknowledgements

An earlier version of this work was presented at the 40th Health Economics Study Group meeting in July 2012; we thank conference participants for their comments and contribution. We are also grateful to Professor R. Hamm and anonymous reviewers for their useful comments and suggestions, as well as to Professor T. Roberts for her advice in structuring and presenting this manuscript.

Funding

Financial support for this study was provided by a grant from the National Institute for Health Research in the UK, through a personal NIHR Doctoral Researcher Fellowship awarded to LA [NIHR DRF 2009-08]. LJB was supported by the Medical Research Council [grant number G0800808]. The funding agreement ensures the authors' independence in designing the study, interpreting the data, wording, and publishing the report. The views expressed in this publication are those of the

authors and not necessarily those of the National Institute for Health Research or the Medical Research Council.

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Table 1. PPoR results for each specified outcome in the NSCLC case study

	Favourable* outcome for Gem+Carb	Inconclusive outcome for Gem+Carb	Unfavourable outcome for Gem+Carb
With research			
Cost	£90,081,664	£86,511,060	£82,960,067
Trial cost	£336,721	£336,721	£336,721
QALYs	8617	8241	7985
Without research			
Cost	£86,868,565	£86,511,060	£85,477,767
QALYs	8425	8241	7931
Net implications			
Net cost	£3,549,820	£336,721	-£2,180,979
Net QALYs	192	0	55
$NMB_{with\ research}$	£168,103,680	£160,370,345	£156,267,944
$NMB_{without\ research}$	£165,881,317	£160,707,066	£152,446,181
Incremental NMB (£30,000 per QALY)	£2,222,363	-£336,721	£3,821,763

* Treatment option associated with the greatest NMB (at £30,000 willingness to pay per QALY) compared to its comparator. NMB: Net Monetary Benefit; QALY: quality-adjusted life year; Gem+Carb: gemcitabine plus carboplatin.

Table 2. Weighted PPoR results for NSCLC case study

Combination	Assigned likelihood weights	Weighted NMB (with research vs. without research)
'Optimistic' combination for Gem+Carb (i.e. greater weight on 'favourable' results for Gem+Carb)	Gem+Carb cost-effective: **0.5** 'Inconclusive' results: **0.25** Gem+Cisp cost-effective: **0.25**	£1,982,442
Neutral combination (i.e. equal weight for each result)	Gem+Carb cost-effective: **0.33** 'Inconclusive' results: **0.33** Gem+Cisp cost-effective: **0.33**	£1,883,444
'Pessimistic' combination for Gem+Carb (i.e. greater weight on 'unfavourable' results for Gem+Carb)	Gem+Carb cost-effective: **0.25** 'Inconclusive' results: **0.25** Gem+Cisp cost-effective: **0.5**	£2,382,292
NMB: Net Monetary Benefit; Gem+Carb: gemcitabine plus carboplatin; Gem+Cisp: gemcitabine plus cisplatin		

Table 3. PPoR results for each specified outcome in the NSCLC case study.

Outcome	DP+Sr89 cost-effective*	Inconclusive	DP cost-effective*	DP+ZA cost-effective*	DP+ZA+Sr89 cost-effective*
With trial					
Cost	£48,994,528	£46,727,957	£46,213,291	£48,822,245	£51,156,266
Trial cost	£2,537,116	£2,537,116	£2,537,116	£2,537,116	£2,537,116
QALYs	4511	4487	4655	4525	4549
Without trial					
Cost	£46,825,405	£46,727,957	£48,838,426	£46,818,994	£46,813,533
QALYs	4183	4487	4648	4204	4206
Net implications					
Net costs	£4,706,240	£2,537,116	-£88,019	£4,540,368	£6,879,849
Net QALYs	328	0	7	320	342
Cost per QALY	**£14,351 per additional QALY**	**Costs for no additional QALYs**	**Cost savings for additional QALYs**	**£14,175 per additional QALY**	**£20,101 per additional QALY**
$NMB_{with\ research}$	£83,798,160	£85,358,679	£90,893,840	£84,383,144	£82,763,340
$NMB_{without\ research}$	£78,666,300	£87,895,795	£90,586,669	£79,313,999	£79,375,245
Incremental NMB (£30,000 per QALY)	**£5,131,860**	**-£2,537,116**	**£307,171**	**£5,069,145**	**£3,388,095**

* Treatment option associated with the greatest NMB (at £30,000 willingness to pay per QALY) compared to the rest of the treatment. NMB: Net Monetary Benefit; QALY: quality-adjusted life year; DP: docetaxel and prednisolone; DP+ZA: docetaxel and prednisolone plus zoledronic acid; DP+Sr89: docetaxel and prednisolone plus strontium-89; DP+ZA+Sr89: docetaxel and prednisolone plus zoledronic acid plus strontium-89

Table 4. Weighted PPoR results for the CRPC case study

Combination	Assigned likelihood weights	Weighted NMB (with research vs. without research)
Alternative Combination A	DP+Sr89 cost-effective : **0.5** 'Inconclusive' results: **0.125** DP cost-effective: **0.125** DP+ZA cost-effective: **0.125** DP+ZA+Sr89 cost-effective: **0.125**	£3,344,342
Alternative Combination B (i.e. greater weight on 'favourable' results for DP)	DP+Sr89 cost-effective : **0.125** 'Inconclusive' results: **0.125** DP cost-effective: **0.5** DP+ZA cost-effective: **0.125** DP+ZA+Sr89 cost-effective: **0.125**	£1,535,084
Alternative Combination C (i.e. greater weight on 'favourable' results for DP+ZA)	DP+Sr89 cost-effective : **0.125** 'Inconclusive' results: **0.125** DP cost-effective: **0.125** DP+ZA cost-effective: **0.5** DP+ZA+Sr89 cost-effective: **0.125**	£3,320,824
Alternative Combination D (i.e. greater weight on 'favourable' results for DP+ZA+Sr89)	DP+Sr89 cost-effective : **0.125** 'Inconclusive' results: **0.125** DP cost-effective: **0.125** DP+ZA cost-effective: **0.125** DP+ZA+Sr89 cost-effective: **0.5**	£2,690,430
Neutral Combination	DP+Sr89 cost-effective : **0.2** 'Inconclusive' results: **0.2** DP cost-effective: **0.2** DP+ZA cost-effective: **0.2** DP+ZA+Sr89 cost-effective: **0.2**	£2,271,831

NMB: Net Monetary Benefit; DP: docetaxel and prednisolone; DP+ZA: docetaxel and prednisolone plus zoledronic acid; DP+Sr89: docetaxel and prednisolone plus strontium-89; DP+ZA+Sr89: docetaxel and prednisolone plus zoledronic acid plus strontium-89.

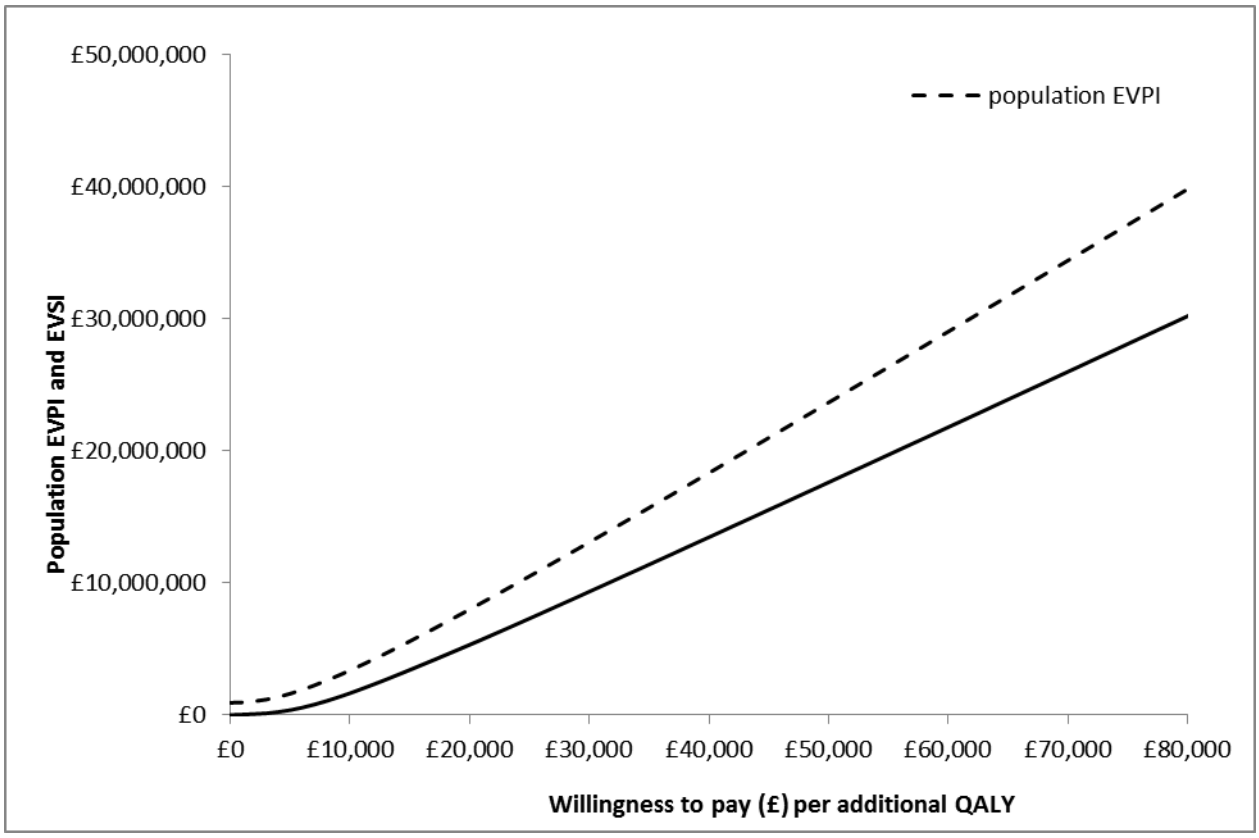

Figure 1: EVPI and EVSI for NSCLC

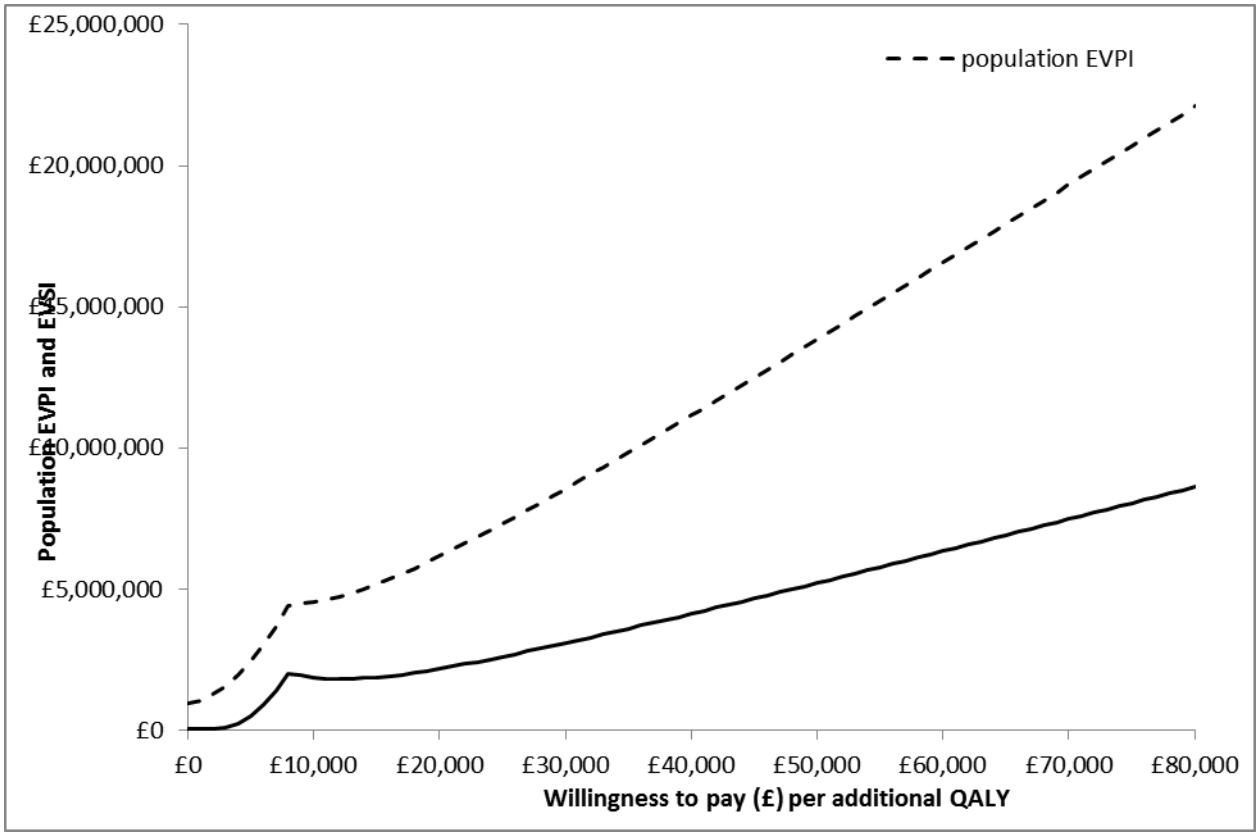

Figure 2. EVPI and EVSI for CRPC

Appendix A. Decision analytic models (web only)

Non-small cell lung cancer (NSCLC) model

The model aimed to compare the cost-effectiveness of Gem+Cisp and Gem+Carb in patients with advanced non-small cell lung cancer (NSCLC). The model comprises three states: (i) progression-free (PG-F), (ii) progression (PG) and (iii) death (D). Patients enter the model in the PG-F state where they are scheduled to receive a 4-cycle course of treatment, either Gem+Cisp or Gem+Carb, with each cycle lasting 21 days. Patients stay in this health state until experiencing disease progression. Upon progression, patients move to PG and, eventually, to the death state D. A graphical representation of the NSCLC model is given in Figure 1 below.

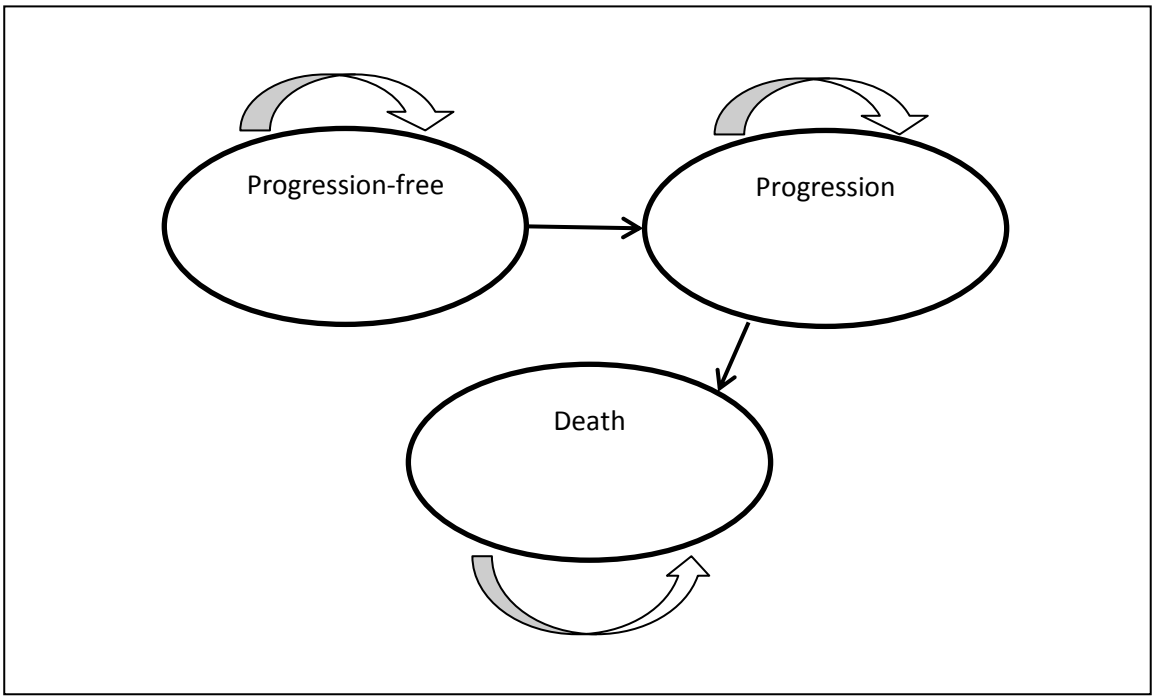

Figure 1 in Appendix A. NSCLC model

Inputs for the decision model were obtained from the available literature. Transition probabilities from PG-F to PG and from PG to D were derived by fitting Weibull distributions to time-to-progression and survival data from the only published randomised phase III trial comparing Gem+Cisp and Gem+Carb available when the trial funding decision was considered {Zatloukal, 2003}. Total per-patient cost was calculated taking into account the cost of drug acquisition and

administration, costs of adverse events, use of other medical resources (additional outpatient visits and examinations) and terminal care costs. No evidence on generic, preference-based quality of life (utility) was identified in the pre-2004 literature, and thus such values were based on expert opinion. All uncertain parameters in the model were assigned probability distributions. Details of the distributions attached to different parameters are given in Table 1 below.

Table 1 in Appendix A. Distributions assigned to input parameters in the NSCLC model

Treatment	Target parameter	Varied parameter	Distribution/ parameter values	Source
Probability of a patient staying in the state 'Progression-free' state at each cycle				
Gem+Cisp	Fitted Weibull progression model, by varying alpha and beta parameters, through varying intercept and regression coefficient used to obtain alpha and beta		Intercept Normal (-2.99, 0.108) Regression coefficient Normal(1.404, 0.047)	Literature [53]
Gem+Carb			Intercept Normal (-2.475,0.110) Regression coefficient Normal(1.287, 0.048)	Literature [53]
Probability of a patient moving to state 'Death' at each cycle				
Gem+Cisp	Fitted Weibull survival model, by varying alpha and beta parameters, through varying intercept and regression coefficient used to obtain alpha and beta		Intercept Normal(-2.808, 0.148) Regression coefficient Normal(1.104, 0.055)	Literature [53]
Gem+Carb			Intercept Normal (-3.350, 0.209) Regression coefficient Normal(1.302, 0.077)	Literature [53]
Drug acquisition and administration costs				
Gem+Cisp	Cost of drug acquisition and administration		Gamma(100, 9.45)	Cost analysis. Mean value: £946 SE is assumed to be 10% of the mean value
Gem+Carb			Gamma(100, 11.33)	Cost analysis. Mean value:£1133 SE is assumed to be 10% of the mean value
Adverse events-related cost				

Gem+Cisp	Cost of adverse events	Expected cost of adverse events, by varying proportions (probabilities) of patients experiencing different adverse events	Anaemia: Beta (10.58, 73.42) Thrombocytopenia: Beta (13.78, 70.22) Neutropenia: Beta (7.98, 76.02) Granulocytopenia: Beta (19.74, 64.26)	Literature [53]
Gem+Carb	Cost of adverse events	Expected cost of adverse events, by varying proportions (probabilities) of patients experiencing different adverse events	Anaemia: Beta(15.84, 72.16) Thrombocytopenia: Beta(28.69, 59.31) Neutropenia: Beta(12.85, 75.15) Granulocytopenia: Beta(26.66, 61.34)	Literature [53]
Cost of other medical resources (same across treatments)				
Gem+Cisp **Gem+Carb**	Cost of other medical resources	Cost of other medical resources	Gamma (16, 45.5)	Literature [54] Mean value: £728 SE is assumed to be 25% of the mean value
Cost of terminal care (same across treatments)				
Gem+Cisp **Gem+Carb**	Terminal care cost	Terminal care cost	Gamma (16, 91.25)	Literature [55] Mean value: £1460 SE is assumed to be 25% of the mean value
Utility values for 'Progression-free' and 'Progression' states (same across treatments)				
Gem+Cisp **Gem+Carb**	Utility value of 'Progression- free' state	Utility value of 'Progression-free' state	Normal (0.65, 0.08)	Expert opinion
	Utility value of 'Progression' state	Difference between utilities of 'Progression-free' and 'Progression' states	Normal (0.2, 0.04)	

Castrate-refractory prostate cancer (CRPC) model

A model was developed to assess and compare the cost-effectiveness of four treatment options: i) docetaxel and prednisolone only (DP); ii) DP plus zoledronic acid (DP+ZA); iii) DP plus strontium-89, and iv) DP plus zoledronic acid plus strontium-89 (DP+ZA+Sr89). The model consists of four health states: (i) 'Progression-free, on treatment' (PGF-OT) where advanced CRPC patients with stable disease receive one of the compared chemotherapy treatments; (ii) 'Progression-free, not on treatment' (PGF), reflecting the state in which patients have not shown signs of progression, but they have stopped receiving treatment, either because they completed the course or because they discontinued before the end of the scheduled treatment period; (iii) 'Progression' (PG), where patients have developed progressive disease, and (iv) 'Death' (D).

A cohort of CRPC patients in stable disease enter the model in the PGF-OT state, where they are scheduled to receive six cycles of chemotherapy, with each cycle lasting three weeks. Patients stay in this state for six cycles, unless they discontinue treatment due to intolerable toxicity (in which case they move to the state PGF), discontinue due to disease progression (in which case they move to the state PG), or die. At the end of the treatment course, patients who have completed all six cycles move to the PGF state. Upon progression, patients move to the state PG and, eventually, to the absorbing state D. A graphical representation of the NSCLC model is given in Figure 2 below.

Transition probabilities and preference-based quality of life (EQ-5D) scores were obtained through patient level data from the phase II TRAPEZE trial. Costs were calculated by taking into account the cost of drug acquisition and administration, the cost of serious adverse events, cost associated with second-line treatment, and the cost of terminal care. The distributions attached to key parameters in the CRPC can be seen in Table 2 below.

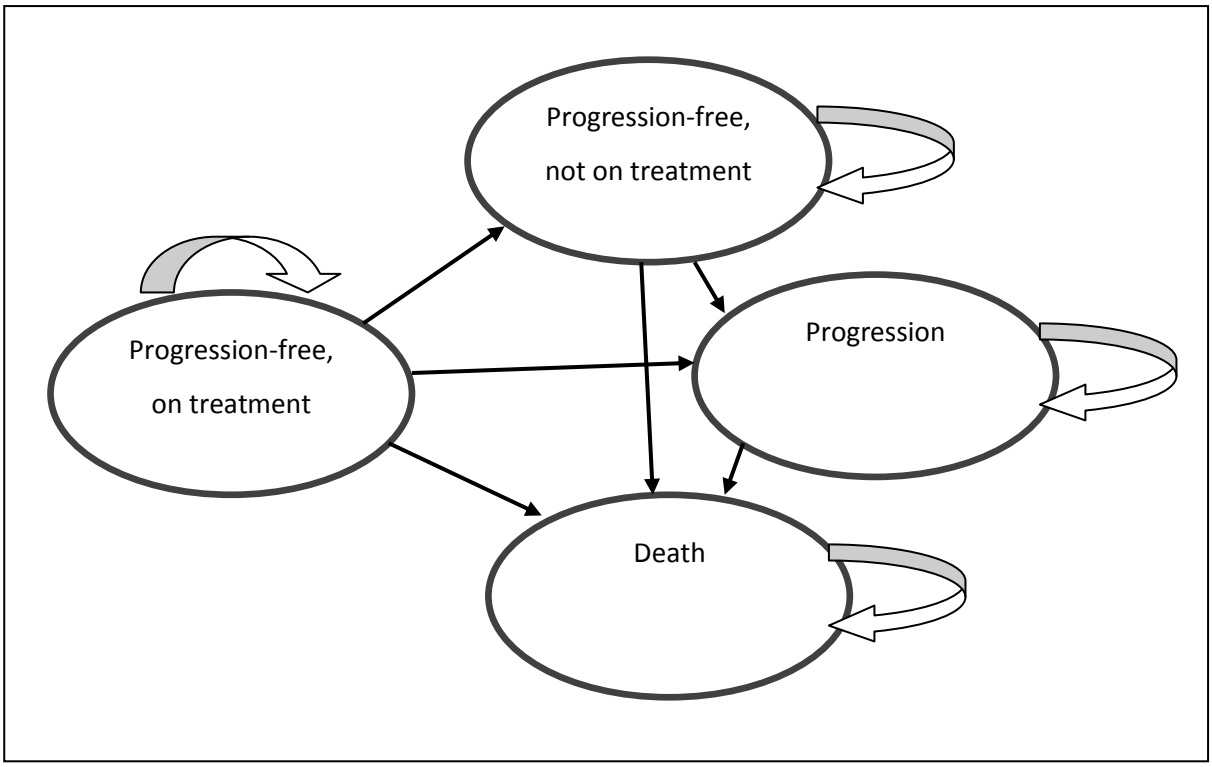

Figure 2 in Appendix A. CRPC model

Table 2 in Appendix A. Distributions assigned to input parameters in the CRPC model

Treatment	Parameter	Distribution	Source/comment
Transition probabilities from state 'Progression-free, on treatment' (PGF-OT) to states 'Progression-free, not on treatment' (PGF), 'Progression' (PG) and 'Death' (D)			
DP	Transition probabilities from state PGF-OT to states PGF, PG and D	Dirichlet(204, 5 ,5, 5)	Calculated using data from the TRAPEZE phase II trial
DP+ZA	Transition probabilities from state PGF-OT to states PGF, PG and D	Dirichlet(203, 4, 4, 6)	
DP+Sr89	Transition probabilities from state PGF-OT to states PGF, PG and D	Dirichlet(204, 5 ,3, 2)	
DP+ZA+Sr89	Transition probabilities from state PGF-OT to states PGF, PG and D	Dirichlet(218, 5 ,2, 3)	
Transition probabilities from state 'Progression-free, not on treatment' (PGF) to 'Progression' (PG) and 'Death' (D)			
DP	Transition probabilities from state PGF to states PG and D	Dirichlet(371, 24, 13)	Calculated using data from the TRAPEZE phase II trial
DP+ZA	Transition probabilities from state PGF to states PG and D	Dirichlet(248, 26, 11)	
DP+Sr89	Transition probabilities from state PGF to states PG and D	Dirichlet(461, 25, 15)	
DP+ZA+Sr89	Transition probabilities from state PGF to states PG and D	Dirichlet(479, 21, 18)	
Transition probabilities from state 'Progression' (PG) to 'Death' (D)			
DP	Transition probabilities from state PG to state D	Beta(29, 567)	Calculated using data from the TRAPEZE phase II trial
DP+ZA	Transition probabilities from state PG to state D	Beta(31, 590)	
DP+Sr89	Transition probabilities from state PG to state D	Beta(26, 454)	
DP+ZA+Sr89	Transition probabilities from state PG to state D	Beta(21, 294)	
Cost of drug acquisition and administration			
DP	Cost of drug acquisition and administration	Gamma(100,11.60)	Cost analysis. Mean value: £1160 SE is assumed to be 10% of the mean value.
DP+ZA	Cost of drug acquisition and administration	Gamma(100, 13.29)	Cost analysis. Mean value: £1329 SE is assumed to be 10% of the mean value.
DP+Sr89	Cost of drug acquisition and administration	Gamma(100, 11.60)	Cost analysis. Mean value: £1160 SE is assumed to be 10% of the mean value. Cost of strontium-89 was varied separately (below)

Treatment	Parameter	Distribution	Source/comment
DP+ZA+Sr89	Cost of drug acquisition and administration	Gamma(100, 13.29)	Cost analysis. Mean value: £1329 SE is assumed to be 10% of the mean value. Cost of strontium-89 was varied separately (below)
Cost of strontium-89 acquisition and administration	Cost of strontium-89 acquisition and administration	Gamma(100, 15.76)	Expert opinion (Nuclear Medicine Department, Queen Elizabeth Hospital Birmingham) Mean value: £1576 (expert opinion) SE is assumed to be 10% of the mean value.
Cost of adverse events			
DP	Cost of adverse events*	Diarrhoea~beta(1, 49) Febrile neutropenia~ beta(3, 47) Haemoglobin~beta(1, 49) Infection~beta(5, 45) Neutrophils/granulocytes~ beta(4, 46) Pain~beta(5, 45) Urinary retention~beta(0, 50) Other~beta(20, 30)	Based on proportions of patients experiencing adverse events obtained from TRAPEZE phase II trial
DP+ZA	Cost of adverse events*	Diarrhoea~beta(1, 48) Febrile neutropenia~beta(3, 46) Haemoglobin~beta(1, 48) Infection~beta(4, 45) Neutrophils/granulocytes~ beta(0, 49) Pain~beta(3, 46) Urinary retention~beta(4, 45) Other~beta(13, 36)	Based on proportions of patients experiencing adverse events obtained from TRAPEZE phase II trial

Treatment	Parameter	Distribution	Source/comment
DP+Sr89	Cost of adverse events*	Diarrhoea~beta(1, 50) Febrile neutropenia~beta(6, 45) Haemoglobin~beta(0, 51) Infection~beta(2, 49) Neutrophils/granulocytes~ beta (2, 49) Pain~beta(7, 44) Urinary retention~beta(0, 51) Other~beta(9, 42)	Based on proportions of patients experiencing adverse events obtained from TRAPEZE phase II trial
DP+ZA+Sr89	Cost of adverse events*	Diarrhoea~beta(2, 48) Febrile neutropenia~ beta(2, 48) Haemoglobin~beta (2, 48) Infection~beta(2, 48) Neutrophils/granulocytes~ beta(0, 50) Pain~beta(3, 47) Urinary retention~beta(1, 49) Other~beta(24, 26)	Based on proportions of patients experiencing adverse events obtained from TRAPEZE phase II trial
Cost of second-line treatment			
DP	Expected cost of second-line treatment†	Chemotherapy~beta(20, 30) Radiotherapy ~beta(2, 48) Radioisotopes~beta(6, 50)	Based on proportions of patients who received second-line treatment in TRAPEZE phase II trial
DP+ZA	Expected cost of second-line treatment†	Chemotherapy~beta(19, 30) Radiotherapy ~beta(6, 43) Radioisotopes~beta(3, 46)	Based on proportions of patients who received second-line treatment in TRAPEZE phase II trial
DP+Sr89	Expected cost of second-line treatment†	Chemotherapy ~beta(20, 31) Radiotherapy ~beta(5, 46) Radioisotopes~beta(2, 49)	Based on proportions of patients who received second-line treatment in TRAPEZE phase II trial

Treatment	Parameter	Distribution	Source/comment
DP+ZA+Sr89	Expected cost of second-line treatment†	Chemotherapy~beta(17, 33) Radiotherapy ~beta(3, 47) Radioisotopes~beta(0, 50)	Based on proportions of patients who received second-line treatment in TRAPEZE phase II trial
Cost of terminal care			
DP **DP+ZA** **DP+Sr89** **DP+ZA+Sr89**	Terminal care cost	Gamma(16, 101.39)	Literature [55] Mean value:£ 1532 SE is assumed to be 25% of the mean value.
Preference-based quality of life (utility) scores			
DP	Utility score for state 'Progression-free, on treatment' (PGF-OT)	Beta(93.14, 55.99)	TRAPEZE phase II data
	Utility score for state 'Progression-free, not on treatment'(PGF) ‡	Normal(0.019, 0.062)	TRAPEZE phase II data
	Utility score for state 'Progression'(PG) §	Normal(0.125, 0.087)	TRAPEZE phase II data
DP+ZA	Utility score for state 'Progression-free, on treatment' (PGF-OT)	Beta(156.75, 53.4)	TRAPEZE phase II data
	Utility score for state 'Progression-free, not on treatment'(PGF) ‡	Normal(0.006, 0.044)	TRAPEZE phase II data
	Utility score for state 'Progression'(PG) §	Normal(0.143, 0.072)	TRAPEZE phase II data
DP+Sr89	Utility score for state 'Progression-free, on treatment' (PGF-OT)	Beta(109.46, 43.78)	TRAPEZE phase II data
	Utility score for state 'Progression-free, not on treatment'(PGF) ‡	Normal(0.212, 0.05)	TRAPEZE phase II data
	Utility score for state 'Progression'(PG) §	Normal(0.211, 0.096)	TRAPEZE phase II data
DP+ZA+Sr89	Utility score for state 'Progression-free, on treatment' (PGF-OT)	Beta (151.39, 50.52	TRAPEZE phase II data
	Utility score for state 'Progression-free, not on treatment'(PGF) ‡	Normal(0.099, 0.059)	TRAPEZE phase II data
	Utility score for state 'Progression'(PG) §	Normal(0.166, 0.085)	TRAPEZE phase II data

*****Varied by varying the probability of a patient experiencing different adverse events.

†Varied by varying the probability of patients receiving second-line chemotherapy, radiotherapy or radioisotope treatment

‡Calculated as score for PGF-OT + (utility increment PGF-OT – PGF)

§Calculated as utility for PGF-OT + (utility increment PGF-OT – PG)

Appendix B. Calculation of expected value of sample information (web only)

The expected value of sample information was calculated in two stages. The first stage involved obtaining a large number of possible (simulated) posterior distributions of the uncertain parameters of interest. In the second stage, each of these posterior distributions was used as input in the NSCLC model and Monte Carlo simulations were run to calculate de novo cost-effectiveness results (NMBs) conditional on the posterior distribution. Calculations were performed in MS Excel 2007® using code written in the VBA® programming language.

Stage 1, steps 1 to 3

1. Draw a set of values of the uncertain parameters φ from their existing (prior) distributions. In the case of NSCLC, parameters of interest were probabilities of disease progression and death at different points in time. These were expressed as Weibull distributions fitted to observed data from Zatloukal et al. [53] through a model representing survival (or progression) S(t) in a linear form:

$$ln[-lnS(t)] = \alpha\, ln(t) - \alpha\, ln\, \beta$$

Regressing $\ln[-\ln S(t)]$ against $\ln(t)$ gives ordinary least square estimates of the model intercept and coefficients, which can be used to obtain the shape α and scale β parameters for the Weibull model. Thus, drawing transition probabilities to the progression and death states involved obtaining values for the shape and scale parameters, through drawing from the coefficients of the linear regression model. The latter were assigned normal distributions with mean and standard errors taken directly from the regression output of the linear model.

For CRPC, the prior distribution of the parameters of interest (i.e. transition probabilities to different health states) is represented by a Dirichlet distribution, with parameters of this distribution showing counts of 21-day cycles that participants spent in specific health states:

$$Draw\ a\ sample\ from\ prior\ distribution\ Pr_i \sim Dirichlet\ (\alpha, \beta, \gamma, \delta)$$

2. On the basis of the drawn values, simulate possible sample results D on φ. Possible sample results conditional on the prior draw obtained in step 1 were simulated using individual patient sampling. This involved simulating the transitions of each of a cohort of hypothetical patients equal to the sample size of the proposed trials (n=450 patients per arm in NSCLC, n= 300 patients per arm in CRPC) to different states (progression-free, progression and death) according to the probabilities of progression and survival drawn in step 1. The number of patients in each health state at each point in time was recorded.

3. Combine prior with simulated (sample) data to get a posterior distribution. The prior distribution (observed number of patients at each state in different points in time) and simulated sample results (i.e. simulated number of patients at each state at different points in time) obtained from step 2 were added as

$$Posterior\ information_i = Prior\ information + Sample\ information_{trial\ i}$$

to give the total number of patients—a representation of posterior information. Posterior information was translated to the posterior distribution, and steps 1 to 3 were repeated k=1000 times for each treatment j to give 1000 posterior distributions.

Stage 2, steps 4 to 7

4. For each of the 1000 posterior distributions obtained in step 3, draw a large number of values (e.g. m=1000) and calculate the resulting NMBs for each treatment j through Monte Carlo simulations using the NSCLC and CRPC models. Each of the obtained 1000 sets was entered in a model one at a time and, for each set, 1000 Monte Carlo simulations were carried out to give 1000 estimates of each treatment's NMBs given the specific posterior.

5. Average across the NMBs obtained in step 4, to get the expected NMBs ($E_{\varphi|D}\ NMB(j,\varphi)$) for each posterior distribution and for each treatment j. Then, obtain the maximum expected NMBs across treatments for each posterior distribution ($max_j\ E_{\varphi|D}\ NMB\ (j,\varphi)$).

6. As it is not known which posterior distribution (i.e. trial results) will transpire, average across the maximum expected NMBs to obtain the expected maximum NMBs ($E_D max_j \, E_{\varphi|D} \, NMB \, (j, \varphi)$). This represents the expected NMBs from making a decision with sample information.

7. Subtract the NMBs associated with a decision made under current information ($max_j \, E_\theta \, NMB \, (j, \theta)$) from those based on a decision with sample information ($E_D max_j \, E_{\varphi|D} \, NMB \, (j, \varphi)$) to get the EVSI.

Appendix C. Specified scenarios for PPoR

Table 1 in Appendix C. Specified scenarios and subsequent change in clinical practice for PPoR application (NSCLC case study)

Scenario	Outcome*	Treatment share
Without research	Gem+Cisp: 0.81 Gem+Carb: 0.87	Gem+Cisp: 50% Gem+Carb: 50%
With research		
• 'Favourable' outcome: Trial shows effectiveness estimates for Gem+Carb to be such that, when these estimates are entered in the NSCLC model and are translated into final cost-effectiveness measures, the treatment appears cost-effective (i.e. costs less than) at £30,000 per QALY (i.e. ICER < £30,000 per QALY).	Gem+Cisp: 0.81 Gem+Carb: 0.64	Gem+Cisp: 25% Gem+Carb: 75%
• 'Inconclusive' outcome: Trial shows effectiveness estimates for Gem+Carb to be such that, when these estimates are entered in the NSCLC model and are translated into final cost-effectiveness measures, the cost-effectiveness of the treatment appears inconclusive at £30,000 per QALY (i.e. ICER near £30,000 per additional QALY or NMBs near 0).	Gem+Cisp: 0.81 Gem+Carb: 0.72	Gem+Cisp: 50% Gem+Carb: 50%
• 'Unfavourable' outcome: Trial shows effectiveness estimates for Gem+Carb to be such that, when these estimates are entered in the NSCLC model and are translated into final cost-effectiveness measures, the treatment appears non-cost-effective at £30,000 per QALY. (i.e. ICER > £30,000 per QALY).	Gem+Cisp: 0.81 Gem+Carb: 0.87	Gem+Cisp: 75% Gem+Carb: 25%

*Expressed as probability of disease progression at 12 month follow-up. NMB: Net Monetary Benefit; QALY: quality adjusted life year Gem+Cisp: gemcitabine plus cisplatin; Gem+Carb: gemcitabine plus carboplatin

Table 2 in Appendix C. Specified scenarios and subsequent change in clinical practice for PPoR application (CRPC case study)

Scenario	Outcome*	Treatment share
Without research	DP: 0.06 DP+ZA: 0.09 DP+Sr89: 0.05 DP+ZA+Sr89: 0.04	DP: 85% DP+ZA: 5% DP+Sr89: 5% DP+ZA+Sr89: 5%
With research		
• 'Favourable' outcome for DP+Sr89 : Trial shows effectiveness estimates for DP+Sr89 to be such that, when these estimates are entered in the CRPC model and are translated into final cost-effectiveness measures, DP+Sr89 appears to be the most cost-effective at £30,000 per QALY (i.e. DP+Sr89 shows the highest NMB amongst the compared treatments)	DP: 0.06 DP+ZA: 0.09 DP+Sr89: 0.04 DP+ZA+Sr89: 0.04	DP: 50% DP+ZA: 5% DP+Sr89: 40% DP+ZA+Sr89: 5%
• 'Inconclusive' outcome: Trial shows effectiveness estimates such that, when these estimates are entered in the CRPC model and are translated into final cost-effectiveness measures, all treatments are shown to be of similar cost-effectiveness ($NMB_{DP} = NMB_{DP+ZA} = NMB_{DP+Sr89} = NMB_{DP+ZA+Sr89}$)	DP: 0.03 DP+ZA: 0.04 DP+Sr89: 0.07 DP+ZA+Sr89: 0.02	DP: 85% DP+ZA: 5% DP+Sr89: 5% DP+ZA+Sr89: 5%
• 'Favourable' outcome for DP: Trial shows effectiveness estimates for DP to be such that, when these estimates are entered in the CRPC model and are translated into final cost-effectiveness measures, DP appears to be the most cost-effective at £30,000 per QALY (i.e. DP shows the highest NMBs amongst the compared treatments)	DP: 0.01 DP+ZA: 0.09 DP+Sr89: 0.05 DP+ZA+Sr89: 0.04	DP: 90% DP+ZA: 3.3% DP+Sr89: 3.3% DP+ZA+Sr89: 3.3%
• 'Favourable' outcome for DP+ZA : Trial shows effectiveness estimates for DP+ZA to be such that, when these estimates are entered in the CRPC model and are translated into final cost-effectiveness measures, DP+ZA appears to be the most cost-effective at £30,000 per QALY (i.e. DP+ZA shows the highest NMB amongst the compared treatments)	DP: 0.06 DP+ZA: 0.01 DP+Sr89: 0.05 DP+ZA+Sr89: 0.04	DP: 50% DP+ZA: 40% DP+Sr89: 5% DP+ZA+Sr89: 5%
• 'Favourable' outcome for DP+ZA+Sr89 : Trial shows effectiveness estimates for DP+ZA+Sr89 to be such that, when these estimates are entered in the CRPC model and are translated into final cost-effectiveness measures, DP+ZA+Sr89 appears to be the most cost-effective at £30,000 per QALY (i.e. DP+ZA+Sr89 shows the highest NMB amongst the compared treatments)	DP: 0.06 DP+ZA: 0.09 DP+Sr89: 0.05 DP+ZA+Sr89: 0.01	DP: 50% DP+ZA: 5% DP+Sr89: 5% DP+ZA+Sr89: 40%

*Expressed as transition probability from 'Progression-free, not on treatment' to 'Progression' for each 3-week cycle. NMB: Net Monetary Benefit; QALY: quality adjusted life year; DP; docetaxel and prednisolone; DP+ZA: docetaxel and prednisolone plus zoledronic acid; DP+Sr89: docetaxel and prednisolone plus strontium-89; DP+ZA+Sr89: docetaxel and prednisolone plus zoledronic acid plus strontium-89.