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Adjusting estimates of the expected value of information for implementation: theoretical framework and practical application.

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Abstract

Background: Value of information (VoI) calculations give the expected benefits of decision making under perfect information (EVPI) or sample information (EVSI), typically on the premise that any treatment recommendations made in light of this information will be implemented instantly and fully. This assumption is unlikely to hold in health care; evidence shows that obtaining further information typically leads to 'improved', rather than 'perfect' implementation.

Objectives: To present a method of calculating the expected value of further research which accounts for the reality of improved implementation.

Methods: This work extends an existing conceptual framework by introducing additional states of the world regarding information (sample information, in addition to current and perfect information) and implementation (improved implementation, in addition to current and optimal implementation). The extension allows calculating the 'implementation-adjusted' EVSI (IA-EVSI), a measure that accounts for different degrees of implementation. Calculations of implementation-adjusted estimates are illustrated under different scenarios through a stylised case study in non-small cell lung cancer.

Results: In the particular case study, the population values for EVSI and IA-EVSI were £25 million and £8 million, respectively, thus a decision assuming perfect implementation would have overestimated the expected value of research by about £17 million. IA-EVSI was driven by the assumed time horizon and, importantly, the specified rate of change in implementation: the higher the rate, the greater the IA-EVSI and the lower the difference between IA-EVSI and EVSI.

Conclusions: Traditionally calculated measures of population VoI rely on unrealistic assumptions about implementation. This article provides a simple framework which accounts for improved, rather than perfect, implementation, and offers more realistic estimates of the expected value of research.

Keywords: value of information; implementation; health care decision making, health care research

Introduction

The increasing demand for evaluative research to support evidence-based clinical practice, coupled with the acknowledgment that decisions to fund such research from the public purse should be subject to the same scrutiny as any other investment of public resources, has given rise to calls for the use of analytic approaches in research prioritisation. [1-4]

A number of such approaches have been put forward as a means of estimating the potential value of research and informing funding decisions. [5-10] Prominent amongst them is 'value of information' (VoI), a methodological framework developed to assist with decision making under conditions of uncertainty. [11, 12] The framework builds on the acknowledgment that decisions made under uncertainty about their payoffs may turn out to be erroneous, and will be associated with an expected loss of benefits. Additional information is useful as it limits the scope for erroneous decisions and reduces this loss of benefits. In essence, VoI infers the value of pursuing additional information through research from the reduction in the expected loss of benefits. [13] Two main concepts in VoI are usually distinguished: the expected value of perfect information (EVPI) and the expected value of sample information (EVSI). [14, 15] EVPI shows the maximum benefits expected to accrue from eliminating uncertainty around a decision problem and is calculated as the difference between the expected benefits from a decision under perfect and current information. On the other hand, EVSI expresses the expected benefits of making a decision in light of sample information drawn from a particular study of a particular design, and it expresses the difference between the benefits expected under sample and current information.

Typically, VoI results represent the expected benefits of acquiring information on the premise of optimal implementation. In essence, it is effectively assumed that, should additional information become available, the decision maker would be able to choose the optimal course of action and this choice will be implemented instantaneously and comprehensively, so that the calculated expected benefits would be attained in full. While this assumption may be realistic for decisions related to other fields where VoI has found application—for example, a decision to purchase a specific piece of machinery [13] or use a particular type of remedial treatment for water contamination [16]—it is less likely to hold

true in health care. Indeed, evidence suggests that very rarely will a decision to recommend a particular course of action (e.g., a particular treatment) result in direct and optimal implementation in clinical practice [17-20]. In reality, many patients continue to receive care which is not considered to be optimal under the existing scientific evidence. [21, 22]

The fact that VoI estimates do not, in their current form, account for the reality of imperfect implementation has a notable implication: the estimated benefits from further research calculated assuming that research results will be perfectly implemented will be an overestimate of the benefits that would be realised under the reality of imperfect implementation. Presented with estimates that overlook the reality of imperfect implementation, a decision maker may favour research which will inevitably result in inferior returns, or even loss of benefits, should the true, 'realisable' benefits from research be lower than the cost of research.

While the need to adjust VoI measures for implementation has often been highlighted [14, 23, 24], the literature on the topic, at least in the health care field, is limited, with only a handful of studies looking into imperfect implementation in relation to value of information. [25-27] Prominent amongst them is an intuitive conceptual framework which proposes ways of assessing the expected value of implementation strategies. [25] However, this work sees the value of perfect information and the value of perfect implementation as related but separate measures. Thus, although in its current form the proposed framework does not aim to account for the impact of implementation on VoI estimates, it offers a useful platform for further extensions.

Within this context, we set out to present a methodology for adjusting VoI results for implementation. In doing so, it is acknowledged that the availability of additional information on the clinical and cost-effectiveness of a treatment is expected to have a bearing on the treatments' use in clinical practice, but it will not necessarily lead to instantaneous and perfect implementation. Adjustments are illustrated by extending the existing framework to include additional 'states of the world' related to information and implementation. The extension enables conceptualising and calculating the Implementation-Adjusted EVSI (IA-EVSI), a measure that expresses the expected returns to research adjusted for imperfect implementation.

Existing framework to accounting for implementation in VoI calculations

In an influential study on the topic, Fenwick *et al.* [25] acknowledge that imperfect implementation leads to inefficiencies and set out to present the monetary benefits expected from different states of the world, where each state represents a unique combination of available information and implementation (top half section of Box 1). In this framework, information is either 'current', (i.e., existing information available prior to any results from further research) or 'perfect', (i.e., a state of absolute certainty about the true payoffs of different actions). Implementation is expressed as a prescription share reflecting the proportion of eligible patients receiving a treatment of interest; this is either 'optimal', (i.e., all eligible patients receive the cost-effective treatment, or 'current' (i.e., only a proportion of the eligible patients receive the treatment that appears to be cost-effective). Rather than to adjust for the value of research, different states are combined to give distinct measures of the expected values of perfect information and implementation. These measures provides a necessary condition (or a 'first hurdle') for committing funds to further research or implementation, though they cannot indicate whether conducting a particular piece of research or undertaking a specific implementation initiative would be necessarily worthwhile..

In calculating the maximum expected benefits from further information or implementation, a key assumption is that acquiring additional information will not, in itself, have an impact on implementation, which will always remain at its current level unless active implementation strategies are put in place to alter it. Fenwick *et al.* [25] note that this is a somewhat simplistic view, as acquisition of information is likely to lead to a change in implementation. In the context of perfect information, this assumption is unavoidable; it is impossible to determine how acquisition of perfect information may affect implementation as the very concept of perfect information is a notional state of the world, serving to highlight the maximum expected returns to research. To identify the effect of implementation on the value of information, one needs to consider the expected benefits expected to accrue from sample, rather than perfect information.

Adjusted measures of information and implementation

The work presented by Fenwick *et al.* [25] offers an intuitive framework for examining the interrelation between information and implementation, and serves as a basis for further extensions. Two additional levels are introduced—sample information and improved implementation. These levels give rise to States K to O, presented in the bottom half part of Box 1.

State K represents a situation where sample information is available, but despite this, implementation remains at current levels. State L reflects a situation where the availability of sample information is followed by optimal implementation, that is, the treatment that is shown to be cost-effective is provided to the entire population of eligible patients). State O shows the pragmatic situation where sample information is available, and, in light of this information, there is a beneficial change in implementation (i.e., increase in the use of the treatment shown to be cost-effective and decrease in the use of non-cost-effective alternatives). This state can be thought of as occupying the 'middle' ground between states L and K. Large changes in uptake that tend towards optimal implementation approach state L, while limited changes would lead implementation levels towards state K. State N represents the situation where availability of perfect information is expected to drive implementation towards an improved level. While unattainable, this hypothetical state is conceptually useful in that it reflects the fact that perfect information may not necessarily lead to optimal implementation. On the other hand, state M reflects a situation where a change in implementation is brought about without obtaining further information. Such a change would be attributed to factors other than the availability of research results, such as effective promotion of the treatment by its manufacturer, availability of the treatment as a generic product at a lower cost etc. State M reflects a situation where there are improvements in the implementation of a decision made under current information. Although this state may be useful in estimating the value of strategies aiming to strengthen the implementation of decisions made under current information, this state is not directly relevant to the purposes of this study.

Two key pieces of information are needed for conceptualising this framework: estimates of the current level of implementation (i.e., current treatment shares) and predictions of the likely trajectory of implementation under two situations: with and without research taking place ('factual' and 'counterfactual' state, respectively). Under the factual state, information is needed on the rate of change in implementation over a given period of time (uptake rate), the total number of periods over which information will be useable (time horizon) and the ceiling level of implementation which may be reached at the end of the time horizon (saturation level). Under the counterfactual state, information is needed on the likely use of treatments in the absence of research results. In general, the availability of information is expected to lead to an increase in the uptake of the treatments shown to be cost-effective, and a decline in the use of non-cost-effective treatments. [28] However, in the absence of specific measures, implementation is likely to reach an 'improved' level, which is likely to be higher than 'current' implementation, but lower than 'optimal' implementation. [29, 30]

A series of measures of the value of information can be derived from combining different states of the world (Table 1). The difference between states D and C gives the EVPI for the population of eligible patients, a measure of the expected net monetary benefit (NMB) from a decision made with perfect, as opposed to current, information, assuming that the decision will be implemented optimally. The comparison between current and optimal implementation gives the expected value of perfect implementation (EVPIM). [25] Under current information, EVPIM shows the difference between providing the superior treatment to the whole population (state C) and continuing with current prescription shares (state A). This value represents the maximum expected gains from investing resources in the pursuit of better implementation of the treatment which is shown to be cost-effective under current evidence.

The difference between the value of a decision made with sample information and optimal implementation (state L), and one made with current information and optimal implementation (state C) gives the non-adjusted EVSI. In calculating this value, it is effectively assumed that the treatment shown to be cost-effective will be provided instantaneously to the entirety of the eligible patients.

Importantly, the difference in NMBs resulting from a state where sample information is available and triggers some change in implementation (i.e. leads to improved implementation), and the 'current' state where current information is available and implementation stays at current levels, gives an implementation-adjusted measure of the EVSI. The Implementation-adjusted EVSI (IA-EVSI) can be thought of as the returns to investing in sample information after accounting for the likely level of implementation, and comprises the benefits expected from the availability of improved information and the gains from a beneficial change in treatment use triggered by the emergence of this information. If the cost of research is known, subtracting this cost from the IA-EVSI can give a measure of the implementation-adjusted expected net benefit of sampling (IA-EBNS) which can be used as a reference point for specifying optimal study characteristics.

Illustrative case study

The extended framework is illustrated through a stylised example representing a decision to fund a clinical trial in non-small cell lung cancer (NSCLC). Advanced stage NSCLC patients eligible for chemotherapy are typically treated with third-generation chemotherapy combined with a platinum analogue—either cisplatin (Cisp) or carboplatin (Carb). [31] While both cisplatin and carboplatin are used widely in clinical practice, they present different toxicological profiles and, by extension, they are associated with different health outcomes and different levels of healthcare resource use. In light of this, a pertinent decision relates to whether public funds should be invested in a clinical trial looking into the effectiveness and cost-effectiveness of cisplatin and carboplatin, each combined with standard gemcitabine chemotherapy. The analysis involved three stages, which are described in turn below.

Decision modelling

A decision model was built to synthesise existing evidence and determine the cost-effectiveness of gemcitabine plus cisplatin (Gem+Cisp) and gemcitabine plus carboplatin (Gem+Carb) in light of this evidence. In brief, the model comprised three health states: progression-free (PG-F), progression (PG) and death (D). Key model parameters, including time to disease progression and death, costs and health related quality of life, were

assigned probability distributions. Results were expressed as cost per additional QALY and were translated into NMBs on the basis of a willingness-to-pay value of £30,000 for a QALY [32], other values are equally applicable. Details on the structure and parameter distributions used in the model are given in Appendix A.

VoI calculations

EVPI and EVSI analyses were carried out on the basis of output from the probabilistic model described above using established non-parametric methods. [33, 34] The process of calculating the EVSI is given in Appendix B. Calculations were based on a clinical trial employing 450 participants per arm, similar to the BTOG-2 clinical trial which has been proposed to compare Gem+Cisp and Gem+Carb in NSCLC. Individual patient EVPI and EVSI values were extrapolated to the population of eligible patients over a 5-year time horizon. The incidence of grade III/IV NSCLC patients eligible for platinum-combined chemotherapy was estimated to be 5680 per year. [35] The population EVPI and EVSI were discounted at 3.5% per year over the specified time horizon. Alternative values were used in sensitivity analyses.

Information on current implementation (i.e. the prescription share of each treatment) suggests an equal split between cisplatin and carboplatin across eligible patients. For the 'factual' state, treatment uptake rates under 'improved implementation' were based on assumptions informed by discussions with experts in cancer treatment commissioning. In the 'base case' analysis of this illustrative study, it was hypothesised that the prescription share of the treatment shown to be cost-effective would increase by 5 percentage points per year in a linear fashion, starting from the current level of 50% and reaching a saturation level of 75% at the end of the 5-year time horizon. Equivalently, the use of the non-cost-effective treatment (Gem+Carb) was assumed to decrease linearly from 50% to 25% over the 5 years (Figure 1). In the absence of research, it is assumed that implementation of Gem+Cisp and Gem+Carb will remain at current levels. Different scenarios were explored in sensitivity analyses.

Sensitivity analysis

Different assumptions around the likely trajectory of implementation were assessed in sensitivity analyses. These involved using non-constant uptake rates which reflect functions commonly employed to represent patterns of diffusion and adoption of technologies over time [36], as well as different saturation levels. Additional analyses were carried out to explore the impact of different time horizons over which information was assumed to be useful, different discount rates and change in the annual incidence of eligible lung cancer patients projected on the basis of current trends. [37]

Results

Cost-effectiveness analysis

Results of the cost-effectiveness analysis suggested that Gem+Cisp is less costly and more effective than Gem+Carb, resulting in mean cost savings of approximately £175 and a mean gain of 0.017 QALYs per patient. At a ceiling ratio of £30,000 the results translate into £11,036 and £10,356 NMBs for Gem+Cisp and Gem+Carb, respectively. At the particular threshold, the probability of Gem+Cisp being more cost-effective than Gem+Carb is 0.58.

Value of information measures

The expected NMBs for different states of the world, and different measures calculated from different combinations are given in Tables 2 and 3, respectively. The EVPI for the population of eligible patients was estimated at £31 million. This value represents the maximum possible returns to acquiring additional information around the specific decision problem, and it can be seen as the upper limit to the resources that could be devoted to pursuing further information.

Under current information, that is, with Gem+Cisp being superior to Gem+Carb, the maximum expected gains from investing resources in the pursuit of better implementation (i.e. the EVPIM) is £9.04 million. The non-adjusted EVSI for the eligible population amounted at £24.99 million, while the IA-EVSI was estimated to be £8.04 million. The latter value

shows the returns to investing in sample research, accounting for the fact that the availability of further information from this research may lead to less than optimal implementation. Figure 2 shows the values of EVPI, EVSI and IA-EVSI calculated at £30,000 per QALY in each time period across the hypothesised time horizon. Both EVPI and EVSI decrease with time owing to discounting. In the case of IA-EVSI, the decrease due to discounting is offset by additional benefit brought about by increases in implementation, that is, increases in the number of eligible patients being offered the treatment which is shown to be cost-effective. The population EVPI, EVSI and IA-EVSI for different values of willingness to pay for a unit of benefit are given in Figure 3.

Impact of alternative assumptions on results

The values of EVPI, EVSI and IA-EVSI calculated on the basis of different assumptions can be seen in Table 4. EVSI and IA-EVSI were greater than their respective base case values when i) future benefits were not discounted (as opposed to discounted at 3.5%); ii) a longer time horizon was specified (10 and 20 years, as opposed to 5 years in base case), and iii) a greater saturation level was specified (85% and 95%, as opposed to 75%). IA-EVSI was lower than the base case value when: i) future benefits were discounted at 6% (as opposed to 3.5%), ii) the specified time horizon was set to be 2 years (as opposed to 5 years) and iii) the annual incidence of eligible patients decreased, in line with observed trends in new cases of NSCLC in the UK. [37, 38]

The change in IA-EVSI compared to the base case IA-EVSI value ranged from a decrease by 57% (when time horizon was set to 2 years) to an increase by 186% (time horizon of 20 years) (Figure 4 online supplement). Alternative assumptions had an effect on the difference between EVSI and IA-EVSI. Compared to the base case value (i.e., £16.5 million), this difference increased when future NMBs were not discounted, as well as when the time horizon was set to be greater than the base case value of 5 years (i.e., 10 and 20 years). On the other hand, the difference between EVSI and IA-EVSI decreased (as compared to the respective base case value) under the assumptions of i) declining incidence of eligible patients, ii) shorter time horizon (i.e. 2 years) and iii) higher saturation levels (85% and 95%) (Figure 5 online supplement).

Different patterns of uptake were explored; these included a 'sigmoid' curve which is often used to represent trends in diffusion and adoption of technologies, as well as curves representing scenarios under which clinical practice is assumed to be more and less responsive to research results (Figure 6 online supplement). The uptake rate does not affect the EVSI as this measure is calculated on the premise of a fixed (optimal) level of implementation. In line with expectations, greater uptake rates which would be realised sooner across the specified time horizon (such as in the 'responsive' case) would lead to greater (lower) numbers of patients receiving cost-effective (non-cost-effective) treatments, higher IA-EVSI and smaller differences between IA-EVSI and EVSI (Figure 7 online supplement).

Discussion

Traditionally, VoI measures have been calculated on the assumption that a decision made under further information will be implemented instantaneously and in full. Although new information is shown to trigger an increase in implementation [28, 39, 40], a decision is unlikely to be fully and instantaneously implemented. [22] In light of additional information, treatment uptake will often be greater than 'current', but lower than 'optimal'.

Failing to adjust for this reality has important consequences for decision making. Assuming that implementation will be optimal, non-adjusted EVSI would overestimate the value of further research, which would inevitably lead to sub-optimal funding decisions and inefficient use of research resources. In the particular example, the non-adjusted EVSI—that is, the expected benefit under the assumptions that every single eligible patient will be treated with the optimal treatment—is £24.99 million. Should a study in NSCLC cost less than this amount—for example £10 million—a decision to fund and conduct the study will be thought to be beneficial, leading to a gain of approximately £15 million in NMB. After adjusting for implementation, the expected EVSI is reduced to £8.04 million, nearly £17 million lower than the non-adjusted EVSI. This difference can be seen as the loss of benefit due to imperfect implementation, which is not accounted for in unadjusted EVSI calculations. Given a hypothetical cost of research of £10 million, conducting the study would not cost-effective, leading to a loss of almost £2 million.

While the reality of imperfect implementation in respect to VoI has been acknowledged [23, 24, 41], the literature around ways of addressing this issues is scant. Apart from the work of Fenwick *et al.* [25] described earlier, only one study proposing a way of dealing with the issue was found in the literature [27]. In this study, Willan and Eckermann set out to relax the assumption of perfect implementation when calculating expected net gains (i.e. the difference between EVSI and a study's expected total cost). This work is set in a context where current evidence is in favour of a new treatment and no further information is expected. Under this scenario, the authors present a way of specifying an economically optimal design for a clinical trial by accounting for the fact that greater sample sizes will lead to stronger evidence and may result in higher uptake rates. In this study, EVSI and expected net gains were calculated through a parametric approach, which assumes that outcomes (for instance NMBs) follow a particular distribution. While the methodology is rigorous, its applicability is constrained by the fact that in many cases, outcomes are unlikely to follow a particular distribution, especially when these come from decision models which combine evidence from diverse sources. [33, 34] As VoI analyses are increasingly carried out on the basis of the simulated output of decision models, our work provides a nonparametric framework which is applicable to a wider range of analytic calculations.

Different factors have a bearing on the results. First, there exist factors which are inherent to VoI analysis and are known to affect the calculation of individual-patient VoI. These include the degree of uncertainty (and, by extension, the expected opportunity loss due to uncertainty) associated with a decision and the monetary value attached to the loss of a unit of benefit, typically represented by a willingness-to-pay threshold. The impact of these factors on VoI measures is well documented. [34] In addition, there exist factors which affect the population VoI. These relate to the number of patients who are expected to benefit from the availability of additional information, and depend on the number of eligible patients per period of time, the time horizon over which information is expected to be useful, and the rate of change in the uptake of a treatment per period of time. The latter has a key effect on the magnitude of the IA-EVSI and the difference between IA-EVSI and other measures of VoI.

High uptake rates will push implementation towards an optimal level. As implementation approaches an optimal level, the IA-EVSI will increase and the difference between IA-EVSI and EVSI will decrease. Further, the shorter the period of time until implementation reaches the 'saturation' level, the lower the number of patients not receiving the optimal treatment, the greater the IA-EVSI and the greater the difference between IA-EVSI and EVSI. A longer time horizon will effectively inflate the number of patients that are affected by the availability of improved information, increase the expected benefit in the population and make further research appear more desirable. A similar effect is expected if the incidence of eligible patients increases over time. The difference between EVSI and IA-EVSI for longer time horizons or greater incidence will be primarily affected by the rate by which implementation increases.

Our work has certain limitations In particular, the case study is based on a simple three-state model. Arguably, a more sophisticated model structure would give more accurate estimates of cost-effectiveness and the uncertainty around them, and more accurate VoI results. In addition, for pragmatic reasons, EVSI was calculated for the uncertainty around the main clinical determinants of the decision problem (i.e., the rates of disease progression and death) rather than all parameters for which a trial may provide further evidence. EVSI calculations on the basis of all possible parameters would be complex and computationally challenging. [34] Similarly, calculations were carried out for a single sample size, which reflects that sample size proposed in a study looking at the particular decision problem in NSCLC (BTOG-2 trial). However, these limitations need to be seen in light of the purpose of the study to illustrate the proposed methodology, rather than to inform actual treatment or research recommendations. As the above limitations are specific to the particular application, it is argued that they do not affect the degree to which the proposed method would be applicable to a more rigorous stylized example, or to a different decision problem. If, for example, the interest is on research evaluating a new, rather than a commonly used treatment, the presented methodology would be equally applicable, with the difference that, in this case, implementation would be expected to start from a very low level.

Evidently, the proposed adjustment requires additional information in the form of estimates of treatments' change in uptake over time. Once such estimates are specified, additional

calculations are minimal and can be readily carried out in widely-available spreadsheet applications. In the presented stylised case study, likely uptake estimates were specified on the basis of expert opinion. Alternatively, estimates may be drawn from different sources, including historic data showing trends in the uptake of technologies and expert consensus exercises using appropriate elicitation techniques. Importantly, in specifying the uptake rate to be included in the calculations, one needs to account for the interplay between different factors which are expected to affect implementation. [42, 43] Such factors may include the strength and quality of the existing and new evidence, the effectiveness of the employed dissemination strategies, the nature of the technology and the extent to which change is practical and feasible (availability of materials and facilities, training needed in using the technologies etc.) and the nature of the regulatory arrangements in the particular setting [9, 44-46]. Inevitably, estimates of future uptake rates will be, in essence, guesses surrounded by uncertainty. However, the use of uncertain information in VoI analysis—for example, the number of years for which the information will be relevant, or the value of willingness to pay for a QALY—is unavoidable and has not precluded the calculations of VoI measures in the first place. Rather than disregarding any proposed adjustments, we argue that efforts should be directed towards ensuring that employed assumptions are made explicit, are plausible, and are based on the best available knowledge.

Faced with finite budgets, public funding organisations are increasingly interested in ensuring that available research resources are allocated efficiently. While VoI analysis offers useful input in this process, it is important that VoI calculations are adjusted to take into account special characteristics of the particular context. We propose a simple and intuitive methodology through which researchers can adjust VoI estimates for implementation. We believe that the proposed adjustments provide further assurance that VoI calculations are not limited by unrealistic assumptions, and are likely to strengthen the case for greater use of VoI in research prioritisation.

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Box 1. Existing and extended matrices showing additional possible states of the world in relation to information and implementation.

Framework introduced by Fenwick et al.

Possible 'states of the world'		Information	
		Current	Perfect
Implementation	Current	A	B
	Optimal	C	D

- $State\ A = \ Pop \times \sum_j (P_j^c \times E_\theta NMB(j,\theta))$
- $State\ B = Pop \times E_\theta \sum_j (P_j^c \times NMB(j,\theta))$
- $State\ C = Pop \times \sum_j (P_j^o \times E_\theta NMB(j,\theta))$
- $State\ D = Pop \times E_\theta \sum_j (P_{j,(\theta)}^o \times NMB(j,\theta))$

Here, Pop represents the eligible population of patients, P_j^c and P_j^o represent the proportion of patients taking treatment j given current implementation and optimal implementation, respectively, while θ represents the uncertain parameter(s) affecting the decisions for which more information is considered.

Extended framework. The framework consists of 5 additional states (K, L, M, N and O). The Net Monetary Benefits associated with each of the additional states are calculated as follows.

Possible 'states of the world'		Information		
		Current	Perfect	Sample
Implementation	Current	A	B	K
	Optimal	C	D	L
	Improved	M	N	O

- $State\ K = [\sum_t AEP_t] \times E_D \sum_j (P_j^c \times E_{\theta|D}\ NMB(j,\theta))$
- $State\ L = [\sum_t AEP_t] \times E_D\ \sum_j (P_j^o(D) \times E_{\theta|D}\ NMB(j,\theta))$
- $State\ M = \sum_t \left[AEP_t \times \sum_j (P_j^i(t) \times E_\theta NMB(j,\theta))\right]$
- $State\ N = \sum_t [AEP_t \times E_\theta \sum_j (P_j^i(t;\theta) \times NMB(j,\theta))]$
- $State\ O = \sum_t [AEP_t \times E_D \sum_j (P_j^i(t;\ D) \times E_{\theta|D} NMB(j,\theta))]$

Here, AEP_t represents the number of eligible patients per year t, D is a sample drawn from the prior distribution of the parameter(s) θ, and P_j^c, P_j^o and P_j^i shows the treatment uptake or proportion of patients taking treatment j given 'current', 'optimal' and 'improved' implementation, respectively.

Table 1. Measures of value of information and implementation

Measure	
Expected value of perfect information (EVPI)	Perfect information, optimal implementation (state D) – Current information, optimal implementation (state C)
Expected value of perfect implementation (EVPIM)	Current information, optimal implementation (state C) – Current information, current implementation (state A)
Expected value of sample information (EVSI)	Sample information, optimal implementation (state L) – Current information, optimal implementation (state C)
Implementation-adjusted EVSI (IA-EVSI)	Sample information, improved implementation (state O) – Current information, current implementation (state A)

Table 2. Revised expected NMBs (in £ million) for different states regarding information and implementation

		Information		
		Current	**Perfect**	**Sample**
Implementation	**Current**	A £284,08 million	B £284,08 million	K £284,080 million
	Optimal	C £293,12 million	D £324,12 million	L £318,11 million
	Improved	M £286,28 million	N £293,81 million	O £292,12 million

Table 3. Expected NMB (in £ million) for different measures of information and implementation

Measure	NMB (at £30,000 per QALY)
EVPI	£30,998,377
EVPIM	£9,037,517
EVSI	£24,988,125
IA-EVSI	£8,040,626

EVSI: expected value of perfect information; EVSI: expected value of sample information; IA-EVSI: implementation-adjusted expected value of sample information.

Table 4. EVPI, EVSI and IA-EVSI for different assumptions explored in sensitivity analyses.

	EVPI	EVSI	IA-EVSI
Base case	£30,998,377	£24,988,125	£8,040,626
Discount rate			
0% per year	£33,166,972	£26,736,252	£8,855,744
6% per year	£29,618,806	£23,876,038	£7,526,637
Time horizon			
2 years	£13,042,471	£10,513,676	£3,451,348
10 years	£57,098,179	£46,027,456	£14,349,885
20 years	£97,576,152	£78,657,185	£22,987,109
Saturation level			
85%	£30,998,377	£24,988,125	£11,379,379
95%	£30,998,377	£24,988,125	£14,718,132
Incidence			
0.49% decrease per year	£30,708,020	£24,754,065	£7,932,139
EVSI: expected value of perfect information; EVSI: expected value of sample information; IA-EVSI: implementation-adjusted expected value of sample information.			

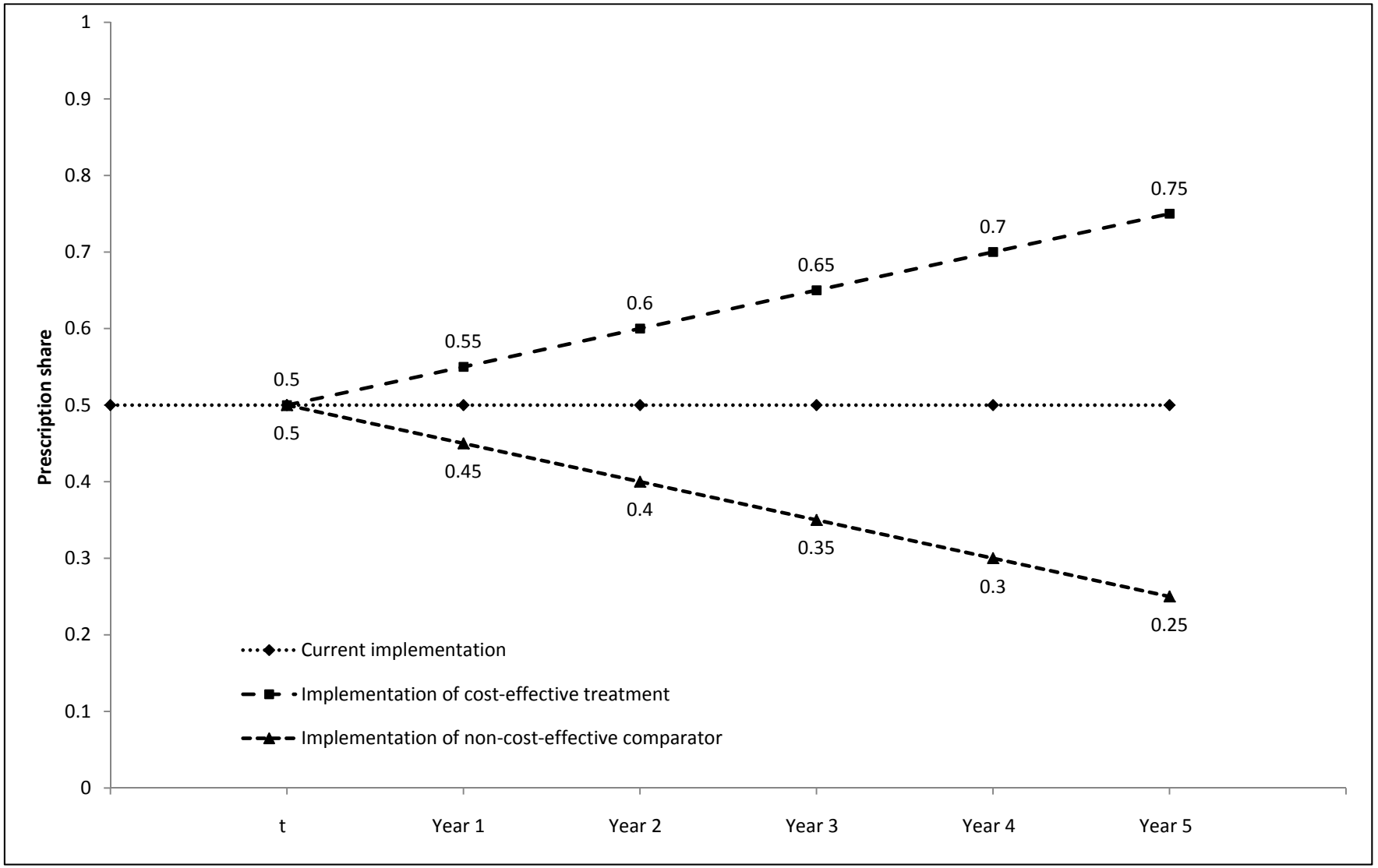
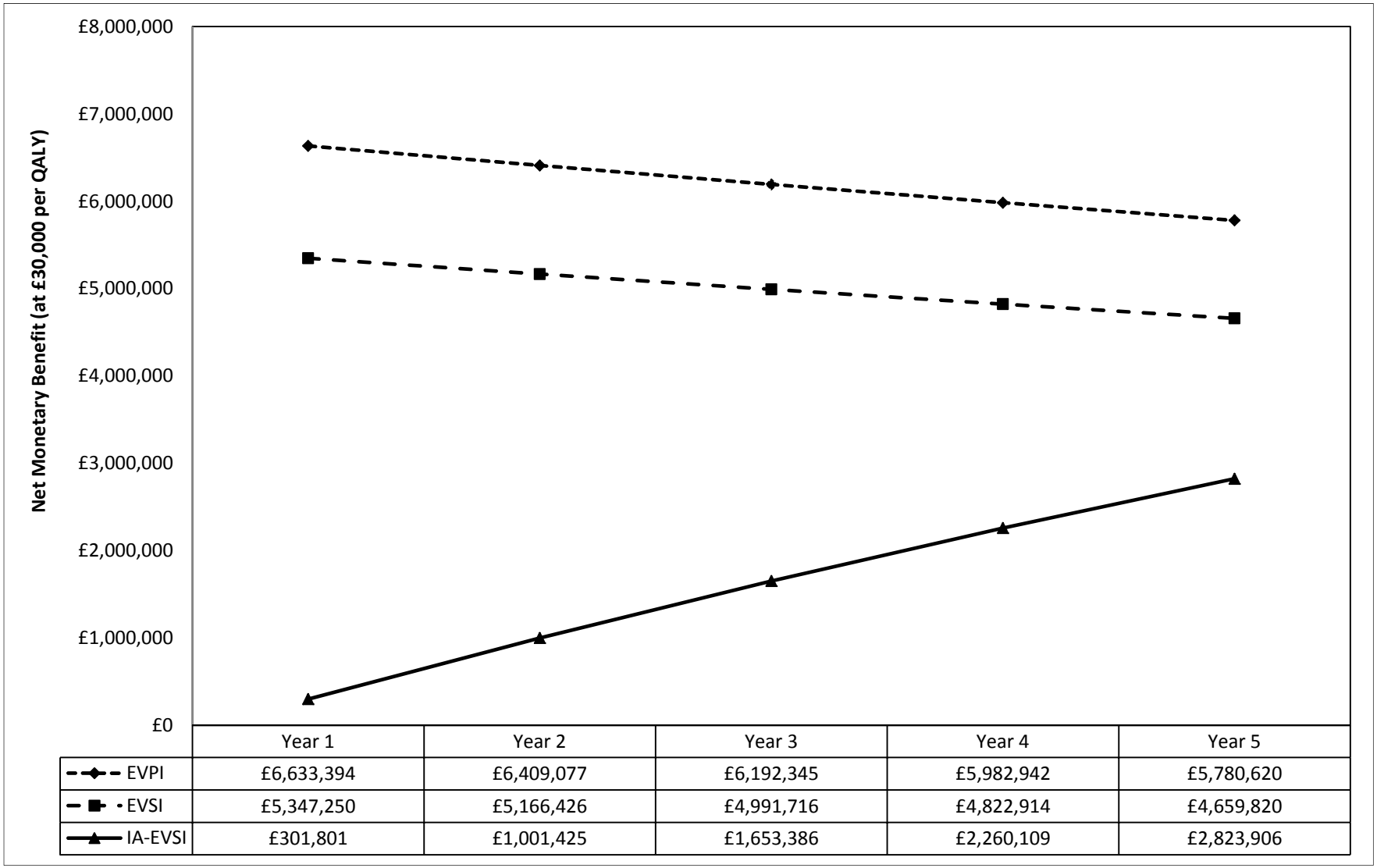


Figure1. Illustrative trajectory of treatment uptake



	Year 1	Year 2	Year 3	Year 4	Year 5
EVPI	£6,633,394	£6,409,077	£6,192,345	£5,982,942	£5,780,620
EVSI	£5,347,250	£5,166,426	£4,991,716	£4,822,914	£4,659,820
IA-EVSI	£301,801	£1,001,425	£1,653,386	£2,260,109	£2,823,906

Figure 2. EVPI, EVSI and IA-EVSI per year over 5 years

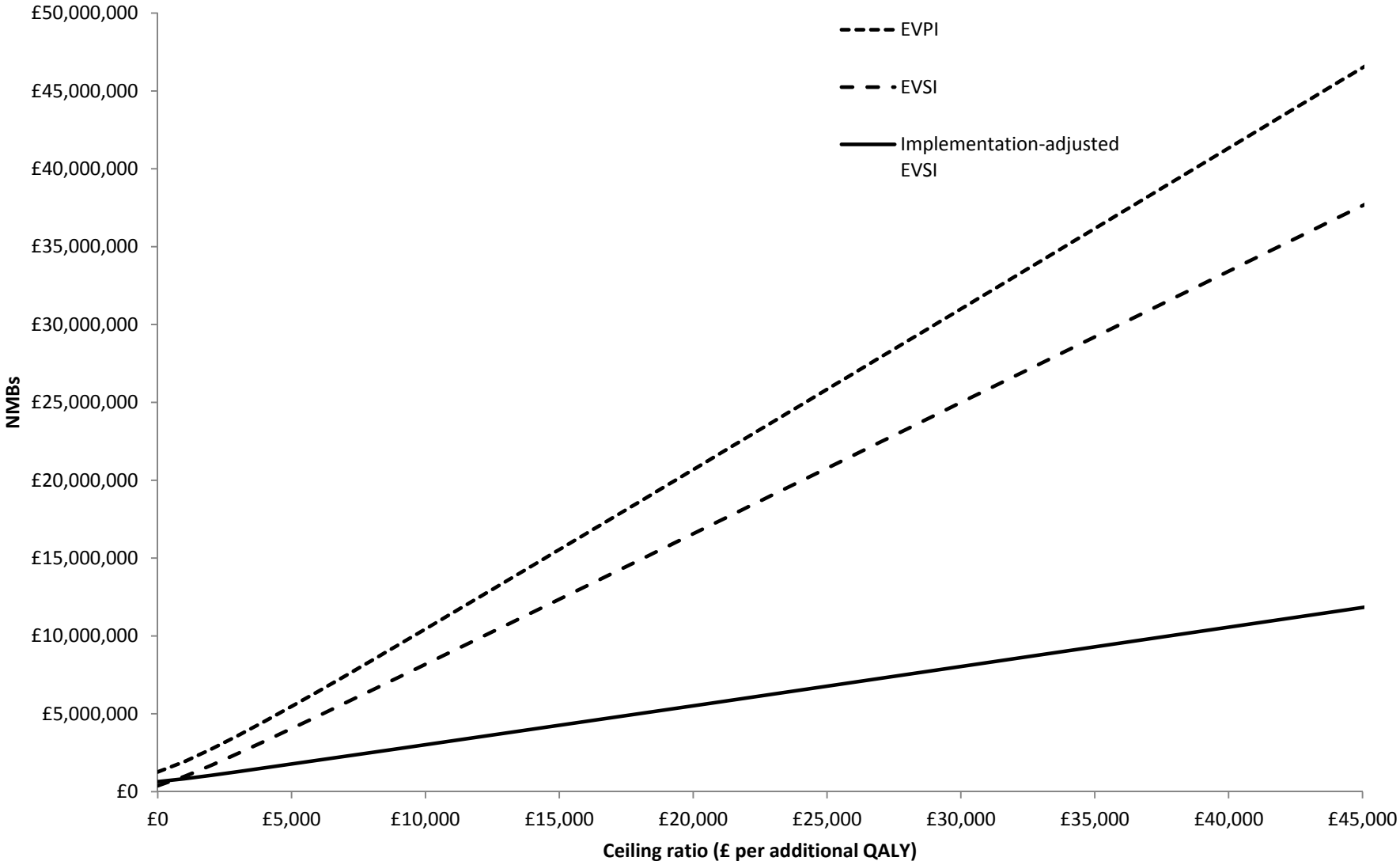


Figure 3: Measures of the expected value of information and implementation for different for different cost-effectiveness ratios.

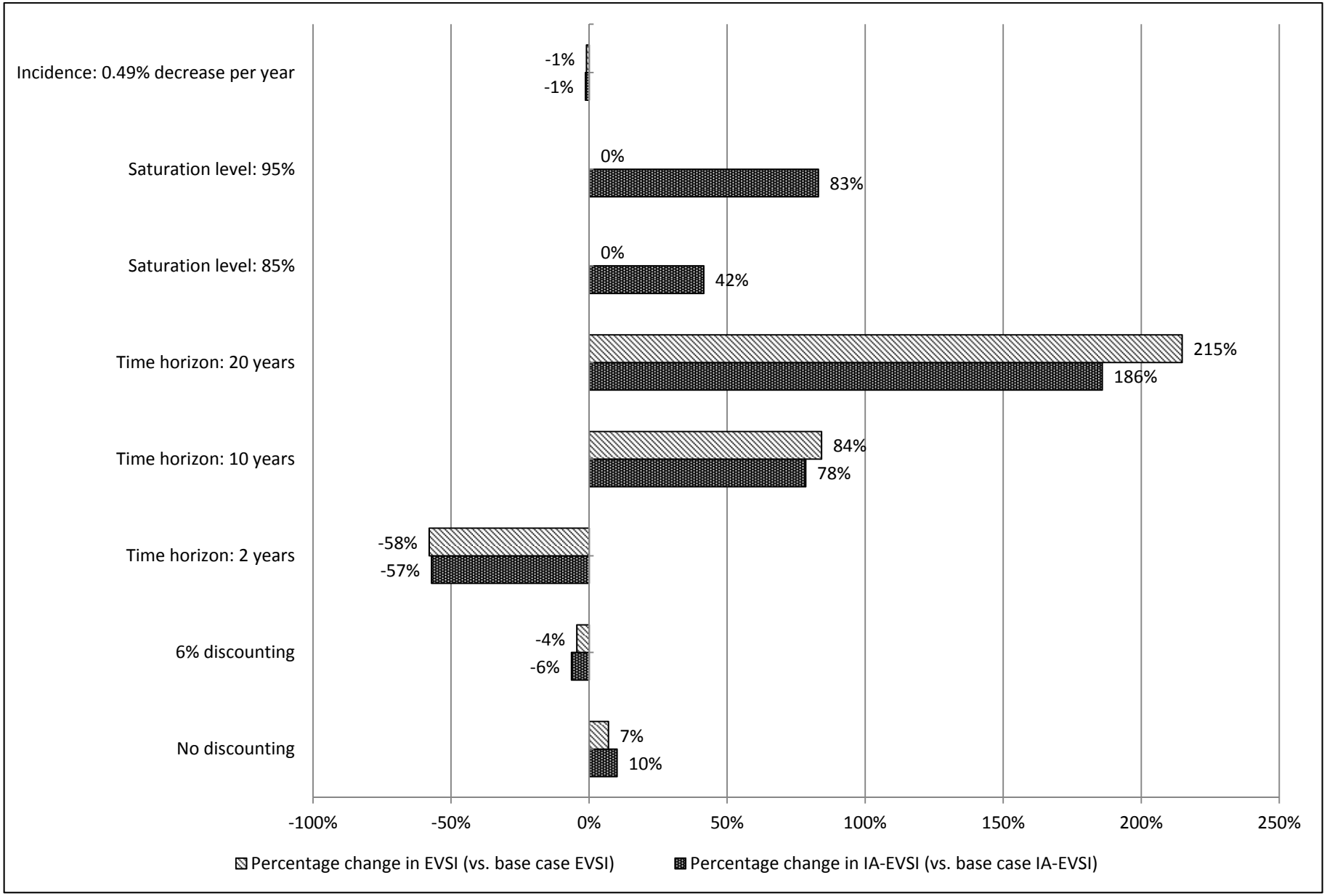


Figure 4 (online supplement). Percentage change of EVSI and IA-EVSI for different assumptions as compared to their base case values.

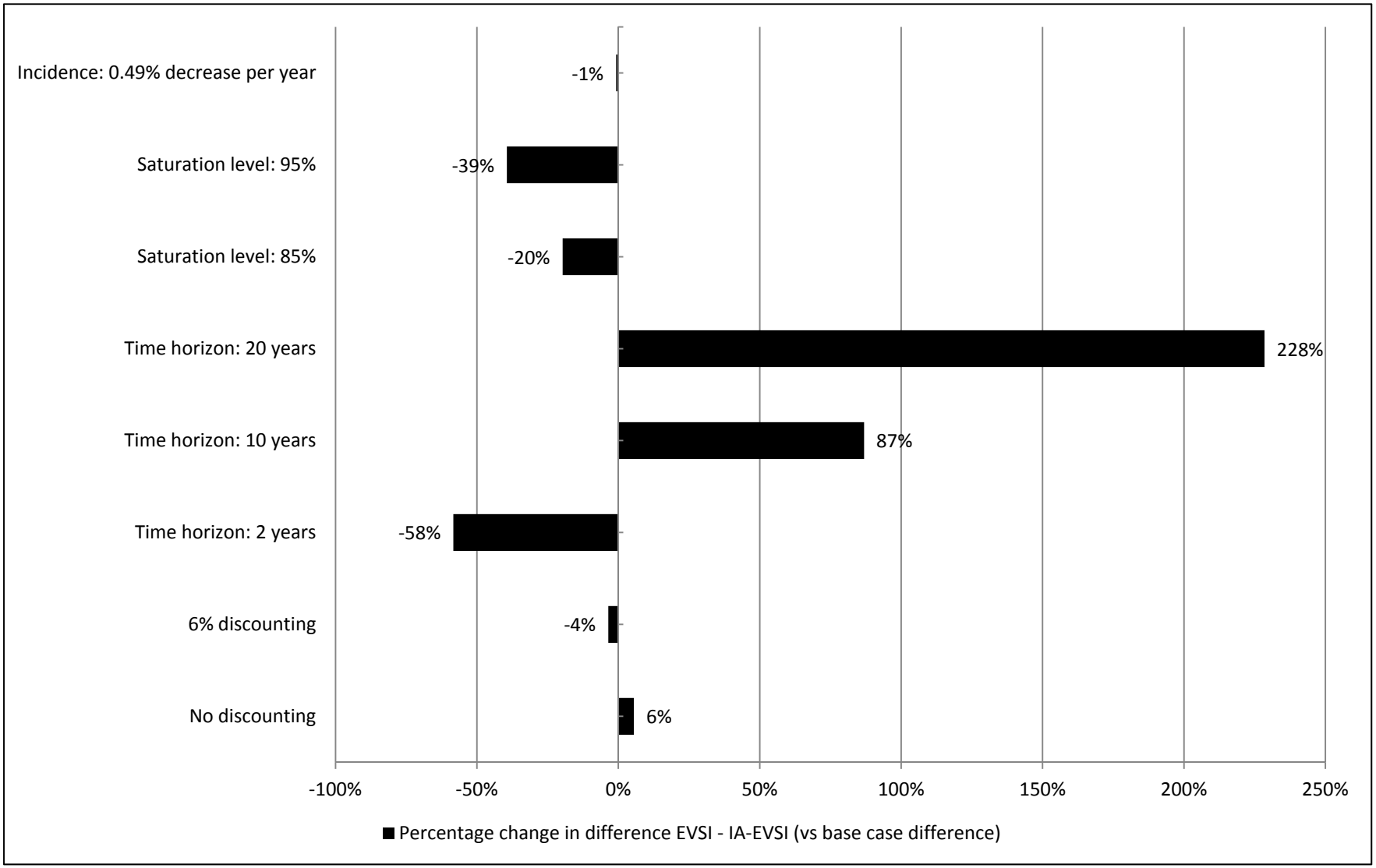


Figure 5 (online supplement). Percentage change in the difference between EVSI and IA-EVSI for different assumptions compared to the respective difference in the base case analysis.

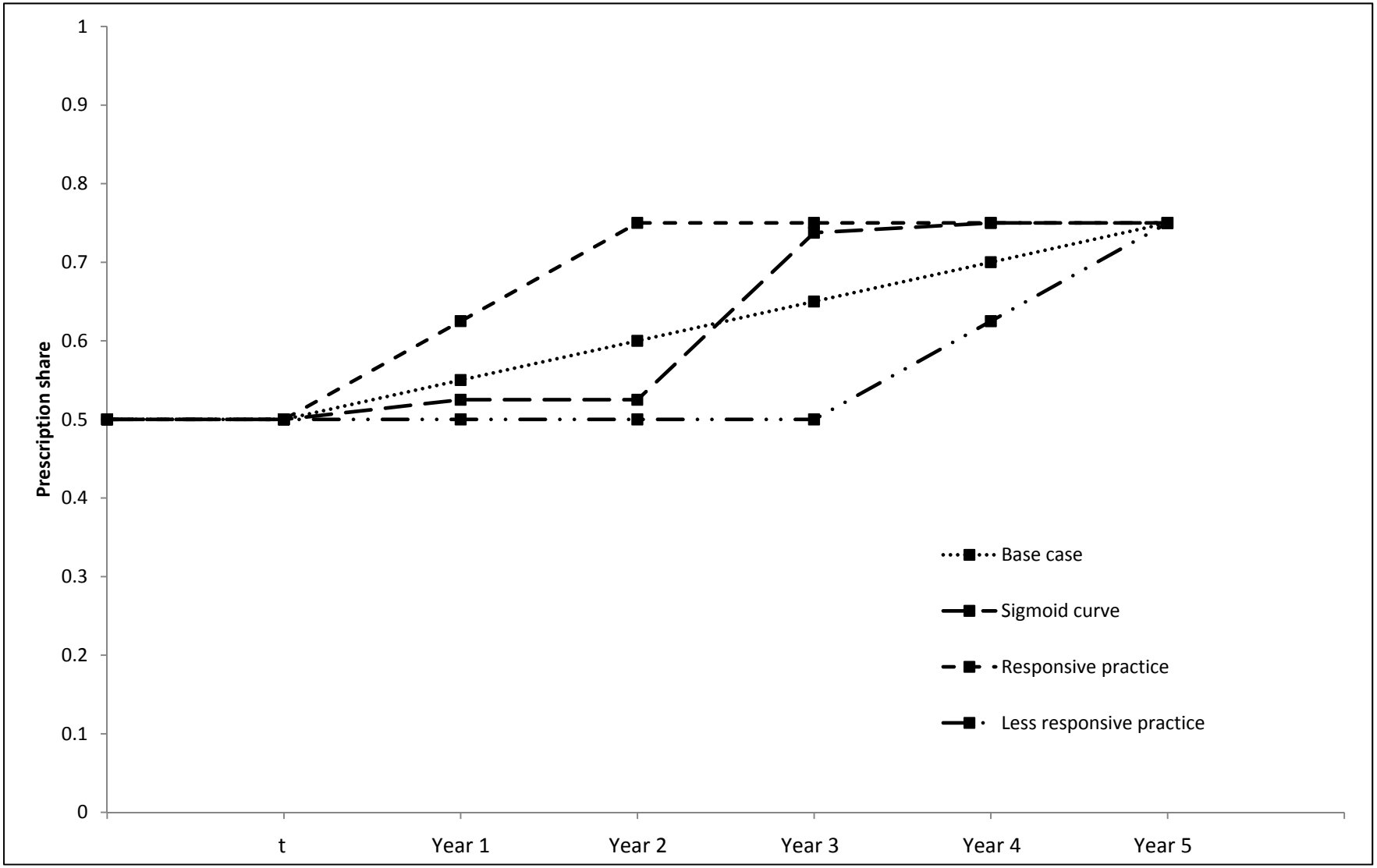


Figure 6 (online supplement). Alternative implementation trajectories assessed in sensitivity analyses

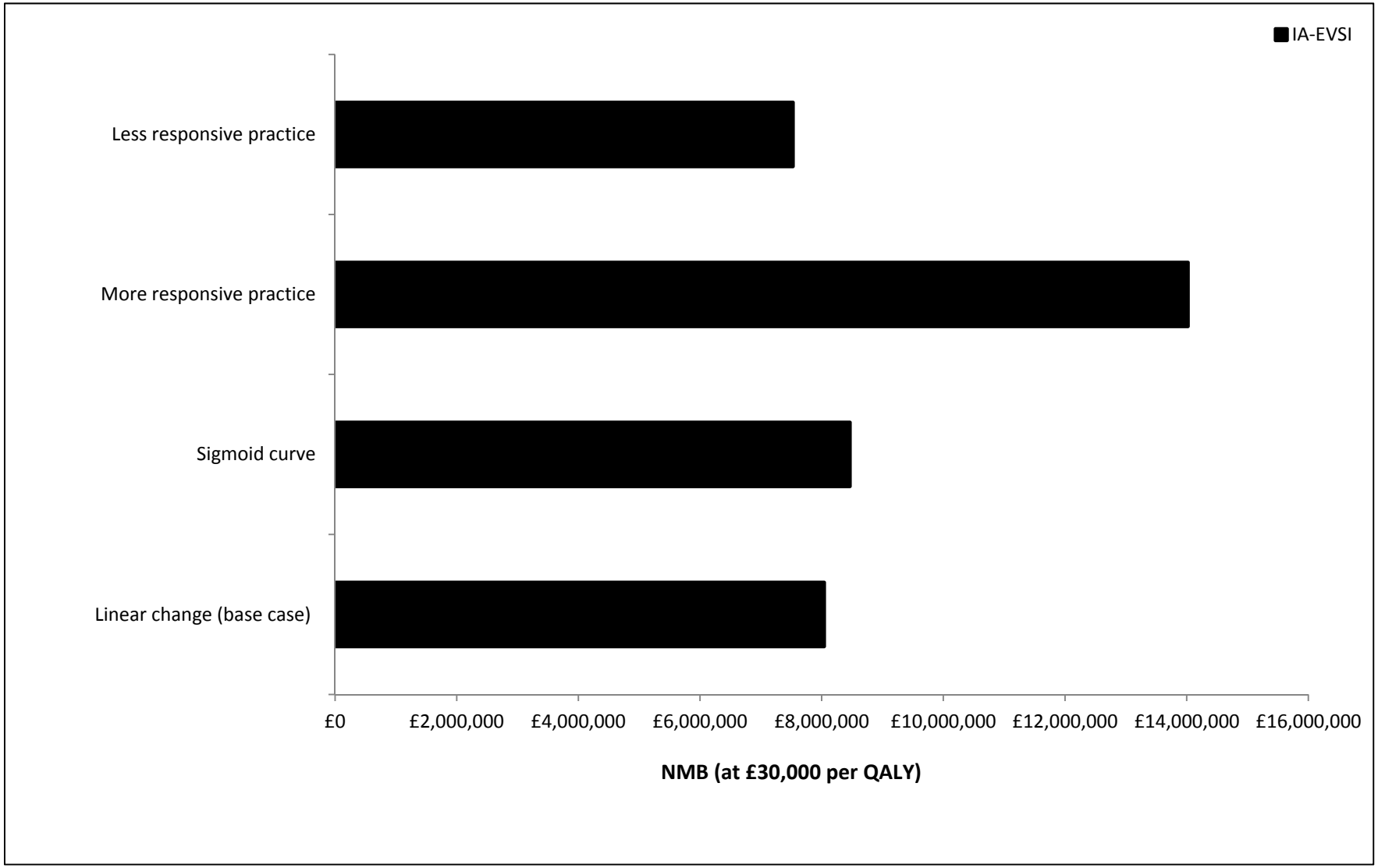


Figure 7 (online supplement). IA-EVSI for different implementation trajectories employed in sensitivity analyses

Appendix A. Non-small cell lung cancer model

This decision model aims to assess the cost-effectiveness of Gem+Cisp and Gem+Carb in patients with non-small cell lung cancer (NSCLC) and 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.

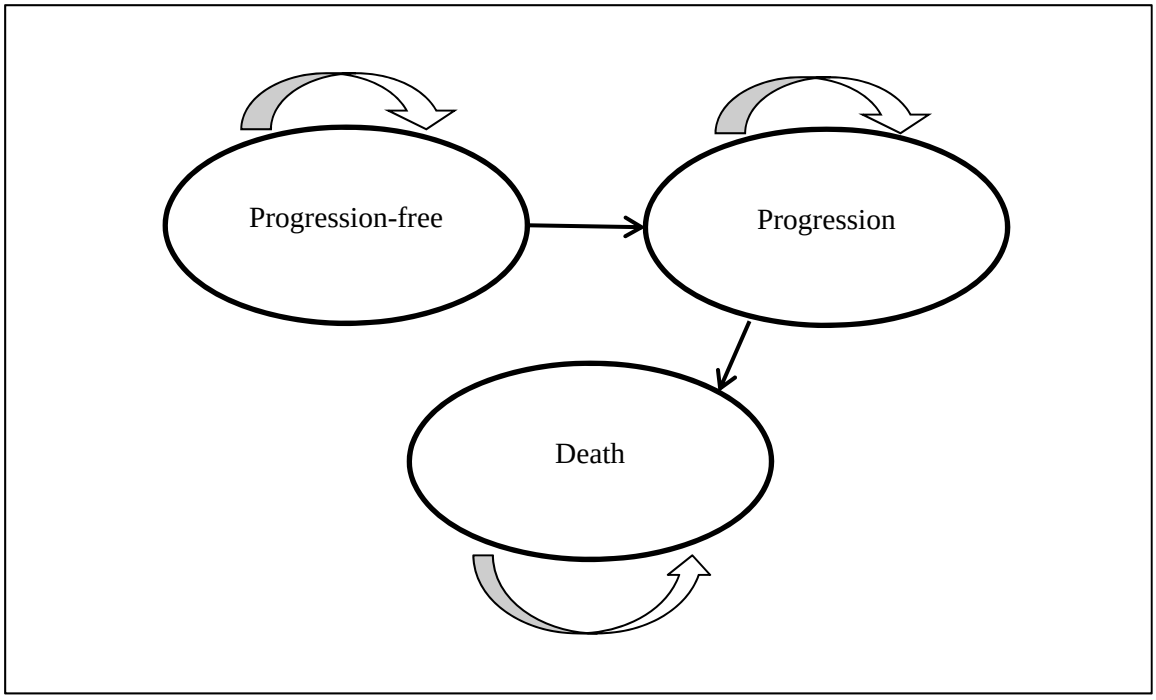


Figure 1 in Appendix A. NSCLC model

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 [47]. 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. Estimates of preference-based quality of life (utility) were taken from the study by Nafees et al. [48] 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 [47]
Gem+Carb			Intercept Normal (-2.475,0.110) Regression coefficient Normal(1.287, 0.048)	Literature [47]
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 [47]
Gem+Carb			Intercept Normal (-3.350, 0.209) Regression coefficient Normal(1.302, 0.077)	Literature [47]
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	Anaemia: Beta (10.58, 73.42) Thrombocytopenia: Beta (13.78, 70.22)	Literature [47]

		events	Neutropenia: Beta (7.98, 76.02) Granulocytopenia: Beta (19.74, 64.26)	
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 [47]
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 [49] 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 [50] 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 (0.653, 0.02)	Literature [48]
	Utility value of 'Progression' state	Difference between utilities of 'Progression-free' and 'Progression' states	Normal (0.18, 0.02)	

Appendix B: Calculation of EVSI (online supplement)

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 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 particular study, 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. [47] through a model representing survival (or progression) S(t) in a linear form:

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

Regressing $\ln[\text{-}\ln S(t)]$ 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.

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 trial (n=450) 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. Draw a large number of values (e.g., m =1000) from each of the posterior distributions obtained in step 3, and calculate the resulting NMBs for each treatment j through Monte Carlo simulations in the NSCLC model. Each of the obtained 1000 sets was entered in the NSCLC 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 NMB ($E_D max_j\ E_{\varphi|D}\ NMB\ (j,\varphi)$). 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.