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Assessing the expected value of research studies in reducing uncertainty and improving implementation dynamics

Running title: Assessing the dynamic value of research

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ABSTRACT

Background: With low implementation of cost-effective health technologies being a problem in many health systems, it is worth considering the potential effects of research on implementation at the time of health technology assessment. Meaningful and realistic implementation estimates must be of dynamic nature.

Objective: To extend existing methods for assessing the value of research studies in terms of both reduction of uncertainty and improvement in implementation by considering diffusion based on expert beliefs with and without further research conditional on the strength of evidence.

Methods: We use expected value of sample information and expected value of specific implementation measure concepts accounting for the effects of specific research studies on implementation and the reduction of uncertainty. Diffusion theory and elicitation of expert beliefs about the shape of diffusion curves inform implementation dynamics. We illustrate the use of resulting dynamic expected value of research in a pre-term birth screening technology and results are compared with those from a static analysis.

Results: Allowing for diffusion based on expert beliefs had a significant impact on the expected value of research in the case study, suggesting that mistakes are made where static implementation levels are assumed. Incorporating the effects of research on implementation resulted in an increase in the expected value of research compared to expected value of sample information alone.

Conclusions: Assessing the expected value of research in reducing uncertainty and improving implementation dynamics has the potential to complement currently used analyses in health technology assessments, especially in recommendations for further research. The combination of expected value of research, diffusion theory and elicitation described in this paper is an important addition to the existing methods of health technology assessment.

Introduction

Implementation of new health technologies has been noted to be low in many countries(1-3). While this is commonly highlighted as a brake on innovation, it also leads to inefficiencies in the health system when the new technologies have been shown to be cost-effective. These inefficiencies pose a burden to the payer in terms of money lost that could be spent more effectively elsewhere, and to patients in terms of health lost. In the United Kingdom (UK) National Health Service, for instance, getting cost-effective technologies into practice has been declared a priority(2). Despite this, there is no standardised procedure in place in the UK that allows an evaluation of implementation measures at the time of health technology assessment(4). In fact, the National Institute for Health and Care Excellence (NICE) does not have a mandate to recommend implementation measures, although it can recommend that further research be conducted if there is large decision uncertainty(4).

Such Recommendation with Research (RwR) or Only in Research decisions can be considered using an existing framework on coverage decisions(5, 6) and can be assessed for their value using expected value of information (EVI) methods(7). However, to our knowledge, the EVI methods used in practice do not consider the effect that the recommended research studies may have on the dynamics of health technology implementation, although other research has shown this to be possible(8). This is an omission because further evidence can influence the implementation of a new health technology(8) and reduce the opportunity cost that low implementation poses to the payer. Research can be designed to address decision uncertainty present in technology assessments, and to improve implementation(8, 9), thereby improving the use of strategies and resources in a budget constrained health system(10).

Acknowledging the importance of health technology implementation to the design of research studies, the effect of imperfect implementation on the value of research studies has been considered previously(8, 11). Willan and Eckermann(8) provide an important contribution to decision-making by presenting a framework for estimating the value of research allowing for imperfect implementation, and by modelling the effect of research evidence on implementation as a function of the strength of evidence. The authors use an analytic solution to calculate the expected value of sample information (EVSI), assuming normality of the expected incremental net benefit distributions(8). The authors further demonstrate that the optimal research design could be found by maximising the expected net gain (that is the EVSI compared to trial costs) associated with different designs(8). The authors found that the EVSI increased with imperfect implementation, which was explained by the expected opportunity loss increasing with imperfect implementation (where a proportion of patients are on the treatment that is expected to be less cost-effective) and the positive effect of research evidence on implementation. In contrast to this, another study that incorporated imperfect implementation in EVSI calculations asserted that EVSIs without adjustments for imperfect implementation are over-estimated(12). This misleading conclusion resulted from not appropriately incorporating the

counterfactual cases with and without further trial evidence(13) and extending an existing framework(9) by adding further static frames(13).

For research studies or implementation strategies that were evaluated in the past, the dynamic nature of implementation was not considered. Instead, the future levels of implementation that could be expected with investment in implementation measures and research were modelled as though fixed levels of implementation arose immediately with such investment and remained at the same current level without investment(8, 14, 15). A further limitation of some research studies is the omission of the counterfactual development of implementation of doing nothing(14). Only two studies have attempted to model implementation dynamics and included a counterfactual. One fitted simple regression methods to extrapolate future implementation(16) without linking to existing diffusion theory(17); and another study extrapolated an s-shaped curve with a passing reference to diffusion theory but without any behavioural parameterisation of it(18). The reason for these omissions may be because the estimation of potentially low and changing implementation in the future can be challenging, especially when the technology has not been introduced(19), and effects of any implementation measures, including research, on implementation are difficult to predict.

We extend the Willan and Eckermann(8) framework by a) allowing implementation to adopt different values in future periods through the incorporation of diffusion curves, b) replacing the assumed functional relationship between strength of research evidence on implementation by evidence obtained by elicitation of experts' beliefs, c) using an alternative to the Central limit theorem method(8) for the estimation of EVSI and d) maintaining a distinction between the expected value of information and implementation proposed by Fenwick et al.(9). Extensions a) and b) have the potential to improve the accuracy of value of research estimates. We are only examining the effects of strength of evidence on diffusion, rather than the effects of different research outcomes. This implies that diffusion is assumed to be independent of study results. Extension c) is made for illustration purposes, to provide an alternative to parametric methods particularly for those analysts who wish to allow for non-normal incremental net benefit distributions. Extension d) is useful for decision-makers who also consider implementation strategies other than research because reimbursement authorities may be interested in the expected opportunity loss associated with both low implementation and uncertainty.

We briefly summarise existing concepts of expected value of information and implementation, then present the calculation of the expected value of research (EVR) as the sum of EVSI and expected value of specific implementation measures (EVSIM), and describe how diffusion curves can be incorporated into this analysis. Evidence for this was obtained through an elicitation of experts' beliefs about diffusion for the counterfactual with- and without-research scenarios. We then apply the dynamic EVR in a real case study of a pre-term birth screening technology. Results are presented for the dynamic EVR analysis and compared with results of static EVR analysis.

Methods

The measures of expected value of information and implementation

Most health technology assessments are associated with decision uncertainty that results from a limited evidence base. *Expected Value of Information (EVI)* methods can estimate the magnitude of the cost linked with decision uncertainty on a monetary or health scale(20). The *Expected Value of Perfect Information (EVPI)* is the expected value of reducing all uncertainty present in a decision. With implementation being less than perfect, the expected value of achieving full implementation of the best technology is of interest. This has been referred to as the *Expected Value of Perfect Implementation (EVPIM)*(9). The EVPIM reflects the losses that the payer will incur because less cost-effective technologies remain partially implemented.

The EVPI can be reduced by conducting further research. The EVPIM can be reduced by investing in implementation measures. Research, however, may also have an impact on implementation as adopters are more convinced by the effectiveness and/or cost-effectiveness of the new technology(8, 9). When this is the case, part of the EVPIM can be resolved by performing research studies relevant to the decision problem. We call this part of the EVPIM the EVPIM that is resolvable by research (i.e. *research EVPIM*), which is relevant to reimbursement authorities and health-care payers who wish to identify the expected opportunity loss associated with imperfect implementation that is caused by decision uncertainty. Consequently, research may result in a reduction of the EVPIM without having executed any other implementation measures. It is of practical importance to distinguish between the research EVPIM and the part of the EVPIM that cannot be resolved by research (i.e. *non-research EVPIM)*. The sum of EVPI and EVPIM has previously been referred to as the expected value of perfection (EVP) in a static framework assuming that these two measures are independent(9). It is important to note that these EVPI measures are theoretical and do not consider the amount of research evidence, time or costs(21) in addressing decision uncertainty or imperfect implementation(21). In value of implementation calculations, diffusion is typically considered dependent on the strength of evidence whilst it is assumed to be independent of the types of study results. If the latter was considered, calculations would be more complex. In this paper, we focus on the value of research study designs in reducing uncertainty and improving implementation. We provide a detailed approach to incorporating the effect of a reduction in uncertainty on the value of implementation, and we briefly discuss an approach to considering the effect of different types of study results on diffusion and the value of research.

Assessing the value of research designs considering imperfect implementation

The value of a particular research study can be calculated using the *Expected Value of Sample Information (EVSI)*(8, 22, 23) and is given by:

$$EVSI = \mathbb{E}_X\left[max_d \mathbb{E}_{\theta|X}\{NB(d|\theta)\}\right] - max_d \mathbb{E}_\theta\{NB(d,\theta)\} \quad \textbf{(1)}$$

where $\mathbb{E}_{\theta|X} NB(d|\theta)$ is the expected net monetary benefit of technology *d* given the uncertain model input parameters θ and data *X* are informative for the input parameters θ.

If implementation is assumed perfect, the resulting EVSI underestimates the true value of research(8). To allow estimation of the expected value of research that allows for both the effects of reductions in uncertainty and improving implementation, we consider the *Expected Value of Specific Implementation Measures (EVSIM)*(8, 9). *The EVSIM is given by:*

$$EVSIM = \sum_{d=1}^{D} \rho_d^{IM}\, \mathbb{E}_\theta NB(d,\theta) - \sum_{d=1}^{D} \rho_d^{C}\, \mathbb{E}_\theta NB(d,\theta) \quad \textbf{(2)}$$

where ρ_d^C is the probability of implementing technology *d* with current information, and ρ_d^{IM} is the implementation with a certain implementation measure *IM* for technology *d*.

Where the unrealistic assumption of perfect implementation is relaxed, Equation (1) still holds in representing the value of research associated with reducing decision uncertainty per se, while the value of additional research in dynamically improving implementation is represented in Equation (2). Equations (1) and (2) then sum to the *Expected Value of Research* (EVR) in Equation (3), which is written out in Equation (A.1) in the appendix. The reduction in (decision) uncertainty and value of implementation of additional research in Equations (1) and (2) are independent of each other and sum to Equation (3) (see appendix Equation (A.2) for the proof). This interaction between the expected value of reducing decision uncertainty and improvement in imperfect implementation, which sum up to the increased expected value of research with an a priori expectation of improved strength of evidence has been described by Willan & Eckermann(8) previously. If study results of the planned research study can significantly alter diffusion, calculation of the Research EVSIM is complicated by diffusion being dependent on study results, but this can be addressed using Equation (A.3) in the appendix. Adjusting the EVSI by implementation would result in no longer assessing the value of a reduction in uncertainty but instead breaking the maximisation in Equation (1) and adjusting net benefits by implementation, which exactly gives the EVSIM. When the implementation measure of interest is a planned research study, the *Expected Value of Research (EVR)* can be used to quantify the value of the proposed study in terms of both effects on implementation and the reduction in

uncertainty. Both effects are independent of each other because they are inherently different: the value of a reduction of uncertainty (EVSI) is calculated by considering what the value of a decision would be under current information and subtracting that from the value of a decision made with future evidence, when we would make a better decision in a greater proportion of PSA runs. The value of improved implementation (EVSIM), however, neglects the reduction of uncertainty and only assesses the value of research in terms of its effect on implementation (proof in appendix Equation (A.2)). Adding both together ensures that both effects are captured in the value of research.

The EVR is therefore the sum of the EVSIM and the EVSI of the proposed research study, which is analogous to the EVP being the sum of the EVPIM and the EVPI:

$$EVR = EVSI(Research) + EVSIM(Research) \quad \textbf{(3)}$$

When accrued over the affected patient population over all periods until the time horizon at which the decision ceases to be relevant, the value measures of information, implementation and research (summarised in Table 1) can be compared to the costs associated with the research study(21). The research is then worth doing if the population EVR exceeds its cost.

Incorporating diffusion curves in EVR analysis

Health technology implementation changes over time, following a process that is called diffusion(3, 24). With implementation levels varying over periods of time, the different value of implementation measures (Table 1) will also vary across each period. We use the EVSIM as an illustrative example for how diffusion can be incorporated in the calculations of value of implementation measures in Table 2. If utilisation of intervention A was at 2% in the first year, then utilisation of comparators B and C would be at 49% each (assuming equal utilisation for the two remaining technologies, due to a lack of knowledge that suggests otherwise), and the EVSIM would be calculated accordingly. In the second year, implementation of A might be at 10%, resulting in 45% of implementation of B and C, and so on. When accrued over the population, the population size needs to be adjusted by the proportion of patients that receives the new intervention. If this is not done, the population value of the EVSIM that the payer will incur is over-estimated because it is accrued over patients that do not benefit from the implementation measure.

To facilitate comparison with static analysis, which is typically presented for the first year, the average taken over all periods can be used to represent an annual estimate of the dynamic EVSIM:

$$EVSIM^{dyn} = \frac{1}{T}\sum_{t=1}^{T} \rho_{t,d}^{X} \pi_t EVSIM_t \quad \textbf{(4)}$$

with $\rho_{t,d}^{X}$ being the mix of achievable implementation of technologies *d* with research evidence *X* in each time period *t,* where *t=1,…,T* is the time period up to the defined time horizon *T*, in years, and π_t is the estimate of the eligible population in each *t*.

The dynamic EVR analysis applied in a case study in pre-term birth screening

The dynamic EVR analysis is applied in a genuine but anonymised case study of a new pre-term birth screening technology that is currently in development. We refer to the new technology as technology A and the comparators are technologies B and C, where technology C is no screening. When patients are tested positive, they undergo treatment that could help prevent pre-term birth. Three health states are possible outcomes of the model. The screening technologies, treatments and health states are associated with costs, and the health states are associated with utilities presented as quality-adjusted life years (QALYs). The expected incremental cost-effectiveness ratios (ICERs) and net monetary benefits are calculated using probabilistic sensitivity analysis (PSA), based on 10,000 simulations. All costs and QALYs are scaled to a per person level and costs are presented in GBP (the exchange rate was GBP £1 = USD $1.53 on 28 Oct 2015).

Two research studies have previously been identified to be relevant to the adoption decision of technology A (subsequently referred to as Study I and Study II). Study I studies the predictive ability of technology A and Study II the response to treatment after screening with technology A. To facilitate assessing the EVR, information is needed on implementation estimates for the counterfactual cases with and without these research studies. We drew on diffusion theory that suggests that cumulative diffusion of new technologies typically follows a sigmoid curve(17). Implementation estimates following such curves were obtained from an elicitation of experts' beliefs about parameters that informed an established model of technology diffusion, i.e. the Bass model of technology growth(25, 26). Beliefs were elicited from three experts and synthesised using a linear pooling method. The elicitation method only required elicitation of three uncertain quantities to generate a multi-period diffusion curve. These uncertain quantities were the total attainable cumulative number of adoptions, the number of adoptions in the first period after technology introduction, and the time it would take to reach the peak number of per period adoptions. Using a minimisation of sum of squared error term method in a number of 1,000 simulations drawn from the probability distributions of the three elicited quantities, the Bass model parameters could be approximated and diffusion curves

generated. This process was undertaken for the following scenarios: 1. baseline diffusion scenario (the counter-factual without executing any implementation initiatives), 2. diffusion scenario with Study I completed, 3. diffusion scenario with Study II completed, and 4. diffusion scenario with both studies I and II completed.

For comparisons with the static analysis, we use the estimate of the maximum attainable number of adoptions for the four scenarios that were obtained from the same elicitation study. A diffusion scenario for perfect information that is relevant to the calculation of the research EVPIM is generated using modifying assumptions on the elicited diffusion curves. To extrapolate the per person values to the population, we use the population of women with a pre-term birth (approximately 20,000 per year, based on the prevalence of pre-term birth(27) and the number of births in England(28)). We use a time horizon of five years, reflecting the relatively quick change in the medical devices landscape(29).

The EVSI is calculated using clinical trial simulation(22, 23, 30). We use sample sizes of 300 patients in both studies and generate a sample of data from a binomial distribution for each draw from the PSA for each study. In Study I, we simulate the proportion of those tested positive with a pre-term birth and those tested negative with no pre-term birth (sensitivity and specificity). In Study II, we simulate the proportion of women responding to treatment compared with no treatment, with patients randomised equally to the two trial arms. We then calculate the EVSI values for both research studies using the GAM regression method(23). The funding source had no role in this study.

Results

Results of baseline cost-effectiveness analysis

Based on the PSA, technology A is expected to be dominating against both technologies B and C, reflecting that it is cost-saving and providing a QALY gain. Technology A is therefore the technology with the highest expected net monetary benefit (Table 3). The results presented in Table 3 are associated with little uncertainty as shown in Figures 1 and 2. Only three percent of the joint distribution for the incremental benefit and incremental cost, when comparing technology A against B lie to the North West of the threshold diagonal, indicating a small chance that technology A might not be cost-effective. The results against technology C are more certain: Less than one percent lie to the North West of the threshold diagonal. That is, we can be quite certain that technology A is cheaper and more effective than technology C. Despite this relative certainty, the consulted experts stated a belief that technology diffusion would be slow and bounded at a value of approximately 30% of the desirable adoptions. This expectation is based on other barriers to adoption, such as budget constraints

of individual organisations that pay more upfront and do not gain from cost reductions associated with the effectiveness of the intervention.

Results of the dynamic EVR analysis

The above analysis shows that decision uncertainty is small. This is supported by the small per person EVPI (Table 4). However, the magnitude of the affected population means that the population EVPI is not negligible. The opportunity loss caused by low implementation is larger than that caused by uncertainty (Table 4). This is because implementation of the dominating technology A is going to be low (at 30%) and there is little uncertainty that technology A is much better than its alternatives. The low implementation in this case study is caused by a variety of issues, including the limited evidence base for technology A in spite of the small decision uncertainty. Not resolving low implementation would represent an opportunity cost to the payer of up to £33 million at the population level (Table 4). A significant part of the EVPIM could be addressed through additional research because of the large research EVPIM. The EVPI and EVPIM alone are not sufficient conditions for decision-making, as research could have zero cost(21). The value of further research can thus only be assessed using the EVR and comparing this to its cost(21).

The EVR (that consists of both the EVSIs and EVSIMs) relating to Studies I and II is £100,000 and £172,000, respectively. Assuming research costs of £300,000 for both Study I and Study II, both studies would yield a negative expected net gain and are thus not worth pursuing. At cheaper costs or longer time horizons, these studies may become feasible. The EVR of both research studies amounts to 7% of the EVP at the per person level but to less than 1% of the EVP at the population level. This reduction in the value of the research studies compared to the EVP at the population level is caused by the EVR only being accrued for those patients who receive technology A. The largest part of the EVP is explained by the EVSIM because the EVSI is small for both Studies I and II. The EVSIM values are larger than the EVSI of the trials, demonstrating that the value of the research studies relate mainly to their associated increase in implementation of the most cost-effective technology A. This is a result of the little decision uncertainty and of the experts' beliefs on diffusion of technology A with and without further research.

Comparison of static and dynamic analyses

Results for the value of implementation measures obtained from the static analysis differ from those obtained from the dynamic analysis (Table 5). In some cases dynamic results are larger (EVPIM and

both EVSIMs) and in one case the dynamic value is smaller (research EVPIM). The reason for the differing values is that they are driven by the difference between the counterfactual with and without research implementation. Static estimates only capture a temporary snapshot of the dynamic development of implementation over time that may not accurately reflect the dynamic average difference between the counterfactual with and without curves. An example of this is illustrated through the combined effect of both research Studies I and II on implementation in Figure 3. In the static analysis, it was assumed that the recommendation decision was followed by an immediate jump to the baseline scenario maximum attainable number of adoptions, shown by the dashed grey line. Further research studies on the treatment effect and the predictive ability of A before the research recommendation would result in immediate implementation shown by the solid grey line in Figure 3. Taking the difference of these estimates resulting from this "snapshot" is clearly not representative of the average difference between the two dynamic implementation curves (shown in dashed black for no further research and solid black for Studies I and II in Figure 3). The difference between the dynamic curves is driven more by the timing at which gains in implementation occur rather than the gain in absolute numbers of cumulative adoptions.

Discussion

We have presented an extension to an existing framework for estimating the value of research studies when considering the effect of new research evidence on implementation(8) by allowing implementation to be dynamic through the incorporation of diffusion curves and by replacing assumptions surrounding the functional relationship between strength of evidence and implementation by evidence obtained from elicitation of expert opinion. As such, the value of this study lies in both, the further development of EVSI methods as well as in providing an extension to applications of the expected value of implementation(14, 16, 18) that have not quantified the dynamics of implementation using diffusion theory. Our results show that including diffusion curves in expected value of research analysis improves its accuracy; which means that incorporating implementation dynamics is essential when assessing the expected value of research. We have also explained why the expected value of research in both, reduction of uncertainty and improvement of implementation, is greater than the EVSI, supporting findings of previous research(8). This conclusion is in contrast to the conclusion drawn by Andronis and Barton(12), who claimed that the value of research is systematically over-estimated when implementation is imperfect but not accounted for in EVSI analysis. However, what they refer to as the "implementation-adjusted" EVSI is in fact the definition of the EVSIM of a research study and this has nothing to do with the reduction of decision uncertainty that can be achieved with the research study. The correct approach is to look at both effects of

research: its effect on the reduction of decision uncertainty as well as its effect on the improvement of implementation, as was done in this study and has been done previously(8).

In practical terms this analysis could have a substantial effect on recommendation with research decisions, which are a type of managed entry agreement used by reimbursement authorities and manufacturers to agree on a process of recommending a new technology(5-7). With this analysis, the value of research is not limited to its impact on decision uncertainty, which can be estimated by the EVSI, but includes the associated value of increased implementation. Of course, a RwR decision requires other preceding analyses(5, 6) to ensure it produces a positive net monetary benefit, otherwise the faster implementation can inflate opportunity costs associated with ineffective schemes.

The strength of this study is the incorporation of implementation dynamics, the estimation of which was based on the theory of diffusion of innovative technologies(17) and an adaptation of the Bass model of new product growth(25, 26), using elicitation of experts' beliefs. This method, which only required the elicitation of three parameters for each diffusion curve, enabled us to take the relationship between information and implementation into account. Explicitly considering this relationship has the potential to make the assessment of implementation measures and the value of research more realistic, both in terms of the implementation that can be achieved and in terms of the counterfactual expected implementation when doing nothing. Illustrating the EVR calculations in a case study of a technology that is still in development is relevant because technology assessments commonly occur before technology introduction and when there is still funding available for further research. We argue that addressing the issue of potentially low implementation at the time of health technology assessment would save the health care system resources and therefore provide health gains for patients.

A limitation of this work is that only the effects of reduction of uncertainty on diffusion were considered, and not the effects of different research study outcomes on diffusion. We have provided the framework to do both, and wish to consider this in an applied example in future research. Resource requirements may be a limitation of this work if adopted by decision-makers. Additional resources would be required for the trial simulation and in quantifying implementation levels with and without the use of implementation measures. The value of dynamic EVR analysis is likely to be greatest in situations where health technologies are expected to have low implementation because the discrepancy between EVSI and EVR will be greatest then, other things being equal. However, to our knowledge, there is no standard way of identifying technologies with potentially low implementation, hinting at the need for a screening process that should precede any further analysis to identify future implementation levels. It may be beneficial to test the dynamic EVR analysis in other exemplary health technology assessments to obtain a better overview of potential outcomes and uses of the framework and processes required to establish this analysis within technology assessments. Such work would also allow us to better understand the situations where the differences between static and

dynamic estimates of research value are greatest. This would help with prioritising any use of the dynamic EVR analysis in future decision making processes.

Optimisation methods have previously been proposed to identify the optimal study design and sample size(8, 31). In further research, our proposed dynamic EVR analysis could be used to choose the best design among a set of designs, although an optimal design cannot be guaranteed, due to a lack of knowledge on the functional relationship between information and implementation. Despite this, we think that we have proposed an important improvement in how the value of research should be estimated. Functional relationships of proxies for strength of evidence and implementation are unlikely to capture the behavioural and information processing factors underlying institutional and individual decision-making. Our elicitation method is much more likely to capture these, but eliciting a large number of different diffusion curves may not be feasible due to time and resource constraints. Further research should be done on finding ways of quantifying the effects of different study designs on implementation, thus potentially enabling trial design optimisation.

In conclusion, implementation dynamics can be applied in the expected value of research analysis to assess the value of research studies in terms of reducing uncertainty and improving implementation. Importantly, if dynamics of implementation are considered, then it makes sense to draw on diffusion theory and its related applied research. We successfully extended an approach to EVR analysis(8) by estimating diffusion based on expert beliefs in a method capable of allowing for the relationship between strength of evidence and implementation. Without such methods, EVSI results underestimate the true value of research. Consequently, we feel that the combination of EVR, diffusion curves and elicitation of experts' beliefs described in this paper is an important addition to the existing methods of health technology assessment.

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Table 1. The expected value concepts of implementation and information

	Value concept	Description
Uncertainty	EVPI	The value of resolving all decision uncertainty
	EVSI	The value of a proposed research study design in reducing uncertainty
Implementation	EVPIM	The value of achieving perfect implementation (from current "baseline" level)
	Research EVPIM	The value of improving implementation by resolving all decision uncertainty, the complement of non-research EVPIM, together summing up to EVPIM
	EVSIM	The value of improving implementation with a proposed implementation measure or research study design
Both	EVP	The value of achieving perfect implementation and resolving all decision uncertainty
	EVR	The value of a proposed research study design in improving implementation and reducing uncertainty

Table 2. Accruing the EVSIM over the implementation-adjusted population

Time *t*	Individual (per person) EVSIM	Discounted population affected	Implementation of cost-effective technology	EVSIM accrued over implementation adjusted population
1	$EVSIM_1$	$\delta\pi_1$	$\rho_{1,d}$	$\rho_{1,d}\delta\pi_1 EVSIM_1$
2	$EVSIM_2$	$\delta\pi_2$	$\rho_{2,d}$	$\rho_{2,d}\delta\pi_2 EVSIM_2$
3	$EVSIM_3$	$\delta\pi_3$	$\rho_{3,d}$	$\rho_{3,d}\delta\pi_3 EVSIM_3$

Table 3. Cost-effectiveness results for case study example

Threshold: £20,000 / QALY	**A**	**B**	**C**
Expected Costs	£19,004	£19,219	£19,409
Expected QALYs	29.224	29.221	29.219
ICER against B	Dominating	-	NA
ICER against C	Dominating	Dominating	-
Expected Net Benefits	£485,474	£485,210	£484,978

Table 4. Dynamic expected value of implementation and information results for case study example

		Per person	Population per annum (20,000 patients affected)	Population over time horizon of 5 years (discounted)
Uncertainty	EVPI	£2.03	£40,530.00	£223,527.00
	EVSI (Study I)	£0.00	£0.00	£0.00
	EVSI (Study II)	£0.02	£452.00	£2,491.00
Implementation	EVPIM	£353.00	£7.06 million	£33.10 million
	Research EVPIM	£41.20	£823,553.00	£3.75 million
	EVSIM (Study I)	£9.11	£22,421.00	£100,551.00
	EVSIM (Study II)	£13.66	£37,709.00	£169,203.00
Both	EVP	£355.00	£7.06 million	£33.30 million
	EVR (Study I)	£9.11	£22,421.00	£100,551.00
	EVR (Study II)	£13.68	£38,161.00	£171,694.00
	EVR (Studies I + II)	£22.79	£60,582.00	£272,245.00

Table 5. Comparison of static and dynamic analysis

Per person values	Static analysis	Dynamic analysis
EVPIM	£264.00	£353.00
Research EVPIM	£49.30	£41.20
EVSIM (Study I)	£1.97	£9.11
EVSIM (Study II)	£2.96	£13.66
EVP	£266.00	£355.00
EVR (Study I)	£1.97	£9.11
EVR (Study II)	£2.98	£13.68
EVR (Studies I+II)	£4.95	£22.79

Figure 1. Cost-effectiveness plane of technology A against technology B.

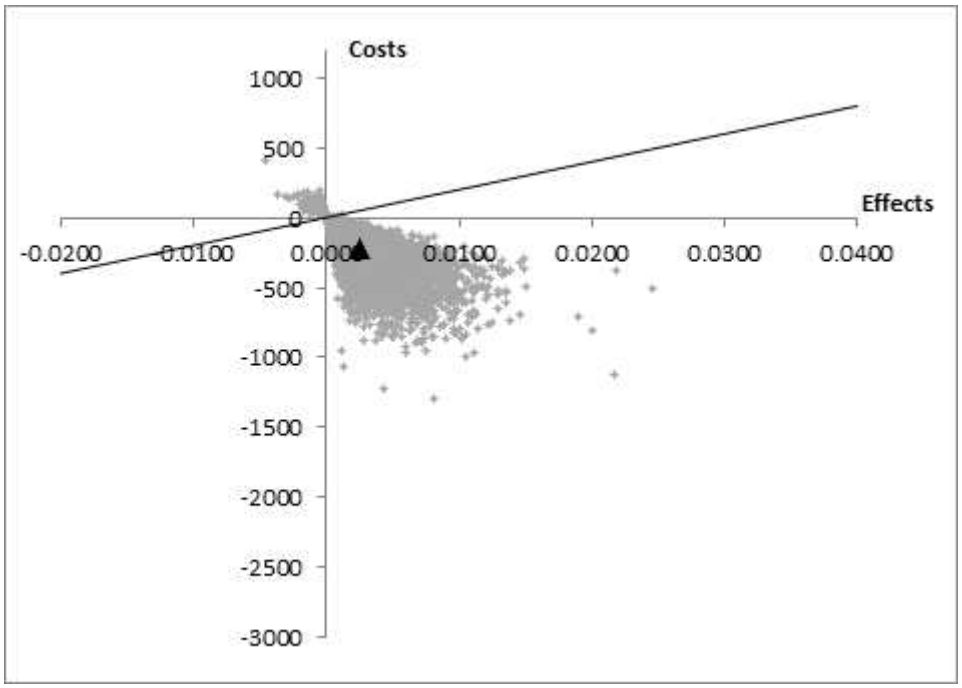


Figure 2. Cost-effectiveness plane of technology A against technology C.

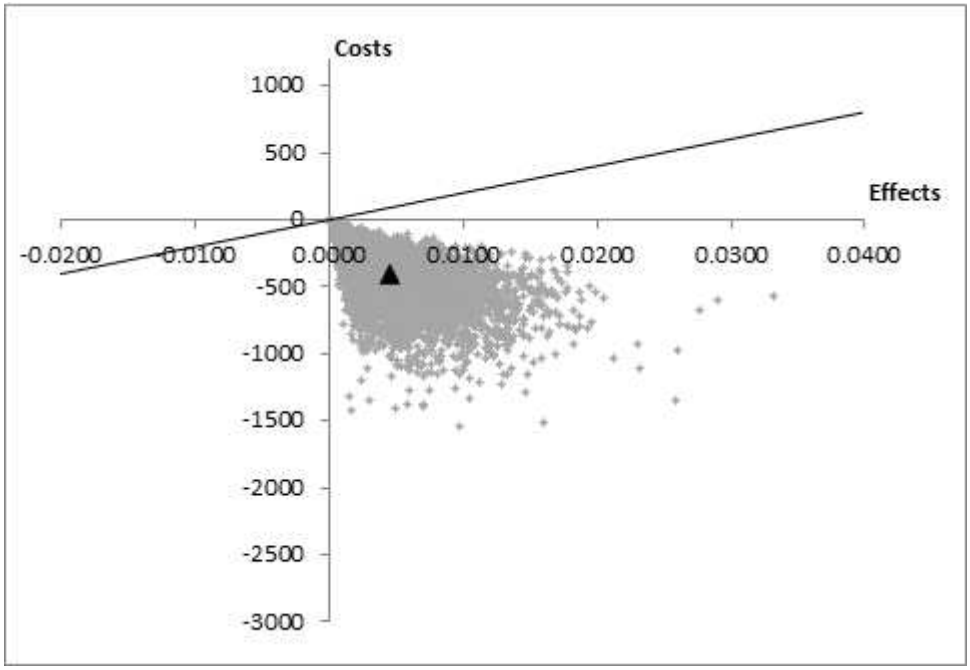
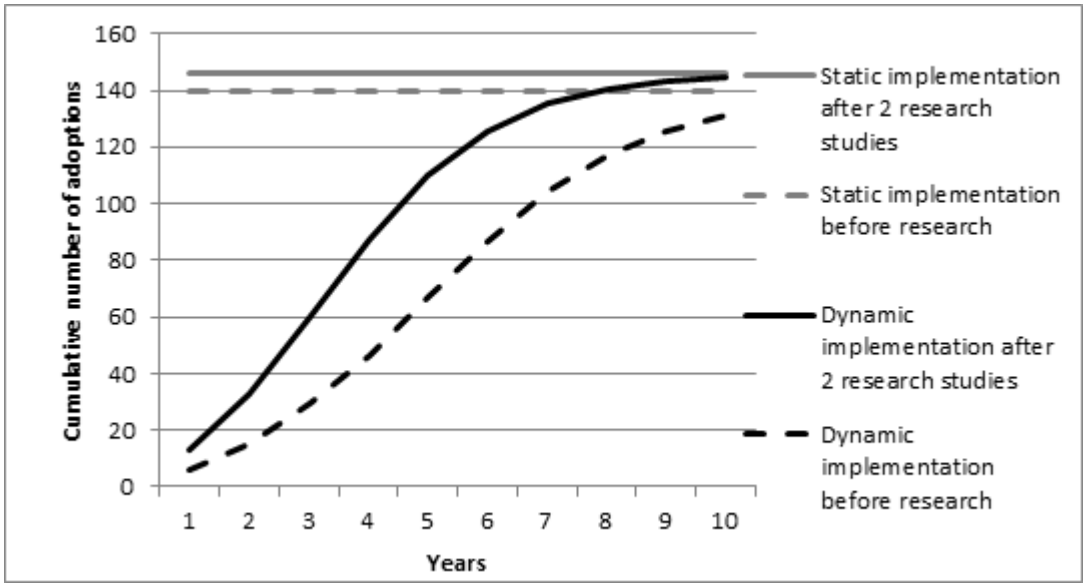


Figure 3. Examples of static and dynamic implementation data.



Disclaimer:

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Appendix

The EVR can be written as:

$$EVR = \sum_{d=1}^{D} \rho_d^X \, \mathbb{E}_\theta NB(d,\theta) - \sum_{d=1}^{D} \rho_d^C \, \mathbb{E}_\theta NB(d,\theta) + \mathbb{E}_X\left[max_d \mathbb{E}_{\theta|X}\{NB(d|\theta)\}\right] - max_d \mathbb{E}_\theta\{NB(d,\theta)\} \tag{A.1}$$

where ρ_d^X is implementation of technology *d*, given data *X* collected in the proposed research study.

The Research EVSIM can be written just like any other EVSIM because the effects of the reduction of uncertainty cancel out with the inclusion of implementation, as is shown in Equation (A.2):

$$\begin{aligned} EVSIM^R &= \mathbb{E}_X\left[\sum_{d=1}^{D} \rho_d^X \, \mathbb{E}_{\theta|X}\{NB(d,\theta)\}\right] - \sum_{d=1}^{D} \rho_d^C \, \mathbb{E}_X\left[\mathbb{E}_{\theta|X}\{NB(d,\theta)\}\right] \\ &= \left[\sum_{d=1}^{D} \rho_d^X \, \mathbb{E}_X \mathbb{E}_{\theta|X}\{NB(d,\theta)\}\right] - \sum_{d=1}^{D} \rho_d^C \, \mathbb{E}_X\left[\mathbb{E}_{\theta|X}\{NB(d,\theta)\}\right] \\ &= \sum_{d=1}^{D} \rho_d^X \, \mathbb{E}_\theta\{NB(d,\theta)\} - \sum_{d=1}^{D} \rho_d^C \, \mathbb{E}_\theta\{NB(d,\theta)\} \end{aligned} \tag{A.2}$$

Where different results of the planned research result in very different diffusion curves and the analyst wishes to capture these effects, elicitation of probability distributions of diffusion curves that are conditional on these different study results is necessary. The Research EVSIM is then slightly more complex and has to be written as in Equation (A.3). The EVR can still be calculated by summing up the independent EVSI and Research EVSIM.

$$\begin{aligned} EVSIM^R &= \mathbb{E}_X\left[\sum_{d=1}^{D} \rho_d^X \, \mathbb{E}_{\theta|X}\{NB(d,\theta)\}\right] - \sum_{d=1}^{D} \rho_d^C \, \mathbb{E}_X\left[\mathbb{E}_{\theta|X}\{NB(d,\theta)\}\right] \\ &= \left[\sum_{d=1}^{D} \mathbb{E}_X\left[\rho_d^X \mathbb{E}_{\theta|X}\{NB(d,\theta)\}\right]\right] - \sum_{d=1}^{D} \rho_d^C \, \mathbb{E}_\theta\{NB(d,\theta)\} \end{aligned} \tag{A.3}$$