The half-life of truth: appropriate time horizons for research decisions?

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Abstract

Purpose: To evaluate alternative approaches taken to estimate the population that could benefit from research and to demonstrate that explicitly modelling future change leads to more appropriate estimates of the expected value of information (EVI).

Methods: A review of the EVI literature identified a number of approaches to estimating the population including: considering only the current population, arbitrary time horizons or threshold population values. However, empirically based estimates of the time horizons for decisions in health exist. We explore different approaches in the context of a stylised model of treatment for acute coronary syndrome and demonstrate the impact of uncertainty in time horizon on expected value of information. We develop a general approach, which explicitly models future changes in technologies, prices, and information, and demonstrate the impact on EVI estimates.

Results: The literature either ignores the value of research for future populations or relies on arbitrary assumptions about finite time horizons. Empirically based estimates of the time horizon may lead to underestimation of the value of information using common assumptions and failing to incorporate uncertainty in the estimates leads to biased estimates of EVI. However, all these approaches implicitly use time horizon as a proxy for future changes in technologies, prices and information. We demonstrate that explicitly modelling future changes means that the EVI for the decision problem may increase or fall over time, but the EVI for the group of parameters that can be evaluated by current research tends to decline. We show that finite and infinite time horizons for the decision problem represent special cases (e.g., price shock or no changes respectively). In addition, we show how this type of analysis can be used to inform the timing of research decisions.

Conclusions: The value of information depends on future changes in technologies, prices, and evidence, and finite time horizons for decision problems may not represent an adequate proxy. However, the challenge of modelling future change also has implications for estimates of cost-effectiveness.

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1. Introduction

There are two conceptually distinct but simultaneous decisions that must be made within any heath care system. Firstly, should a technology be adopted or reimbursed given the existing evidence? Secondly, is additional evidence required to support the adoption or reimbursement decision? Bayesian decision theory and value of information analysis provides an analytic framework that can be used to establish the value of acquiring additional information to inform a decision problem. These methods have firm foundations in statistical decision theory, have been successfully used in other areas of research such as engineering and environmental risk analysis and are increasingly being used in health technology assessment. In particular measures of the expected value of prefect information (EVPI) have been proposed and applied as a means of establishing a necessary condition for conducting research and identifying research priorities in health are [refs pilot]. However the value of information which could be acquired depends crucially on the number of future patients who could benefits from it, i.e., the time horizon over which this information would be useful. This paper attempts to address this issue by reviewing methods currently used in the general EVI literature and then considering whether choosing a finite time horizon for the value of information is really a proxy for a more complex and uncertain process of future changes to the decision problem. We start with a brief outline of value of information analysis.

Expected Value of Perfect Information

If the objective of a decision maker is to maximise health outcomes subject to a budget constraint, then the decision to adopt or reimburse an alternative (j) should be based on the cost (C), and outcomes (Q) of the competing alternatives, and the cost effectiveness threshold (λ). The cost-effectiveness of an alternative j can be expressed in terms of net benefit ($NB_j = Q_j.\lambda - Cj$). However, NB_j will be uncertain and a decision must be made before it is known how the uncertain parameters in the model (θ) will resolve. The optimal decision with current information is to choose the intervention that generates the maximum expected net benefit ($\max_j E_\theta NB(j, \theta)$).

With perfect information, decisions can be made when it is known how the uncertain parameters in the model will resolve so the intervention that maximises net benefit for a particular value of θ can be selected ($\max_j$ NB(j, θ)). However, the true values of θ are unknown, so the expected value of a decision taken with perfect information is found by averaging the maximum net benefit over the joint distribution of θ ($E_\theta \max_j$ NB(j, θ)). The expected value of perfect information for an individual patient episode is simply the difference between the expected value of the decision made with perfect information about the uncertain parameters θ, and the decision made on the basis of existing evidence:

$$EVPI = E_\theta \max_j NB(j,\theta) - \max_j E_\theta NB(j,\theta) \qquad (1)$$

This can be generalised to consider the value of perfect information associated with particular groups of parameter within the decision problem and to consider the expected value of sample information [refs].

However, all measures of the value of information must consider the future population that can benefit from it, since all information has public good characteristics (it is non-rival). The exiting literature which has applied EVI in health care has calculated the population EVPI (PEVPI) based on some assessment of the time horizon for the information (T), estimates of incidence over this period (I_t) and a discount rate (r) [ref]:

$$PEVPI = EVPI \sum_{t=1}^{T} \frac{I_t}{(1+r)^t} \qquad (2)$$

The time horizon T is the period over which information about the current decision problem that could be acquired in the near future would be useful. Choosing T poses a number of questions: i) On what basis could T be assessed? ii) Should the uncertainty in any assessment of T be integrated within estimates of EVPI? iii) Will the assessment of T differ for different types of decision problems, which include different types of technologies? iv) How can T reflect the intuition that some types of information be expected to be useful for longer than others?, i.e. information about natural history of disease might be expected to be valuable for a longer period than information about the relative effect of a technology which may be obsolete within a few years. These questions have not yet been addresses in the EVI literature and as the review will demonstrate the most that has been done is to present the results

conditional on a range of possible values for T. However, this simply passes the problem back to decision maker to make some informal assessment of which value is more appropriate. In some circumstances this may be clear if the value of information is less than the costs of research for all values of T. In other circumstances the decision to acquire information and the prioritisation of alternative research may be sensitive to 'reasonable' values of T.

2. Current approaches to the time horizon

Review of EVI literature

A recent systematic review of the use of value of information methods in the health risk management literature identified a total of 44 applications in 42 papers [ref Yakota and Thompson]. The criteria used by the authors were that: i) the paper was published in English in a peer-review journal by the end of 2001; ii) it included calculations by the authors of the key components of EVPI or EVSI; and iii) focused on a decision that involved the management of a health risk.

The applications ranged from general medical care and clinical trials assessments, to general environmental health, water contamination and toxicology. Only 12 applications (27%) aggregated their EVI estimates to the total affected population and 16 (36%) took account of the time horizon for the useful life of the information. These papers were obtained and reviewed in order to identify the methods used to estimate either the population expected to benefit from information or the effective time horizon for the useful life of that information.

10 of the 12 applications aggregating the EVI estimates to consider the full population affected came from the medical or clinical trials literature. These articles used the methods outlined in the introduction, choosing 10 or 20 years as a time horizon. However, it is not clear why these time horizons were chosen. The principal argument cited for choosing a finite horizon was that information would not be valuable indefinitely, and that, to some extent, information generated today would become obsolete at some time in the future. However, it seems that this argument is made on the basis of a finite timeframe for information regarding a particular technology as

apposed to information regarding the decision problem in its entirety and provides no justification for the particular value chosen.

The remaining two articles came from the water contamination and toxicology literature. These articles used a threshold calculation, i.e., they calculated the minimum size of the population for which additional research in the area would remain cost effective. However, this approach simply passes the problem back to the decision maker, who would need to make some implicit assessment of the size of the future population to establish whether further research is worthwhile.

There were an additional five applications within the water contamination literature that considered the time horizon without explicitly aggregating for the total affected population. This is because, within this field, the health risk can largely be regarded as a single exogenous shock which would affect a single population over time. Nevertheless, this approach neglects that fact that information generated now may well have an impact on other decisions made in the future. However, as before, finite time horizons appeared to be chosen arbitrarily.

An unbounded time horizon?

The literature has either only considered the current population or assumed a finite and arbitrary time horizon. An alternative and extreme assumption would be that information acquired now will always be valuable for all future patients. However, due to discounting, this does not lead to unbounded estimates of the PEVPI because the present value of an asset which pays benefits (b) every period can be approximated by b/r. Therefore, the population EVPI for an unbounded time horizon is the current period PEVPI/r, assuming the numbers of episodes each period are constant. However, this approach was not used in the reviewed EVI literature despite the natural interpretation that this should at least be an upper bound on PEVPI.

Review of empirical estimates

None of the reviewed EVI papers used empirical estimates of the time horizon or elicited priors from experts. Despite this the literature was also searched for possible empirical estimates of the time horizon. The following key words were used in a

broad title and abstract search of the Medline database: “clinical research OR clinical information”, “future population OR future technology”, “time horizon”, “survival”.

The search identified 27 potential articles. On the basis of the title and abstract, two were considered relevant and obtained in full. One of the papers contained no quantitative information and was therefore not considered relevant for this study. The other provided an empirical estimate for the time horizon and an additional article was identified through a citation search of this article.

Both articles presented a ‘half life’ of truth survival in clinical and surgical literature. Hall and Platell [ref] attempted to estimate the half life of truth relating to the practice of surgery. The authors obtained copies of all the first 20 abstracts regarding general surgery published in the journal *Surgery Gynaecology and Obstetrics* in the even numbered months for each fifth year between 1935 and 1994. By summarising the conclusion of each article and asking a panel of seven surgeons to each indicate which, out of a random sample of 260 of the summaries were true or false, the authors investigated the relationship between time and the proportion of positive (indications of true) responses. This suggested that the half life of truth was 45 years. Poynard et al [ref] investigated the factors associated with the survival of truth of clinical conclusions. Using methods similar to the earlier study of surgical conclusions and data derived from a systematic search of original studies on hepatitis or cirrhosis published in the *Lancet* or *Gastroenterology* between 1945 and 1999, the authors found no relationship between the quality of the study and the survival of the clinical conclusions. They too estimated the half life of truth to be 45 years.

Based on this half-life estimate, the average survival of clinical conclusions can be estimated by assuming that the survival time follows an exponential distribution. Since the half life (H) is is estimated to be 45 years and:

$$H = \frac{\ln(2)}{\lambda},\ \mu = \frac{1}{\lambda}, \qquad (3)$$

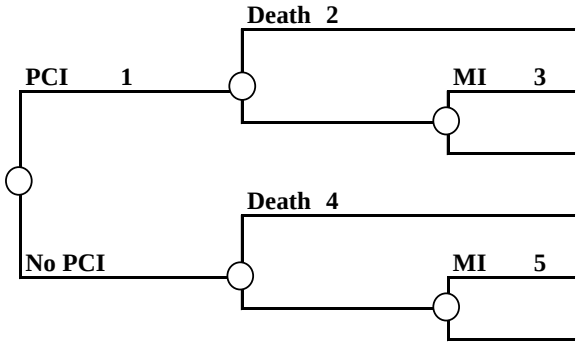
then $\lambda = 0.015$ and the average survival time (μ) for clinical conclusions is 64 years. This is somewhat higher than the arbitrary estimates that have been used in the EVI literature. Although the generalisability of the results of these studies to other decision problems maybe questionable, it is useful to consider the possibility of using

empirically based estimates or elicitation of priors for T. It is also useful to consider the impact of uncertainty in any estimates of T and variability in information survival times. For this reason we explore the impact of the range of approaches which could be taken using a simple stylised decision problem.

2.1. An illustrative example

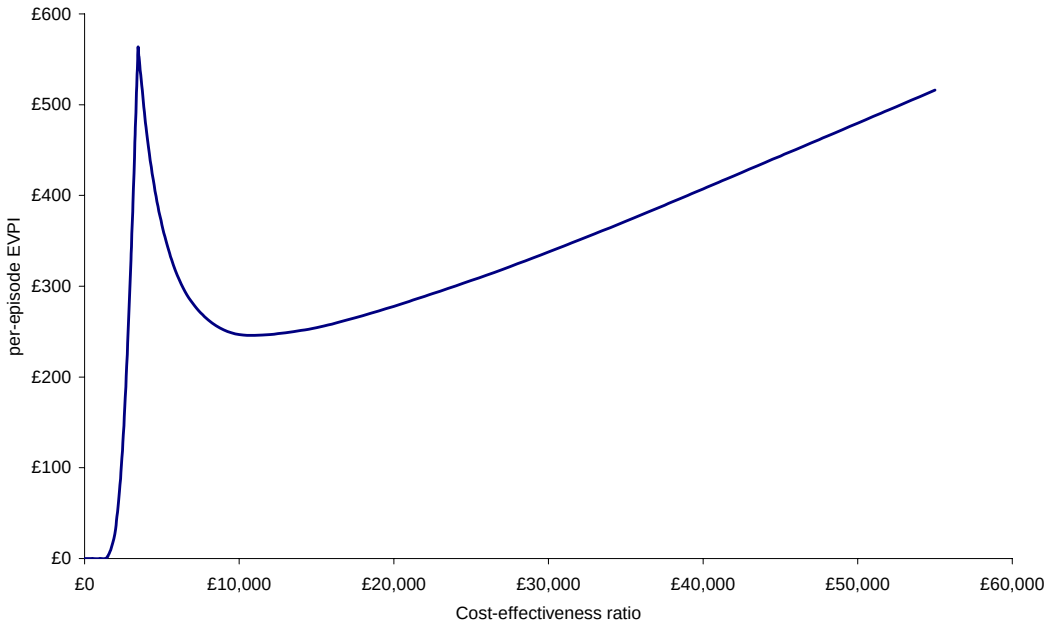
The impact on estimates of the EVPI of using finite, unbounded and empirically based estimates of the time horizon is illustrated by applying them to stylised decision problem. This is loosely based on an Assessment Report for NICE and relates to the treatment of acute coronary syndromes (ACS) and evaluates a hypothetical new drug treatment against current practice. The decision tree structure for each comparator is illustrated in Figure 1.

Figure 1 Decision tree structure



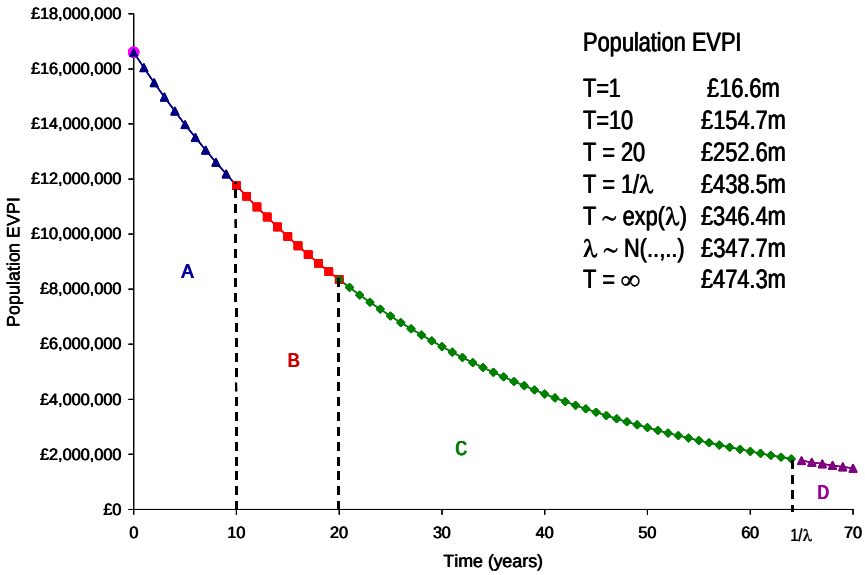
Only NHS costs are considered and health outcomes are measured in QALYs. Uncertainty is characterised by assigning distributions to the uncertain model parameters. These are detailed in table 1. Net benefit is multi-linear with respect to the uncertain parameters and all are independent. Probabilistic sensitivity analysis using Monte Carlo simulation was used to provide estimates of expected costs, QALYs, net benefit and the per-episode EVPI. The incremental costs effectiveness ratio for this hypothetical treatment is £3,461 and the EVPI is illustrated in figure 2 for a range of values for the cost-effectiveness threshold.

Figure 2. Per-episode EVPI



At a cost-effectiveness threshold of £20,000 the per episode EVPI = £278 and assuming a constant incidence of 59,756 per period the current period population EVPI = £16.6m. Assuming a discount rate of 3.5% the range of possible estimates of population EVPI are illustrated in figure 3.

Figure 3. Population EVPI for a range of time horizons



Clearly the selection of time horizon has a substantial impact on the estimates of population EVPI, ranging from 16.6m if only the current period is considered to almost 475m for an unbounded horizon (areas A+B+C+D). Of course this may not change a decision to conduct research but in some circumstances it will. It also illustrates that doubling the time horizon will not double the estimates of EVPI (A>B) so that the impact of alternative values of T is smaller (greater) when time horizons are longer (shorter). It also seems to suggest that an unbounded T may provide a finite upper bound to population EVPI. This proposition is more fully considered later.

Uncertainty and variability in the time horizon

However, this simple approach of choosing a fixed value of T is unsatisfactory because there will be uncertainty in any estimate of T and variability in information survival times. Both will effect the expectation of the PEVPI since the relationship between T and the population EVPI is non linear due to discounting. In this example expected survival times are assumed to be exponentially distributed. Given a fixed value of expected survival time (μ=64, λ=0.015) there will be variability in survival times:

$$T \sim \exp(\lambda) \qquad (4)$$

Integrating this variability, by sampling from this distribution and calculating PEVPI for each sampled survival time (given λ=0.015) and then taking the expectation of these sampled PEVPIs, generates lower expected population EVPI (EPEVPI) of £346.4m. This reflects the non linear relationship between PEVPI and T due to discounting as illustrated in figure 3, i.e., lower than expected sampled survival times reduce PEVPI substantially but higher than expected survival time tend to increase PEVPI more modestly. However, T and therefore λ are also not known with certainty and λ will have a prior distribution. In this example:

$$\lambda \sim N(0.015,0.004) \qquad (5)$$

Now, by sampling a value of λ (an outer loop), and given this value, sampling survival times and calculating expected PEVPI (inner loop), both uncertainty and variability can be integrated. This also leads to lower estimates of the expected population EVPI (£347.7m) for the same reasons as before. However, in this example the EPEVPI when both uncertainty and variability are integrated is slightly higher

than with variability alone. This is because although λ has a symmetrical distribution exp(λ) is negatively skewed, making higher than expected survival times more likely.

This demonstrates that if empirical evidence or priors elicited from experts are used to provide estimates of the time horizon, then both the uncertainty in expected survival time and the variability in survival times will effect the estimate of the expected population EVPI. Clearly this adds to computational burden as two loops of sampling are required in addition to the sampling required to estimate the per-episode EVPI, but it does provide a means to move away from arbitrary selected fixed time horizons

3. Modelling uncertain future change

Although estimates of the time horizon could in principle be based on empirical evidence or formal elicitation of priors, with the uncertainty surrounding these estimates and the variability in survival times integrated into EPEVPI, two related conceptual problems remain. Firstly, any estimated and sampled value of T suggests that the value of information for each episode remains constant until T and then falls to zero. But EVPI will only change if the decision problem changes, so this implies that at some point in the future the decision problem changes so profoundly that information that can be acquired now will immediately become completely irrelevant. Such immediate and catastrophic change seems somewhat unrealistic. Secondly, some types of information might be expected to be valuable for much longer than others, e.g., evidence about the natural history of the disease rather than the relative effect of a technology which may quickly become obsolete. It may be tempting to assign different estimates of T to different types of parameters. However, this would imply that at some point the EVPI associated with one of the parameters in the decision problem would fall to zero but the EVPI for the others would remain constant. This can not be, as any change to the decision problem which would cause EVPI for some parameters to fall would also change the EVPI associated with the others. This reflects the fact that even when parameters are independent the EVPI associated with then is not.

Both these related conceptual problems suggest that selecting a value of T is essentially a proxy for a more complex and uncertain process of future changes to the

decision problem which impact on the EVPI. There are three possible types of future changes that we consider:

i) Prices change

If the price of a technology falls, for example when a new drug therapy comes off patent, this will impact on the relative cost-effectiveness of that technology and hence decision uncertainty. If the technology is already regarded as (not) cost effective before the price fall then we would expect decision uncertainty to (increase) fall and EVPI may also fall (will unambiguously increase if there are only two alternatives).

ii). Information changes

If new information becomes available (for example, on the natural history of disease, treatment effects or quality of life) it can be combined with prior information to create a posterior distribution of the parameter(s) of interest. This may impact on expected cost effectiveness but will inevitably impact on decision uncertainty. It may be expected that if expected costs effectiveness remains unchanged then more information will reduce uncertainty and the EVPI. However, this intuition is examined more fully later.

iii). Entry of new technologies

The previous EVI literature has often justified choosing a finite value of T in terms of the obsolescence of the technology. To become obsolete other technologies must be developed and become new comparators in the decision problem. This will change the relative cost effectiveness and the uncertainty surrounding existing alternatives. The impact on decision uncertainty and EVPI will depend on the nature of the new competitor i.e. its relative effectiveness, costs and the uncertainty associated with these estimates.

Of course the incidence of patient episodes may change over time and these changes will also be uncertain. We do not illustrate the impact this type of change here as it does not have a direct effect on the decision problem but operates in the same way as uncertainty over T which was dealt with in section 2.1 (uncertainty in changes in incidence will effect the expectation of the population EVPI due to discounting in the same way as uncertainty over T). Here we attempt to demonstrate the impact of those

changes which will effect the per episode EVPI using the stylised example described in section 2.1. We take each of these possible changes in turn, exploring the impact of uncertainty in the nature of any change, its timing and the variability in timing of events. In doing so we hope to illustrate the relationship between estimates of expected population EVPI and the complex and uncertain process of future change.

3.1. Prices change

The previous estimates of EVPI have assumed that the new drug treatment has a fixed and constant price of £3,000 over the time horizon. However, prices are likely to change over time for example due to patient expiry. Initially we assume that a known change in price will occur at time t* after which there will be no further changes ($T = \infty$). The impact of such a fixed price change on the estimates of expected population EVPI is illustrated in figure 4a when at t*=5, the price falls to 0.8 of the original value (undiscounted values in this and subsequent figures are presented for ease of exposition). In this case the EVPI falls because the technology was regarded as cost-effective at the original price, so a fall in price reduces the decision uncertainty and the per-episode EVPI. The estimate of EPEVPI is reduced from £474m with no price change to £424m. Of course, in this example, a more extreme fall in price could lead to EVPI falling to zero at t*, i.e., a situation where selection of a time horizon of T = 5 would be appropriate. However, in other circumstances, e.g., when the technology is not currently regarded as cost-effective, a fall in price would increase decision uncertainty and the EVPI, indicating that setting and unbounded time horizon may not be an upper bound on the population EVPI.

However, any price change will not generally be known in advance and there will be uncertainty in what the price change will be. Assume that the expected future price can be based on the expected proportion of the original price ($\delta = 0.8$), but the uncertainty surrounding this prior mean can be represented by a beta distribution:

$$\delta \sim \text{Beta}(12, 3), \quad E(\delta) = \frac{\alpha}{\alpha + \beta} = 0.8 \qquad (6)$$

The expected population EVPI can be estimated by sampling possible price changes from this prior distribution, calculating population EVPI for each sampled value of δ and then taking the expectation of these sampled population EVPIs. The impact of

uncertainty in expected price change is demonstrated in figure 4a. In this case integrating the uncertainty surrounding the future price change increases the expected PEVPI. Although the relationship between price and net benefit is multi-linear and since the parameters are independent the uncertainty in price does not effect the expectation of net benefit), the relationship between price and per-episode EVPI is markedly non linear (not illustrated here). The direction of the effect of non linearity will depend, among other things, on whether the technology is cost-effective before the fall in price. However, what is clear from figure 4a is that the uncertainty in future price change as well as the expected nature of the change matters for estimates of population EVPI.

Figure 4a. Expected PEVPI with an uncertain price change

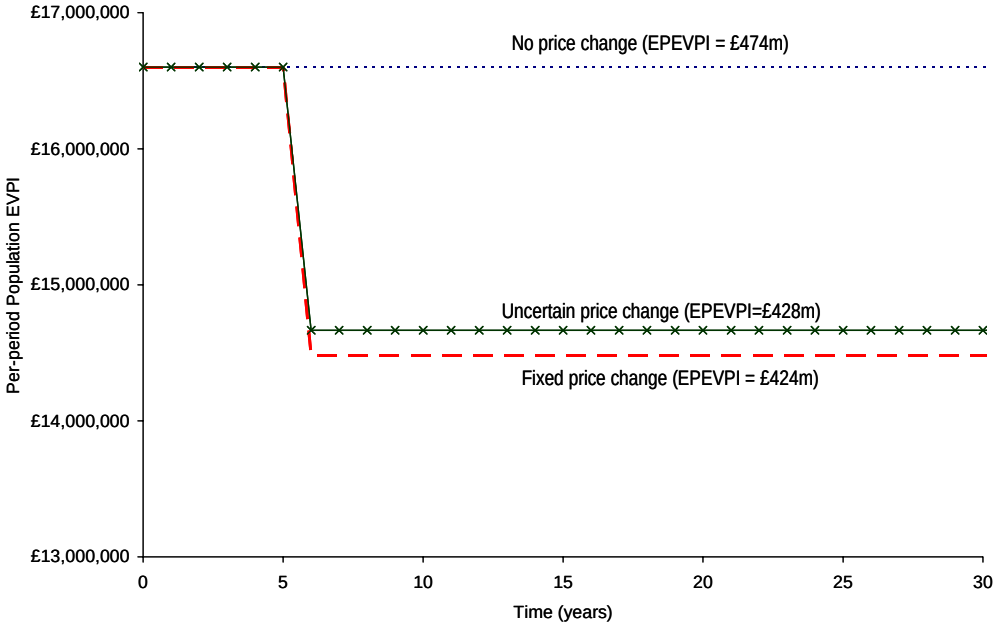
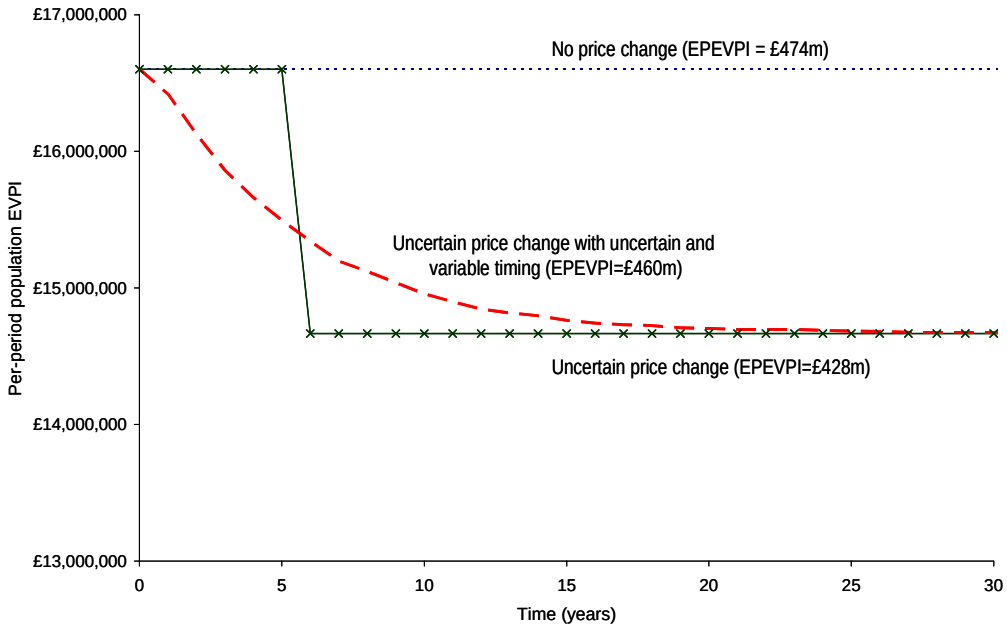


Figure 4b. Expected PEVPI with uncertain and variable time of change



The nature of future price changes will be uncertain but the expected timing of such changes may also be uncertain and there will also be variability in time to price change. We demonstrated in section 2.1 that the uncertainty in expected survival time and the variability in survival times will effect the estimate of the expected population EVPI because of the non linear relationship between population EVPI and T due to discounting. The same is true in this context. In this example, we assume that the expected time to price change is 5 years ($\lambda = 0.2$) but now λ is uncertain with a prior distribution:

$$\lambda \sim N(0.2, 0.0025) \qquad (7)$$

For a particular value of λ there will be variability in the time to price change:

$$T \sim \exp(\lambda) \qquad (8)$$

A possible price change (δ) and an expected time for this change (λ) must be sampled. Then, given the sampled values of δ and λ, PEVPI must be calculated for the possible sampled times for this change (T). Taking the expectation over T and then δ and λ provides the expected PEVPI. Figure 4b illustrates the impact on EPEVPI. Integrating uncertainty in the price change, the expected time of change and variability in timing generates an expected PEVPI of £460m which compares to £424m when uncertainty and variability is ignored and £428m when only uncertainty in price change is considered. However, a future changes in price is only one of many

types of change all of which may occur which will have an impact on expected population EVPI.

3.2. Information changes

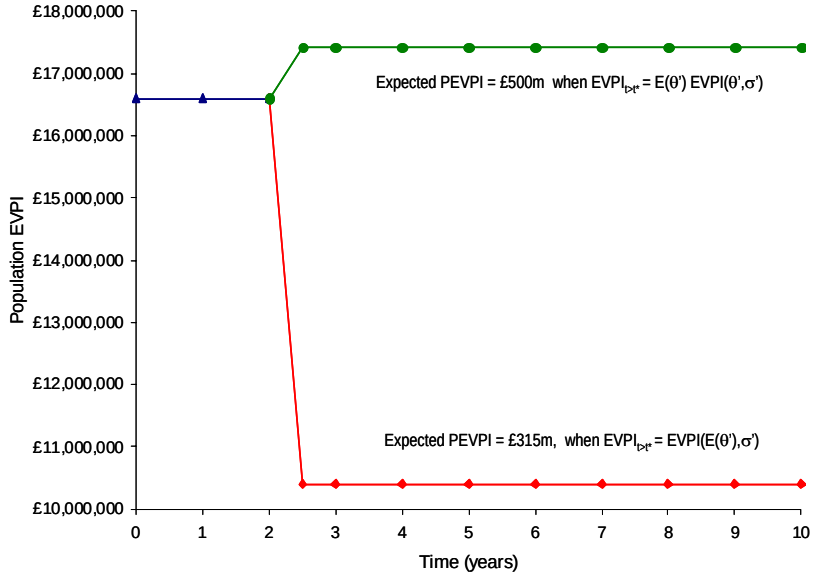
Another source of change is evidence being produced in the future which can inform the decision problem. Any research conducted now will have more limited value if current uncertainties may be expected to be resolved by research commissioned and conducted independently elsewhere. Often when decisions about the adoption of a technology are being made some information about ongoing trials which are recruiting, trials about to report and proposed trials are available. To examine this issue and the possible impact on estimates of the population EVPI we consider a situation when it is known that a trial will report in 2 years (t*=2), that it is also known how many patients will have been recruited at the time it reports (n*=1000) and it is also know that the trial will only provide information about the relative effect of the hypothetical drug treatment detailed in table 1. When this trial reports the information can be used to update the prior distributions on the model parameters (with means, θ and standard deviations, σ) to form posteriors (θ', σ'), reducing the uncertainty surrounding those parameters which are included as endpoints within the trial. Any assessment of the value of conducting research before this trial reports must account for the impact that this future information will have on the value of current research.

A naïve approach to this problem would be to take the expected posterior means from this trial E(θ') and the posterior standard deviations (σ'), and calculate the EVPI when this new information become available. Since the expected posterior mean will be equal to the prior mean (E(θ')=θ) and since the model is multi linear with independent parameters expected cost-effectiveness will be unchanged. The only effect is to reduce the uncertainty surrounding the values of these parameters (σ'<σ). The expected per-episode EVPI when the trail reports (t>t*) could be calculated given the expected posterior means and posterior standard deviations,

$$EVPI_{t>t^*} = EVPI(E(\theta'), \sigma') \qquad (9)$$

Clearly the EVPI must fall as the only change is a reduction in uncertainty. This is illustrated in figure 5 where the expected population EVPI falls from 474m to 315m.

Figure 5. Expected PEVPI with information change



However, this approach is naïve and potentially very misleading. The problem (as seen previously) is that although net benefit is multi linear with respect to θ (so that $NB_j(j, E(\theta')) = E_\theta, NB_j(j, \theta)$) the EVPI is not. Therefore, the EVPI must be calculated for each sampled predicted posterior mean which could result from the trial. The expected EVPI at t>t* is found by taking the expectation of EVPI over these possible posterior means:

$$EVPI_{t>t^*} = E_{\theta'} EVPI(\theta', \sigma') \neq EVPI(E(\theta'), \sigma') \qquad (10)$$

Since EVPI is markedly non linear in the value of the parameters there is no reason to expect the EVPI will necessarily fall. In this case, which is illustrated in figure 5, the expected EVPI is greater after the trial reports than before and the expected population EVPI increases to 500m when this expected information change is accounted for. Again, this challenges the notion that an unbounded time horizon provides an upper bound for the population EVPI.

Of course, as illustrated in the price change example above, additional uncertainties could be integrated into the estimates of expected population EVPI. These may include uncertainty in the design of the trial (e.g. expected sample size and included

endpoints) and the uncertainty and variability in when the trial may report. For trials reporting in the immediate future at least, this information may be known in advance. However, even when we are aware of on-going trials, with target sample sizes and report dates, there will still be uncertainty. As shown above with the price example, this uncertainty and variability matters for estimates of the expected PEVPI. Finally this example, like the uncertainty in price change, demonstrates the importance recognising the non linear relationship between EVPI and the value of parameters even when the relationship between net benefit and the parameters is linear.

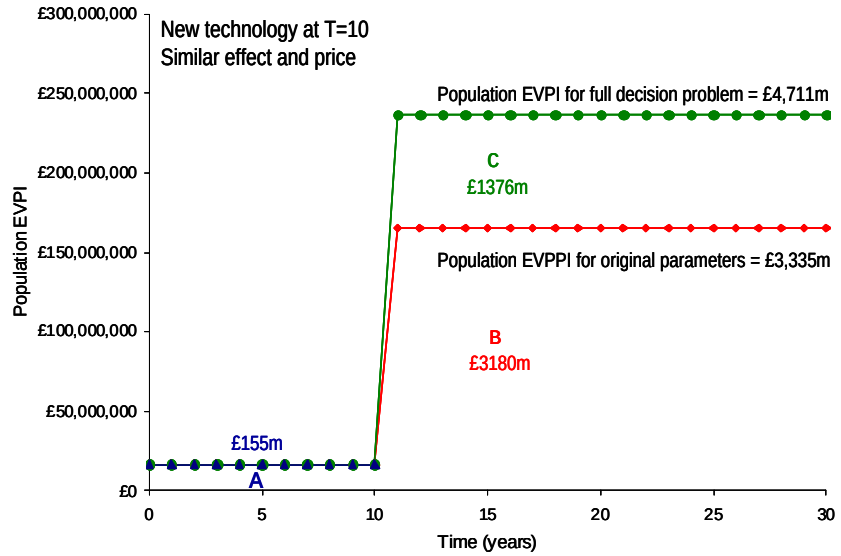
3.3. Entry of new technologies

It is inevitable that a new technology will enter the market at some point in the future. This will change the relative cost effectiveness and the uncertainty surrounding existing alternatives. The impact on decision uncertainty and EVPI will depend on the nature of the new competitor: the new technology may have similar effect and price (a 'me too'); may be more effective but have a higher price; or may be more effective and have a lower price. We examine the impact of the nature of technological change using three scenarios in our illustrative example, initially assuming that a new technology enters with a known price at time ($t^*=10$) and assuming that the uncertainty surrounding its relative effect is similar to the existing technology.

First, consider an example of a 'me too' competitor which has a similar relative effect and price as the original technology. Until time $t^*=10$ the per period EVPI for the decision problem remains unchanged and the population EVPI to this point is represented by area A in figure 6a. However, at $t^*=10$, the decision problem changes, there are now three rather than two alternative. The parameters upon which the current EVPI was based become a subset of all the parameters in this new decision problem at $t>t^*$. Research which could be conducted now can not provide information about a technology which is not yet available and can only provide information on what will become a subset of parameters in the future. Since the new technology has similar effect and price, we would expect decision uncertainty and the EVPI for the decision problem to increase. This is illustrated in figure 6a where EVPI for the full decision problem increases (area C+B). However the EVPPI for the set of original

parameters also increases (area B). Overall the expected population EVPI of research which could be conducted now, before the new technology enters, increases from £474m to £3,335m. Again this suggests that unbounded time horizons do not provide and upper bound to population EVPI.

Figure 6a. Entry of a 'me too' technology

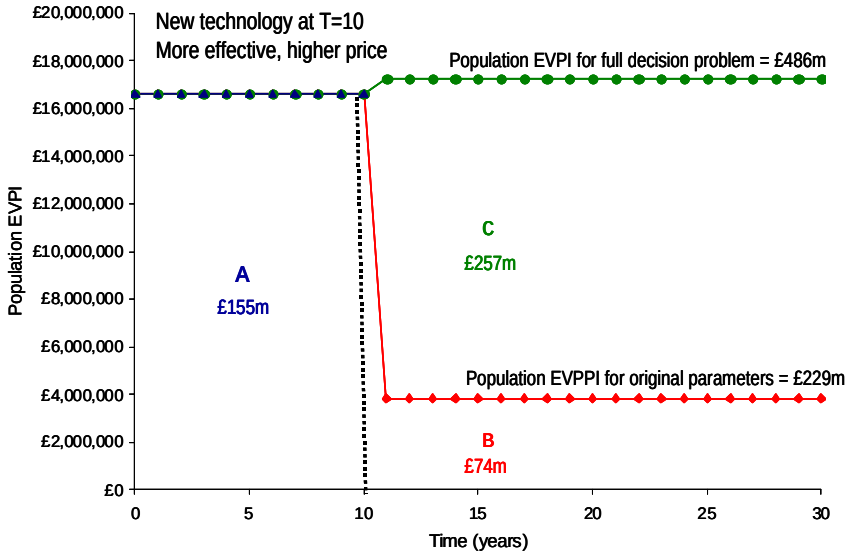


This analysis can also be used to consider the timing of research. If there is only one opportunity to conduct research then a decision maker could choose to conduct research now with a maximum return of A+B, or wait until expected technological change occurs and achieve and maximum return of C+B. By waiting they gain area C but loose area A (information is not available to inform treatment choice for episodes during $t<t^*$). In this case C>A, and it may be better to delay research until the technological changes has occurs. Of course, if research could be conducted now and at t^* then there maybe no reason to delay unless there are substantial sunk costs associated with the research.

Second, we can also consider the entry of a more innovative technology which is more effective but also has a higher price (see table 1) with an expected ICER of £2,191. This is illustrated in figure 6b. In this particular case the entry of the technology increases the EVPI associated with the new decision problem at $t>t^*$. However, the EVPI associated with the parameters in the original decision problem

falls, i.e., the new technology will be regarded as cost-effective and in this case information about the current technology less likely to change the decision.

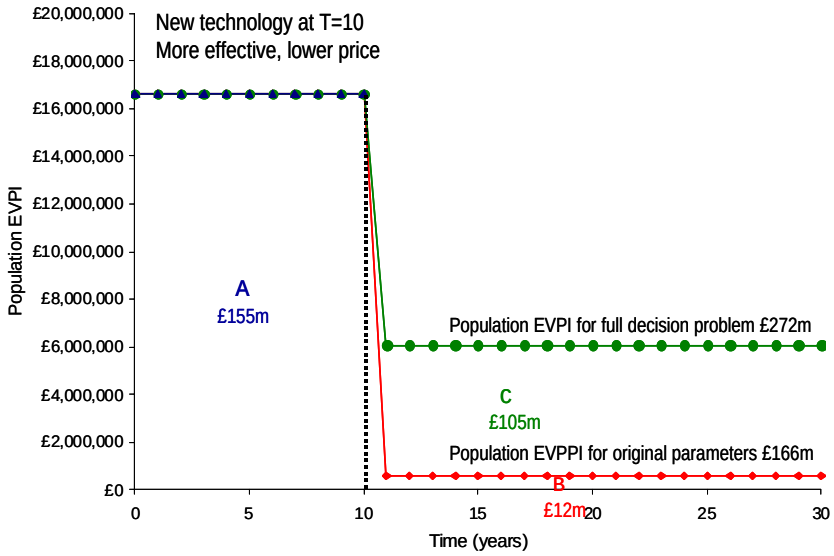
Figure 6b. Entry of a more effective and more costly technology



As previously, if the decision maker is forced to choose between conducting research now or waiting until the technological change occurs then it may be better to delay as C>A.

Finally, we consider entry a technology which is more effective but also has lower costs with and expected ICER of £409. This is illustrated in figure 6c and represents most closely the notion that the existing technology will become obsolete since the new technology dominates the old and decision uncertainty and EVPI is also reduced following entry. The EVPPI associated with the original parameters for the decision problem falls to very low values so that the expected population EVPI=£164m. In this particular case selecting a finite time horizon of 10 years would not be unreasonable (population EVPI = £155m). Indeed, it is the value of information associated with the base line parameters rather than the relative effect of the original technology which continues to have some value beyond t*. In these circumstances the research should not be delayed as C<A.

Figure 6c. Entry of a more effective and less costly technology



These scenarios are only indicative of the wide range of potential impacts that entry of technologies can have on estimates of population EVPI. The effect will depend on the whether the existing technology is regarded as cost effective and the associated uncertainty. It will also depend on the nature of the new technology and the uncertainty surrounding is effect and cost. In almost all cases the nature of technological change (effect, cost and uncertainty) will be uncertain as will the timing of any entry. We have already established that these uncertainties matter in the sense that they will effect the expected population EVPI. Of course in principle it would be possible to integrate over all these uncertainties. However, the computational challenge posed is considerable.

4. Discussion

What seems to be clear from this exploration is that the current approach to selecting a finite and somewhat arbitrary time horizon for the value of information generated by research is, in essence, an attempt to proxy an uncertain and complex process of future changes, which impact on the current decision problem and the expected value of information for the future population. It also seems clear that any uncertainty in

any estimated expected time horizons, whether based on historical evidence or on priors elicited from experts, and the variability in survival time will matter, i.e., it will effect on the expectation of population EVPI due to discounting. However, even if estimates of the time horizon are not chosen arbitrarily but based on evidence or formal priors they remain a proxy for a complex and uncertain process. Unfortunately we have also demonstrated that even an unbounded time horizon may not necessarily provide an upper bound on population EVPI. However, innovation and price competition leading to entry of 'better' technologies will ultimately reduce the value of information about existing alternatives. The problem is that it is difficult to know how good a proxy any particular time horizon would be.

One response to this problem would be to attempt to formal model all possible future change. However, a moment's consideration suggests that this would be at best heroic. We have already demonstrated that the computation required to account for the uncertainty in the nature of a single change and the uncertainty and variability in its timing is challenging. However, there are unlimited possible future changes, non of which are independent or mutually excusive. The prospect of formally modelling all possibilities would be futile and an inappropriate use of research resources. Therefore, it is important to ask what the purpose of this type of analysis really is: is it to measure some notional 'true' value of information or is it to inform decisions. If the former then those readers that believe that there are true values of EVPI, or any other parameter for that matter, waiting to be uncovered by dedicated researchers are referred to Rober Pirsig's Zen and the art of motorcycle maintenance, in an attempt to either preserve their metal health or their honesty in interpreting any analysis which is to be used for policy purposes.

However, if it's the latter then the prospects are less depressing. There is no truth, just more or less reasonable estimates leading to more or less reasonable decisions. The rightness or wrongness of the decision or the estimate can never be known. But we do know some things: i) sometimes the decision about the need or otherwise for research will not turn on the question of the time horizon. It will be obvious for certain decision problems that research (and some type of research based on estimates of EVPPI) is clearly needed or it is not. ii) We do know that changes that are likely to happen in the near rather than distant future will be more important and be more

predictable. Anticipating these changes, which are likely to have a bigger impact on EVI, are more amenable to formal analysis and are more likely to have and impact on decisions. iii) The reality of a complex and uncertain future is present in all decisions both in health care and elsewhere, whether or not it is subject to formal analysis. This suggests that these issues have implications for estimates for the cost effectiveness its self (particularly where there a sunk or implementation costs) not simply for value of information. It also suggests that other areas of research and analysis may have also attempted to grapple with this type of problem and found proxies for future change. For example, the use of derivatives and real options in financial economics and investment decisions are an example of simplifying an uncertain and complex prospect to a few tractable equations by making certain assumptions about the process of change and its independence over time. In searching for an appropriate proxy it is best to understand and appreciate the process you attempt to proxy. That has been our purpose in this paper.

Finally, one more thing we know is that if the process of distal change is unknown (it's random) then there maybe no reason to believe a-priori that it will affect some decision problems differently to others. Therefore, once we have accounted for the effects of anticipated and more immediate future changes, the selection of (possibly empirically based) remaining time horizon may not be unreasonable and would enable the relative value of conducting research in different area to be compared and research to be prioritised. Of course the alternative is to say we just don't know – the decisions about when additional research is needed and which areas of research should be prioritised will not disappear – it will simply be passed to others to make in the absence of formal analysis which makes explicit the key judgments required. Those readers who prefer this course are again refereed to Pirsig in an attempt to save their souls from the eternal damnation of abdication of responsibility for social decisions on the one hand and the madness that ultimately results from a comfortable, quaint but profoundly mistaken view of science on the other.

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Table 1. A stylised example

Probabilities

		Baseline risk			**Relative risk: new treatment 1**			**Relative risk: new treatment 2**		
	Distribution		Parameters		Distribution	Parameters		Distribution	Parameters	
Branch		Mean	Alpha	Beta		Mean	SD		Mean	SD
1	Beta	0.05	53	980	Lognormal	0.6	0.05	Lognormal	0.4	0.05
2	Beta	0.13	8	53	Lognormal	0.79	0.18	Lognormal	0.56	0.18
3	Beta	0.12	6	45	Lognormal	0.55	0.01	Lognormal	0.23	0.01
4	Beta	0.10	102	927	Lognormal	0.74	0.26	Lognormal	0.54	0.26
5	Beta	0.10	93	834	Lognormal	0.57	0.34	Lognormal	0.23	0.34

Outcomes

	Distribution	Parameters	
		Mean	SD
Survival (No MI)	Lognormal	17	1.2
Survival (MI)	Lognormal	7	1.1
Utility decrement (No MI)	Gamma	0.2	0.2
Utility decrement (MI)	Gamma	0.05	0.1

Costs

	Distribution	Parameters	
		Mean	SD
PCI	Gamma	£8,169	£1,009
MI	Gamma	£4,031	£301
Death	Gamma	£935	£264
New treatment 1	Fixed	£3,000	-
New treatment 2	Fixed	£3,500	-