# Assessing the potential role and value of analytic approaches in assisting research priority-setting

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### Background and aims

Evaluative research, such as clinical trials, provide much needed evidence for cancer treatment coverage decisions. Given limited research budgets, public funding organisations are required to make hard choices on which research programmes to fund. Such resource-allocation decisions could benefit from explicit, numerical estimates of the potential value of a proposed trial. Various analytic frameworks to provide such estimates have been proposed– the most prominent being the 'value of information' (VoI) and 'payback of research'– but their role in informing priority-setting is still ambiguous.

The paper discusses the potential role and value of these frameworks, with regards to methodological issues associated with them, the extent of assumptions required, their practicality and their possible fit into current research priority-setting processes.

### Methods

VoI and payback (PATHS model) methods were applied to a case study representing a proposals for primary research in the area of lung cancer. This application, which involved summarising existing evidence and carrying out VoI and payback analysis, gave estimates of the value of research and formed the basis for the assessment.

### Results and discussion

Results were in broad agreement, with both approaches suggesting a high value (in expected net monetary benefits) associated with further research. Compared to VoI, payback requires additional assumptions about possible change in clinical practice following research results. The analyses can be done in a timely manner, and can be useful in both researcher-led and commissioned research funding streams.

## Introduction & aims

Clinical evaluative research, such as randomised clinical trials, has been seen as the 'crown jewel' of experimental research and a prime source of evidence on the effectiveness of health care interventions(1). Input from clinical trials, synthesised through evidence syntheses and economic evaluations, is commonly used to inform treatment-adoption decisions(2). However, clinical trials are costly undertakings and, as the budget for research is limited, hard decisions are often needed on which research proposal to fund and carry out. Given this, research funding programmes, such as the NIHR Health Technology Assessment (NIHR HTA) and Efficacy and Mechanisms Evaluation (EME) have set up formal mechanisms for research priority setting(3;4).

Research funding decisions are typically made using 'deliberative' methods, where the value of researching a specific topic or carrying out a proposal is established by appointed expert panels through discussion

against criteria. Criteria vary across programmes, but typically relate to the importance of the topic or problem to be considered, and the scientific quality of the proposals put forward to address it. Deliberative approaches have important advantages: they are simple to use, give answers in a timely manner and make use of experts' informed views (5), but they have been seen as subjective and implicit (6).

This has given rise to suggestions that priority-setting for research would benefit from the use of more transparent, analytic approaches (6-10). A number of different analytic models have been proposed in the past, and these have been categorised into two overarching frameworks 'payback of research' and 'value of information' (10-12). These frameworks are based on different principles, but they have the same objective: to provide numerical estimate of the potential value of conducting evaluative research (11;13;14).

This paper aims to discuss the value and possible role of these frameworks in research priority-setting, by drawing on the application of these two frameworks to a case study representing a proposal for primary research. To this end, the following section gives the methods involved in this work, followed by the obtained results. The final section discusses the performance of value of information and payback and draws conclusions with regards to their sensitivity to different assumptions, practicality and possible fit into existing processes of research priority-setting.

## Methods

To get an insight into the frameworks, we applied the models to a case study representing a proposal for a randomised clinical trial (BTOG-2 trial) in the area of non-small cell lung cancer (NSCLC).

Advanced stage NSCLC patients eligible for chemotherapy are typically treated with gemcitabine, which is considered as the bedrock of chemotherapy for this patient group. This agent is typically combined with platinum analogues (cisplatin or carboplatin) and although such combinations are commonly used in clinical practice, there is no definite evidence on their effectiveness and cost-effectiveness. The proposed trial aimed to compare the effectiveness of gemcitabine plus cisplatin (Gem+Cisp) and Gemcitabine plus carboplatin (Gem+Carb) in non-small cell lung cancer (NSCLC). The proposal was submitted for funding to Cancer Research UK in 2004.

Given this, two relevant decisions were distinguished: a decision on which of the two treatments to adopt and provide to the population, and a decision on whether conducting the proposed trial would represent good use of the available resources. These decisions are closely related, as evidence generated from funding and conducting further research will provide input for the adoption-related decision.

The analysis was carried out in steps. The first step involves identifying information existing up to the point when the research proposal was submitted for funding, and synthesising this information through a decision model to obtain a current estimate of the treatments' cost-effectiveness. The developed decision model formed the basis for the second step, where payback and VoI analyses were applied to the case study.

## *1. Decision modelling*

The first part involved determining what is known with available information (this is a necessary step for both approaches). This involved identifying information through a systematic review and models to synthesise all the information that was available up to 2004.

A literature review identified 15 studies investigating the effectiveness of NSCLC chemotherapy combinations, only one of which was a Phase III RCT assessing Gem+Cisp and Gem+Carb in a head-to-head comparison(15). Evidence on the cost-effectiveness of chemotherapies was scarce. Nine studies were identified, of which only one compared Gem+Cisp and Gem+Carb. This was a cost-minimisation analysis carried out in the United States in 1999 (16). In this study, Gem+Carb was found to be more expensive than Gem+Cips, resulting in an additional cost per treatment cycle of approximately £1650 (2004 prices).

A decision analytic model was built to synthesise all available (pre-2004) information. The model followed chemotherapy-eligible NSCLC patients through three health states: progression-free (PG-F), progression (PG) and death (D). Patients in the model start in PG-F where they are scheduled to receive a 4-cycle course of chemotherapy, each cycle lasting 21 days. Patients stay in this health state until experiencing disease progression. Upon progression, patients move to PG and eventually to state D.

Input for the decision model was obtained from the available literature. Transition probabilities from PG-F to PG and from PG to D were obtained by fitting Weibull models to time-to-progression and survival data reported in Zatloukal *et al.* (15). Total per-patient cost was calculated taking into account the cost of drug acquisition and administration, costs of adverse events, other medical resources used (additional outpatient visits and examinations) and terminal care costs. In so doing, evidence on health care resource use obtained from the literature was weighted by unit cost estimates taken from national published sources (17;18). No evidence on relevant preference-based quality of life was identified in the pre-2004 literature, and thus such values were derived from expert opinion. To account for uncertainty, key parameters in the model were attached probability distributions. A table with details on distributions attached to model parameters is given in the Appendix.

The analysis adopted an NHS perspective and, in line with current NICE recommendations, both costs and benefits (QALYs and life-years gained) were discounted at a rate of 3.5% per year(19). Results were obtained using Monte Carlo simulations, where 5000 sets of input parameter values were drawn at random from their respective distributions to give 5000 estimates of per-patient costs and QALYs. Results are expressed in terms of cost per QALY ratios, as well as net monetary benefits (NMB)(20), a measure which translates health gains in monetary terms using as exchange rate a decision maker's willingness to pay (ceiling ratio) for a unit of health benefits. Uncertainty surrounding cost-effectiveness estimates is depicted in cost-effectiveness planes(21) and cost-effectiveness acceptability curves (CEACs)(22;23).

## *2. VoI analysis*

Value of information analysis is part of a decision theoretic framework which asserts that, under conditions of uncertainty, the optimal choice between alternative actions is the one that leads to the greatest expected payoff. A separate decision is then needed on whether more evidence should be pursued to reduce the uncertainty around this choice (24-26).

The framework can be easily applied to health care treatment adoption decisions: treatments should be reimbursed if they appear to offer the greatest benefits over their comparators, and a separate but related decision is required on whether or not more evidence should be collected through research to reduce decision uncertainty and substantiate this choice (27;28). According to this framework, the latter decision is important, because uncertainty entails a risk of making the wrong adoption decision, which imposes a possible (expected) opportunity cost: the loss of benefits if the wrong decision is made and patients are provided with an inferior treatment. Conducting research enhances the available information, limits the possibility of making the wrong decision and reduces the expected opportunity loss(27). Given this framework, the value of conducting further research can be measured in terms of the reduction in the expected opportunity loss it brings about and, on this basis, value of information analysis has been seen as potentially useful in informing research funding decisions (11;14;29).

A key concept in value of information analysis is the expected value of perfect information (EVPI). EVPI represents the difference between the net monetary benefits (NMB) to be gained if a decision is made under perfect information (effectively, the correct decision that would give the maximum possible NBs) and the decision made in light of current, imperfect information. Using the output of a non-linear probabilistic model, EVPI is given by the formula

$$\mathrm{EVPI} = \mathrm{E}_{\theta}\, \max_{\mathrm{j}} \mathrm{NMB}(\mathrm{j}, \theta) - \max_{\mathrm{j}}\ \mathrm{E}_{\theta}\mathrm{NMB}(\mathrm{j}, \theta)$$

where *j* represents alternative interventions or technologies, and $\theta$ represent all uncertain parameters affecting the decisions (30;31). EVPI calculated in this way represents the expected benefits due to making a decision about treating an individual patient with perfect information. Once information is generated, it can be used to inform every decision made for eligible patients over a number of years (30;32). The EVPI for the population of eligible patients is the sum of the individual EVPI multiplied by the discounted number of patients affected by the decision in each period summed over the time horizon for which the generated information is expected to be useful, starting from the point when information is disseminated. In this study, the time horizon was set at 5 years, giving a total discounted number of 13,797 eligible NSCLC patients.

EVPI shows the expected maximum gains from research, and, in a decision theoretic framework, it can be seen as the ceiling value that society should be paying for research. If the cost of research is higher than the gains from acquiring perfect information through research (expressed in monetary terms), conducting research is not worthwhile. In this sense, EVPI has been considered as a first hurdle to committing resources to further research (10;27).

EVPI analysis can be extended to derive the value of research to eliminate uncertainty around one or a subset of all uncertain parameters affecting an adoption decision. Formally, the expected value of perfect parameter information (EVPPI) for a group of uncertain parameters $\varphi$ of all uncertain parameters $\theta$ associated with a decision between j alternative interventions is given by

$$\mathrm{EVPPI}_{\varphi} = \mathrm{E}_{\varphi}\, \max_{\mathrm{j}} \mathrm{E}_{\psi|\varphi}\mathrm{NMB}(\mathrm{j}, \varphi, \psi) - \max_{\mathrm{j}}\mathrm{E}_{\theta}\mathrm{NMB}(\mathrm{j}, \theta)$$

This represents the difference between the NMB accruing from a decision made with perfect information about the group of parameters $\varphi$ (and imperfect information about the remaining parameters $\psi$) and a decision made with current, imperfect information about all parameters $\theta$.

EVPPI determines the expected gains from – and, by extension, the value of– eliminating uncertainty about particular parameters affecting a decision. Due to this, it can highlight those parameters for which more accurate estimates would be more valuable and, as a result, indicate the type of research that would be most beneficial (27;33;34). As a decision rule, if the expected benefits of eliminating uncertainty about a group or a single parameter (population EVPPI) through carrying out a research programme exceed the cost of the programme, conducting research is potentially worthwhile (30;33).

### *3. Payback analysis*

A number of models following the principles of the 'payback' framework are available in the literature (7-9;35), the most recent of which is the Preliminary Assessment of Technologies for Health Services (PATHS)(13). The model has been developed by researchers at Brunel University building on the principles of earlier work(7;35) with which it shares a number of characteristics. The framework is based on the idea that evidence generated through clinical evaluative research is valuable because it stimulates beneficial changes in clinical practice (that is, the use of cost-effective treatment expands, and non cost-effective treatments are discontinued). Changes in clinical practice lead to additional benefits to the population and, on this basis, these additional benefits are seen as a proxy of the value of the proposed research. To estimate these benefits, one needs to compare two 'states of the world': a) a state with research taking place and informing changes in clinical practice, and b) a state without research, where clinical practice remains as it is. In essence, the approach resembles a cost-effectiveness analysis of two interventions, with the difference that here the comparison is between different possible 'states of the world'.

To estimate the population cost and benefits expected to accrue in each of these states of the world, one needs to have information on two factors: (a) the per-patient costs and effectiveness of the treatments provided to patients and (b) the use of these treatments in clinical practice, in terms of the proportion of patients receiving each treatment. In a prospective framework, per-patient costs and benefits are unknown (although some prior evidence may exist) and are expected to be revealed by research. To address the fact that research results cannot be known in advance, the approach specifies different scenarios in the form of a series of hypothetical but possible trial results (possible outcomes). These possible outcomes are assumed to represent the true effectiveness and cost-effectiveness of the compared treatments, and are expected to have an impact on clinical practice. Combining the per-patient cost effectiveness (as specified under each possible outcome) with the proportion of eligible patients expected to use the treatment gives an estimate of the total costs and benefits in the population.

Given possible outcomes and the hypothesised change in clinical practice, a measure of the value of research can be obtained by comparing costs and benefits accruing in the 'with research' and 'without research' states using the formula

$$ICER_i = \frac{C_{st} + C_{r,i} - C_{nr,i}}{E_{r,i} - E_{nr,i}}$$

Here, *i* is an indicator for the possible outcomes, *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 benefits (e.g. QALYs) associated with research and without research respectively, under outcome *i*. Expressed in terms of incremental net monetary benefits, the formula can be written as

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

Here, $\lambda$ stands for the ceiling ratio, a hypothetical value of a decision-maker's willingness to pay for an additional unit of benefit (here an additional QALY). The above formulae give the benefits accruing from each possible outcomes, but only one of these outcomes will come true. Although it is not known in advance which of the outcomes represents the true effectiveness and cost-effectiveness of the treatment, it is possible to obtain a summary measure of the proposed study's payoff by creating combinations where scenarios are weighted according to their likelihood of occurrence. For example, an 'optimistic' combination may give greater weight to the likelihood of observing a favourable exemplar outcome (e.g. 0.5 probability of positive results, 0.25 probability of either inconclusive and negative results). Following the previous notation, the weighted cost per QALY associated with a combination is given by:

$$Weighted\ ICER_k = \frac{\sum_i p_i \times (C_{st} + C_{r,i} - C_{nr,i})}{\sum_i p_i \times (E_{r,i} - E_{nr,i})},$$

or, equivalently, expressed in incremental net monetary benefits (INMB) by:

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

where *k* is an index for combinations and $p_i$ is the probability of observing study outcome *i*. Last, per patient NMBs were extrapolated to the population that stands to benefit from additional information over a time horizon of 5 years after research results are disseminated.

In this study, and in line with existing literature (12;13), three broad outcomes were specified:

a. Favourable outcome: Trial shows the effectiveness of Gem+Carb to be such that when this evidence is entered in the NSCLC decision model, Gem+Carb is cost-effective ( i.e. $ICER_{Gem+Carb}$ below £30,000 per additional QALY).

b. Inconclusive outcome: Trial shows the effectiveness of Gem+Carb to be such that when this evidence is entered in the NSCLC decision model, Gem+Carb appears non-conclusively cost-effective (i.e. $ICER_{Gem+Carb}$ near £30,000 per additional QALY).

c. Unfavourable outcome: Trial shows the effectiveness of Gem+Carb to be such that, when this evidence is entered in the NSCLC decision model, Gem+Carb appears not cost-effective compared to Gem+Carb (i.e. $ICER_{Gem+Carb}$ well above £30,000 per additional QALY).

Estimates of the effectiveness of Gem+Carb (in term of probabilities of progression) needed to be specified in order to match the favourable, inconclusive and unfavourable outcomes. In the NSCLC model, the probability of progression at each model cycle has been drawn from a Weibull distribution with shape parameter *alpha* and scale parameter *beta*. Thus, in order to change these progression probabilities to match the specified possible outcomes, the shape parameter of the Weibull progression model need to be

adjusted. The scale and shape parameters for the Weibull models for NSCLC disease progression are given in Table 1 with the parameters changed to match each possible outcome appearing in bold. According to this, a favourable outcome for Gem+Carb (i.e. $ICER_{Gem+Carb}$<£30,000 per QALY) would be realised if the proposed trial showed that Gem+Carb progression follows a Weibull(1.287, 17).

**Table 1: Parameters of Weibull distribution for disease progression for different possible outcomes (NSCLC).**

| | Favourable outcome | | Inconclusive outcome | | Unfavourable outcome | |
|---|---|---|---|---|---|---|
| | Alpha | Beta | Alpha | Beta | Alpha | Beta |
| Progression (Gem+Cisp) | 1.404 | 12.17 | 1.404 | 12.17 | 1.404 | 12.17 |
| Progression (Gem+Carb) | 1.287 | **17** | 1.287 | **14.26** | 1.287 | **9.85** |

The new parameters of the Weibull model translate to Gem+Carb progression probability at 12 months follow up of 0.64, 0.72 and 0.87 for a favourable, inconclusive and unfavourable research outcome respectively.

Observing each of these outcomes is expected to have an impact on clinical practice, in terms of Gem+Carb and Gem+Cisp prescription shares. The extent of this change depends on a number of variables, including the magnitude of the results and dissemination-related factors. In this study, possible prescription patterns following the specified outcomes were determined with the help of experts in cancer services commissioning based at the NHS Pan Birmingham Cancer Network (Table 2).

Under current (2004) practice, Gem+Cisp and Gem+Carb were prescribed in equal proportions. In the absence of further research, it was assumed that prescription shares were unlikely to change. In the event of an outcome favourable to the 'new' intervention and appropriate dissemination of results through publications and guidelines, it was agreed that the use of Gem+Carb would be likely to increase up to a level of approximately 75%, with Gem+Cisp being prescribed to 25% of the eligible population. Following an inconclusive outcome, it was assumed that there would be no change in clinical practice and the current prescription patterns would continue, with Gem+Cisp and Gem+Carb being provided in equal proportions. Last, observing an unfavourable outcome was assumed to have an effect of the opposite direction to the favourable outcome, bringing the use of Gem+Cisp up to 75% of the population.

**Table 2: Assumed treatment uptake following possible research outcomes**

| Research outcome | Results of cost-effectiveness analysis | Prescription in 'with research' state | Prescription in 'without research' state |
|---|---|---|---|
| Favourable to Gem+Carb | Gem+Carb cost-effective ($ICER_{Gem+Carb\ vs\ Gem+Cisp}$ = £16,700) | Gem+Cisp: 25%<br>Gem+Carb: 75% | |
| Inconclusive | Gem+Carb not clearly cost-effective ($ICER_{Gem+Carb\ vs\ Gem+Cisp}$ =30,280) | Gem+Cisp: 50%<br>Gem+Carb: 50% | Gem+Cisp: 50%<br>Gem+Carb: 50% |
| Unfavourable to Gem+Carb | Gem+Carb not cost-effective (Gem+Carb dominated) | Gem+Cisp: 75%<br>Gem+Carb: 25% | |

# Results

This section reports on results obtained from the decision model given existing evidence, as well as results from the application of value of information and payback to the proposed research.

## *Cost-effectiveness analysis*

The cost-effectiveness analysis revealed that, with existing evidence synthesised in the NSCLC model, Gem+Cisp appears less costly than Gem+Carb, resulting in cost savings of approximately £740 and improved outcomes in the magnitude of 0.015 QALYs (Table 3). Translating the findings into Net Monetary Benefits (NMB) at a ceiling ratio of £30,000 shows Gem+Cisp and Gem+Carb to result in £11,660 and £10,472 NMBs respectively, giving a negative Incremental Net Monetary Benefits$_{\text{Gem+Carb vs Gem+Cisp}}$ of £1188.

**Table 3: Cost-effectiveness results**

| Treatment | Total cost | Total QALYs | ICER (£ per QALY) | Incremental Net Monetary Benefits (Gem+Carb vs Gem+Cisp at £30,000 per QALY) |
|---|---|---|---|---|
| **Gem+Cisp** | £5830 | 0.583 | - | - |
| **Gem+Carb** | £6568 | 0.568 | Dominated | -£1188 |

Cost-effectiveness acceptability curves depicting the probability of each treatment being cost-effective at different values of a decision makers' willingness to pay are given in Figure 1. Assuming a ceiling ratio of £30,000 per QALY gained, the probability that Gem+Cisp is more cost-effective than Gem+Carb is approximately 0.64. In other words, if society is willing to pay £30,000 for an additional QALY, there is a 64% chance that Gem+Cisp is the optimal treatment.

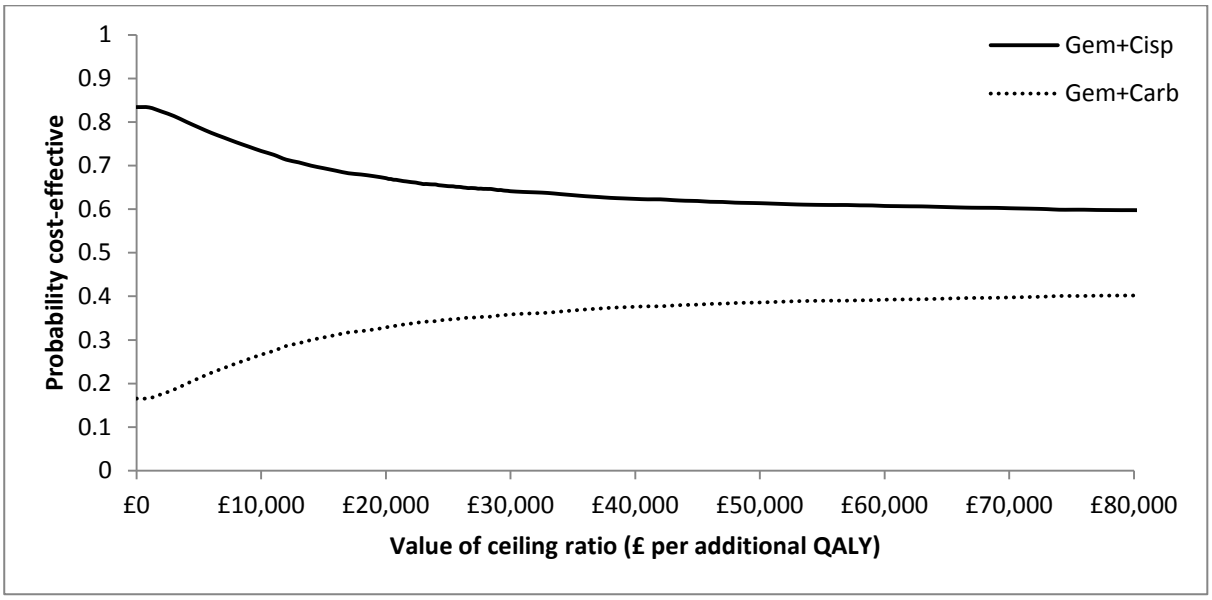


**Figure 1: Cost Effectiveness Acceptability Curves**

As there is a possibility that an intervention with the highest probability of being cost-effective at a given value of ceiling ratio may not result in the highest NMBs at this ceiling ratio due to non-linearity in the model, results should be also presented in the form of CEAFs, formed by a curve representing the

intervention with highest NMB value over a range of ceiling ratio values (22;36). As Gem+Carb never result in the highest NMBs across different ceiling ratios, the relevant CEAF corresponds to the CEAC for Gem+Cisp. All in all, results suggest Gem+Cisp to be the optimal treatment. However, there is considerable uncertainty around parameter input in the model, most importantly transition probabilities. At a willingness to pay value of £30,000 per QALY, there is a 0.36 probability that Gem+Cisp should not be the preferred treatment.

### *Results of value of information analysis*

EVPI and EVPPI analyses were conducted in a non-parametric fashion, to indicate the gains from eliminating uncertainty around uncertain parameters affecting the treatment adoption decision.

The EVPI plotted as a function of the ceiling ratio can be seen in Figure 2. At a ceiling ratio value of £0, there is little uncertainty around Gem+Cisp being the optimal treatment, and the value of eliminating this uncertainty around a treatment decision affecting a single patient is relatively low, at about £66. The value increases as the ceiling ratio rises, reaching a value of £950 at £30,000 per QALY. Extrapolating the individual EVPI to all eligible patients affected by the decision over a 5-year time horizon (13,797 patients(37)) gave a population EVPI of £13.08 million (at £30,000 per QALY).

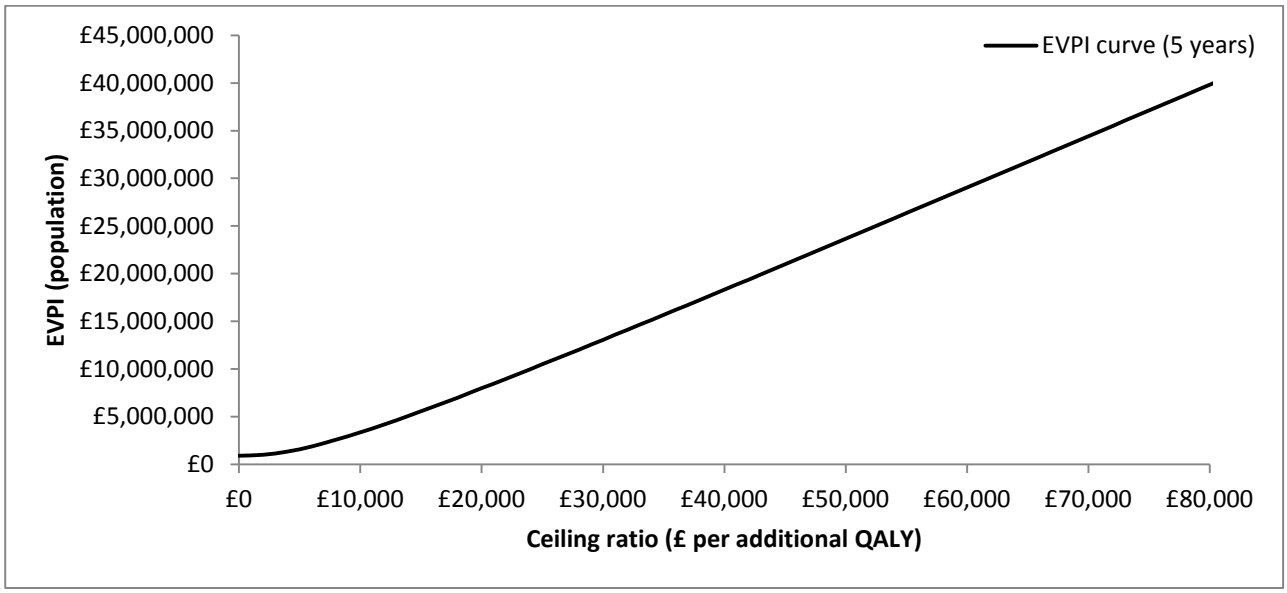


**Figure 2: Population EVPI**

In addition, the EVPPI was calculated for five groups of parameters: preference-based HRQoL (utility) values; transition probabilities for Gem+Cisp and Gem+Carb, and costs associated with Gem+Cisp and Gem+Carb. At a ceiling ratio of £30,000 per QALY, the parameters with the highest population EVPPI were transition probabilities for Gem+Cisp and Gem+Carb, at £5.52 million and £9.07 million, respectively. The value of research associated with Gem+Cisp and Gem+Carb costs appeared low, at £51,250 and £35,000, respectively, while the EVPPI associated with utility scores was £0. EVPPI curves for different values of the ceiling ratio are plotted in Figure 3. The proposed trial looking into the effectiveness of Gem+Cisp and Gem+Carb in delaying transition to worse health states appears to well exceed its cost (approximately £340,000). However, the benefits from research on cost and utility scores is unlikely to exceed the cost of a

standalone study investigating these parameters, but such investigation could take place as part of a trial looking into the treatment effectiveness.

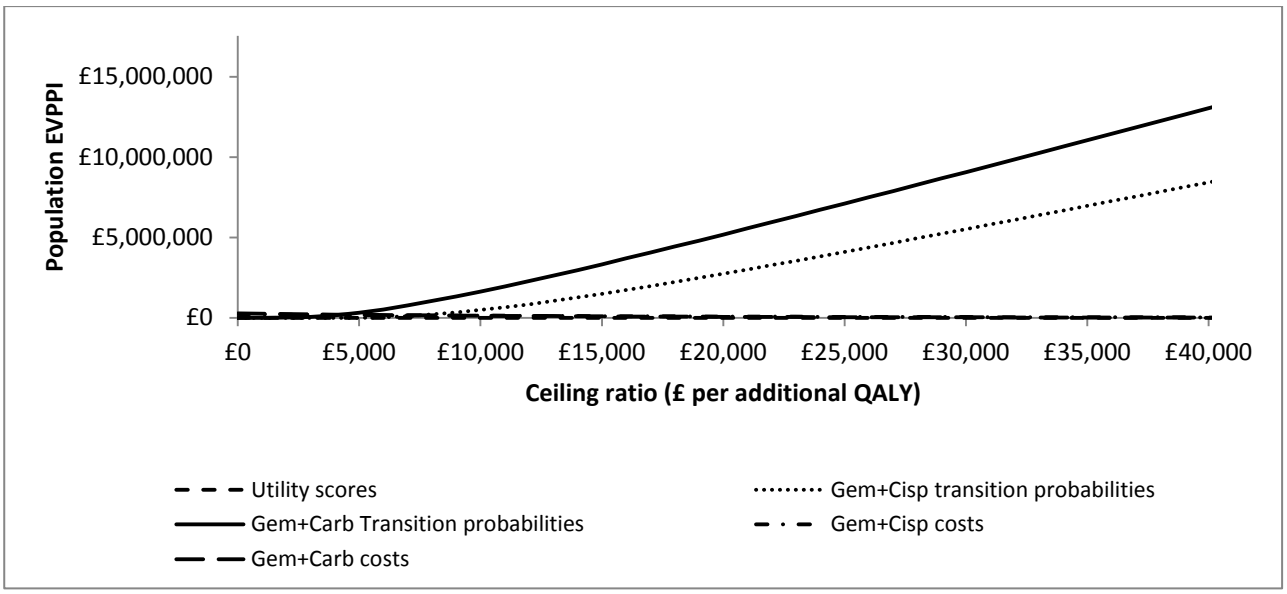


**Figure 3: Population EVPPI for different parameters**

### *Payback results*

Given the specified possible outcomes and the matched transition probabilities, the cost effectiveness of Gem+Carb is expected to assume the values in

**Table 4: Cost-effectiveness results based on favourable, inconclusive and unfavourable outcomes**

| Research outcome | Gem+Cisp | | Gem+Carb | | ICER (Gem+Carb vs Gem+Cisp) |
|---|---|---|---|---|---|
| | Total Cost | Total QALYs | Total Cost | Total QALYs | |
| Favourable to Gem+Carb | £5830 | 0.583 | £6762 | 0.639 | £16,700 |
| Inconclusive | £5830 | 0.583 | £6710 | 0.612 | £30,280 |
| Unfavourable to Gem+Carb | £5830 | 0.583 | £6560 | 0.567 | Dominated |

and the change in clinical practice that is assumed to follow each of these outcomes, the non-weighted results of the PATHS model appear in Table 5 below.

Under the favourable outcome, carrying out research is estimated to result in greater costs and more QALYs compared to a situation without research. As obtaining an additional QALY in this case is expected to cost less than the £30,000, conducting research results in positive INMBs of about £2.22 million (ICER of £18,450 per QALY). Given the inconclusive outcome, conducting research results in no additional QALYs (as no change in prescription 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 a negative INMB of -£336,700. Last, under the unfavourable outcome, conducting research is associated with an increase in QALYs and

cost-savings. In this situation, carrying out research appears particularly appealing, as it is predicted to result in INMBs of approximately £3.82 million.

**Table 5: Non-weighted payback results**

| | Favourable outcome | Inconclusive outcome | Unfavourable outcome |
|---|---|---|---|
| **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 |
| **Cost per QALY** | **£18,450 per additional QALY** | **Costs for no additional QALYs** | **Cost savings for additional QALYs** |
| $NMB_{with\ research}$ | £168,103,680 | £160,370,345 | £156,267,944 |
| $NMB_{without\ research}$ | £165,881,317 | £160,707,066 | £152,446,181 |
| **INMB (£30,000 per QALY)** | **£2,222,363** | **-£336,721** | **£3,821,763** |

To reflect the fact that different outcomes are associated with different likelihood of occurrence, these were assigned likelihood weights and formed different combinations. In line with previous literature (13), three combinations were formed: a) an optimistic combination, where the probability of observing a positive, inconclusive and negative outcome is 0.5, 0.25 and 0.25 respectively; b) a neutral combination, where each outcome has an one-third probability of being observed, and c) a pessimistic combination, where the probability of observing a positive, inconclusive and negative outcome is 0.25, 0.25 and 0.5, respectively. Under the optimistic and neutral combinations, the analysis suggests that carrying out research will incur an extra cost of £11,960 and £6900 for every additional QALY gained respectively, while under the optimistic combination there will be cost savings for additional QALYs. Thus, assuming a ceiling ratio of £30,000 per additional QALY, carrying out research appears is estimated to result in positive INMB of £1.98 million, £1.88 million and £2.38 million under the optimistic, neutral and pessimistic combinations respectively.

It appears reasonable to assume that the true cost-effectiveness of Gem+Carb is likely to be near the values estimated from the NSCLC model. This would make that the pessimistic combination the most likely to occur and, under this premise, conducting research and changing clinical practice accordingly is expected to result in cost savings of approximately £119,000 and 75 additional QALYs.

## Discussion

Payback and VoI results appeared in broad agreement, suggesting that a trial assessing Gem+Cisp and Gem+Carb for NSCLC patients would be a potentially cost-effective investment. However, there are important differences in the way results are derived and interpreted. In the case of VoI, the results show the maximum NMBs that would be expected from eliminating uncertainty around parameters affecting the treatment adoption decision for NSCLC. Within this framework, results are driven by the extent of existing uncertainty (i.e. the probability that the treatment appearing inferior under current information (i.e. Gem+Carb) is actually more cost-effective than the one that currently appears superior (Gem+Cisp)), and the expected loss of benefits due to this uncertainty(27;30). Given this, further research is more desirable when uncertainty is high, and the expected (possible) losses due to this uncertainty are expected to be substantial. It must be noted that, using the results for allocating research presumes agreement with the idea that the purpose of primary research is to reduce the uncertainty around parameters affecting a decision problem.

On the other hand, the results of the payback analysis represent the NMBs that would be realised should clinical practice around chemotherapy for NSCLC changed in light of possible results from the proposed trial. Two factors affect the magnitude of the payback results: a) the extent to which the cost-effectiveness of the treatment of interest as revealed by research will differ from the currently perceived cost-effectiveness, and b) the extent of a beneficial change in clinical practice in light of new results. In this respect, payback will show greater desirability for research proposals on treatments which are used commonly in clinical practice, but for which no conclusive evidence exists to substantiate their use. Here, the important assumption is that the value of research lies in its ability to induce a beneficial change in clinical practice. However, this stance has been criticised on the grounds that conducting primary research is neither the least costly nor the most effective way of changing clinical practice(10;14).

The application of the frameworks to the case study gave an insight into the sensitivity of the results– and the methods themselves– to assumptions. In several occasions throughout this application, empirical estimates of the uncertainty around parameters were not available and were replaced by assumptions. In such cases, if uncertainty is overestimated (e.g. by using wider standard errors for uncertain parameters), VoI results are inflated. On the other hand, underestimating the uncertainty will lead to artificially low VoI results, which will make research appear less desirable.

Far greater use of assumptions is needed for payback calculations. Choices of hypothetical research results, as well as assumptions about change in the prescription share of Gem+Cisp and Gem+Carb under different trial results and choices of likelihood weights for the weighted analysis are, in essence, arbitrary. As these parameters have a significant effect on the results, payback calculations appear very sensitive to these assumptions. Last, both the approaches are sensitive to assumptions about the population that stands to benefits from the results of research. In specific, there is uncertainty around the time-horizon over which research will retain its usefulness, as well as uncertainty around the number of new patients (incidence) in the future. A way of dealing with these weaknesses may be through formal elicitation exercises, where the informed views of experts are requested on aspects such as the possible change in clinical practice and the appropriate time horizon. Another possible way may be by recognising the stochastic nature of these parameters and presenting uncertainty through a probabilistic framework.

To a great extent, the use of the approaches in practice depends on the degree to which the approaches are practical(11). Indeed, this is important as potential users, such as research funding organisations, need to be able to turn decisions around quickly. In the past Claxton and colleagues(10) concluded decision modelling and VoI would take a team of researchers of different mix approximately 10-12 weeks to complete. With regards to payback, Townsend *et al.* (13) found that PATHS analysis would require between 1 and 4 weeks' work for a researcher. Both studies suggested that payback and VoI results can be obtained within tight timelines.

This exploration found the preliminary steps needed for the application of the analytic frameworks to be the most time-intensive elements of the analysis. A considerable amount of time was devoted to identifying evidence, designing and populating the decision model. However, it must be noted that in the present study, these tasks were carried out by a single researcher, whereas, in practice, this work would be in all likelihood undertaken collaboratively, by a team of researchers including information specialists, health economists and mathematical modellers. In addition, if an up-to-date systematic review and a good quality decision model are already available, there would be considerable savings in time.

As soon as cost-effectiveness results from Monte Carlo simulations become available, carrying out EVPI and EVPPI analysis is relatively straightforward. Methods for conducting non-parametric EVPI and EVPPI analysis are now well established (30;31). Compared to EVPI, EVPPI analysis requires far greater computational time. This would be a detractor for teams of scientists when deadlines are tight. Much of the time devoted to EVPPI was taken up by developing MS Excel macro commands and running replications. However, in simple, linear models shortcuts can be used to cut-down the computational time (38), and research to simplify EVPPI calculations is currently ongoing (39). With regards to payback, time was required for gathering information, in specific, elicitation of expert opinion about the likely change in prescription in light of different results. If the analysis is to include formal elicitation techniques, there may be a need for additional time, although this requirement is unlikely to be substantial.

How can these frameworks be used in practice? Potential users of the approaches could be research funding programmes such as the NIHR HTA and EME, which fund pragmatic trials for health technology assessment. Typically, such institutions operate 'commissioned' and 'researcher-led' streams(3).

In researcher-led (reactive) streams, researchers develop and submit proposals for primary research to funding organisations directly, on topics of their choice. Research proposals go through a two-stage process. In the first stages, outline proposals are considered and shortlisted according to the importance of the topic they are concerned with. In the second stage, detailed versions of shortlisted proposals are submitted and are considered taking into account the scientific quality of the planned study. At the first stage, there may be a scope for using VoI (EVPI) and payback calculations to rule out topics for which research will not be potentially worthwhile (EVPI< cost of research and negative INMB for VoI and payback, respectively). At the second stage, where the focus is on the scientific quality of a proposal, EVPPI calculations may be useful in establishing the degree to which the submitted study plan this agree with these calculations.

The possible role of VoI in commissioned streams, such as the stream operated by the NIHR HTA, has been discussed by Claxton and colleagues(10). In such funding streams, possible topics identified through are

through consultations with the NHS, other stakeholders and the public, are shortlisted, and the ones that appear promising are summarised in vignettes. Topics are then considered in light of vignettes and a decision is made on which of them to be advertised in calls for proposals. The second stage involves researchers submitting research proposals in response to calls, which are then judged according to their quality and feasibility. In this context, it has been suggested that VoI can be used in the first stage, alongside vignettes, to determine whether research in the topic would be potentially worthwhile (10). In the same way, payback calculations may be used to indicate the desirability of conducting research on a specific topic and rule out topics for which research is not considered worthwhile, alongside other criteria considered important. In addition, for primary research, EVPPI can be carried out to show what information should be sought in a future study. This information can be included in commissioning briefs to provide instructions for teams of researchers submitting proposals. In the second stage, where specific primary research proposals are appraised, there may be a role for expected value of perfect information (EVSI) analysis, which show the expected value of conducting sample research and may be used to establish optimal design characteristics and, possibly, compare submitted research proposals against these standards.

A question arises as to who should be undertaking the VoI and payback analyses. In the context of researcher-led streams, although it appears sensible for researchers to undertake the analyses, this would in all likelihood be a significant burden and may discourage applications. In addition, it is very likely that there will be capacity problems due to limited number of researchers with expertise in decision modelling and VoI and payback analyses (10). As an alternative, funding organisations may wish to commission academic institutions to carry out such analysis, possibly for proposed studies which are expected to be particularly costly.

Obviously, the burden of conducting these analyses will be significantly eased if decision models and reviews of available evidence are available. Indeed, in cases where a decision model has been developed for technology appraisal reports, a collaboration between NIHR and NICE may be useful, in which NIHR could benefit from using these models as a basis for payback and VoI calculations to inform its research funding decisions. If the topic has not been looked at in a TAR report, there may be a scope for collaboration between NIHR and NICE to establish whether the topic warrants appraisal, in which case decision modelling and VoI/payback calculations can be performed to inform an adoption decision by NICE and a research-funding decision by the NIHR HTA.

## Conclusion

Given finite resource and infinite needs, treatment adoption decisions are nowadays typically informed by the results of analytic methods, such as economic evaluations. In contrast, when it comes to research, choices on which proposal to fund and carry out are based solely on deliberations. Analytic approaches have the potential to improve transparency and introduce accountability in research priority-setting, nonetheless, for methods such as VoI and payback to be introduced and used in practice, there is a need for a clear understanding of their strengths, weaknesses and potential role.

Although they are based on different principles and use different methods, VoI and payback analyses came to similar conclusions: the expected benefits from a new trial comparing Gem+Cisp and Gem+Carb are likely to surpass its cost. However, to a large degree these results are affected by assumptions, the use of

which is unavoidable. In general, payback results appear particularly sensitive due to the need for a series hypotheses on possible outcomes and resulting change in clinical practice. Expert elicitation methods or appropriate characterisation of uncertainty through a probabilistic framework may be useful in strengthening the validity of payback results, and further research on these aspects would be useful.

The time and effort required to undertake these analyses, particularly EVPPI, are often an important consideration for possible users. However, ongoing research is taking place to establish more efficient calculations for VoI measures, and as the method is increasingly used, it is likely that there will be an increase in capacity, with more researchers being able to carry out such calculations. Finally, payback and VoI can be used to help in different aspects of existing research priority-setting processes, including assessment of studies proposed directly by researchers as well as commissioned research. In addition, 'economies of scale' may be generated through collaboration between institutes responsible for research-funding and adoption decision (NIHR and NICE). All in all, if achieving greater transparency and accountability is an important goal in research priority-setting, analytic approaches can play an important role.

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# Appendix

**Table 6: Parameters and assigned distributions for transition probabilities by treatment**

| 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)<br><br>Regression coefficient ~ N(1.404, 0.047) | Literature (15) |
| **Gem+Carb** | | | Intercept ~ Normal (-2.475,0.110)<br><br>Regression coefficient ~ Normal(1.287, 0.048) | Literature (15) |
| **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)<br><br>Regression coefficient ~ Normal(1.104, 0.055) | Literature (15) |
| **Gem+Carb** | | | Intercept ~ Normal (-3.350, 0.209)<br><br>Regression coefficient ~ N(1.302, 0.077) | Literature (15) |
| **Drug acquisition and administration costs** | | | | |
| **Gem+Cisp** | Cost of drug acquisition and administration | | Gamma(100, 9.45) | Cost analysis–<br>SE is assumed to be 10% of the mean value |
| **Gem+Carb** | | | Gamma(100, 11.33) | Cost analysis–<br>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)<br><br>Thrombocytopenia: Beta (13.78, 70.22)<br><br>Neutropenia: Beta (7.98, 76.02)<br><br>Granulocytopenia: Beta (19.74, 64.26) | Literature (15) |

| | | | | |
|---|---|---|---|---|
| **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)<br><br>Thrombocytopenia: Beta(28.69, 59.31)<br><br>Neutropenia: Beta(12.85, 75.15)<br><br>Granulocytopenia: Beta(26.66, 61.34) | Literature (15) |
| **Cost of other medical resources (same across treatments)** | | | | |
| **Gem+Cisp**<br>**Gem+Carb** | Cost of other medical resources | Cost of other medical resources | Gamma (16, 45.5) | Mean value: £728 from literature (40)<br>SE is assumed to be 0.25 of the mean value |
| **Cost of terminal care (same across treatments)** | | | | |
| **Gem+Cisp**<br>**Gem+Carb** | Terminal care cost | Terminal care cost | Gamma (16, 91.25) | Mean value: £1,460 from literature (41)<br>SE is assumed to be 0.25 of the mean value |
| **Utility values for 'Progression-free' and 'Progression' states (same across treatments)** | | | | |
| **Gem+Cisp**<br>**Gem+Carb** | Utility value of 'Progression- free' state | Utility value of 'Progression-free' state | Normal (0.65, 0.08) | Expert opinion (Professor L. Billingham, University of Birmingham) |
| | Utility value of 'Progression' state | Difference between utilities of 'Progression-free' and 'Progression' states | Normal (0.2, 0.04) | |