Dangerous Omissions: The Consequences of Ignoring Decision Uncertainty

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Purpose: To demonstrate that decisions based on expected incremental net benefit (INB) will be inappropriate when agencies cannot commission or mandate additional research. To establish the opportunity costs of decision uncertainty and illustrate their impact on appropriate decision rules in cost-effectiveness analysis.

Background: The decision to adopt a technology should be based on expected INB and the uncertainty around that estimate should inform the simultaneous decision to demand or commission further research. However, institutions with the remit for making adoption decisions often lack the remit to demand that further research is conducted and are separated from those responsible for commissioning research. Such decision-makers do not directly control future research, so the adoption decision is their only policy instrument.

Methods: The prospects of acquiring further evidence about a technology are not independent of the adoption decision. In the face of a positive adoption decision, incentives for conducting future research can be reduced and further experimental research may be regarded as unethical. Hence, the opportunity loss of adoption should include the forgone expected value of information (EVI) for current and future patients. The opportunity loss of rejecting an apparently cost-effective technology will be the INB forgone by current and future patients. Using decision theory and value of information analysis, it is possible to establish appropriate decision rules which take account of these opportunity losses and an assessment of the uncertainty surrounding when new evidence may become available.

Results: The expected net benefits of immediate adoption vary between a maximum gain equal to INB of the optimal strategy based on current evidence and a maximum loss equal to EVI. We show that the expected net benefits of adoption fall as the incremental cost-effectiveness ratio (ICER) approaches the threshold and decision uncertainty increases. This introduces incentives on sponsors to provide more evidence or reduce the price of technologies. By integrating over the uncertainty surrounding the arrival of further evidence, it is possible to determine decision rules in terms of expected opportunity loss.

Conclusions: Decisions based on expected INB do not account for the full opportunity loss of a decision to adopt a technology. Failure to account for this opportunity loss results in decision rules that are too permissive and will undermine the evidence base for clinical practice.

1. Introduction

A number of decision rules have been proposed for identifying the optimal treatment strategy and optimal course of action based on the results of formal cost-effectiveness analysis (CEA). A Bayesian decision theoretic approach and an option value approach are among those that explicitly incorporate a consideration of decision uncertainty.[1 2] The way in which uncertainty is handled by these methods differs from the classical frequentist approach of calculating a test statistic in order to determine statistical significance. Decision-makers appear to have accepted the irrelevance of inference argument,[1] as none discernibly recommend the use of traditional inferential rules such as *p*-values, confidence intervals or significance testing around the results of CEA. However, those same guidelines issued by decision-makers such as the National Institute for Health and Clinical Excellence in the UK (NICE)[3] and the Canadian Coordinating Office for Health Technology Assessment (CCOHTA)[4] do not include a formal method for considering decision uncertainty. Thus they may not convince their constituency that they have considered the relationship between decision uncertainty, the adoption decision and decisions about future research. Arguably decision-makers may be informally considering decision uncertainty. However, when methods exist to quantify the impact of that uncertainty with little additional work above that required to provide an unbiased estimate of expected net benefit (NB) this potentially inconsistent and opaque approach may appear redundant.

In this paper we highlight the potential opportunity loss of failing to consider decision uncertainty in adoption decisions. We present a decision rule that applies to decision-makers with the remit to allocate health-care resources, but who cannot themselves initiate the collection of additional evidence. Importantly we consider the effect an adoption decision can have on the potential or option for future research.

2.1 Decision-making: how it should work[1]

Economic evaluation compares the costs and consequences of relevant alternative health-care interventions. In the absence of dominance (one alternative is found to be most effective and least costly) in order to establish whether one alternative is more cost-effective than another, a decision rule must be applied.[5] It has been proposed that the incremental cost-effectiveness ratio (ICER) be compared to the some acceptable price per effectiveness unit, based on the shadow price of the budget constraint ($1/\lambda$). Once the price per effectiveness unit has been established, this decision rule can be used to express the results of a CEA in terms of net benefits

(either monetary or health benefits). This is shown in equations (1a) and (1b) where the costs, C_j, and health outcomes, U_j, of treatments *j* are used to calculate an ICER for comparison to an acceptable threshold value, or rearranged to calculate net monetary benefit:

(1a) $$ICER = \frac{C_2 - C_1}{U_2 - U_1} < \lambda$$

(1b) $$NB_1 = \lambda U_1 - C_1 > 0$$

Irrelevance of inference

It has been argued that inference, based on the notions of significance testing, confidence intervals and *p*-values, is irrelevant for the decision about which health-care programmes to adopt and/or fund. If the objective is to maximise health gain for a given budget, the adoption decision should be based on the mean expected NB, regardless of whether any differences are regarded as statistically significant.

However, even though the distribution of NB is irrelevant to the choice between mutually exclusive alternatives, it is argued that it is still relevant to the decision of whether to collect more information to inform this choice, either now or in the future. There is an expected cost of decision uncertainty (i.e. the uncertainty in the estimated NB) which is determined by the probability that a sub-optimal programme was selected (probability that incremental NB (INB)<0), and the size of the opportunity loss given a wrong decision. The upper bound of this cost is the expected value of perfect information (EVPI), as in the presence of perfect information (zero uncertainty), we would not make a wrong decision.

(2) $$EVPI = \underbrace{\mathrm{E}_\theta \max_j NB(j,\theta)}_{\text{I}} - \underbrace{\max_j \mathrm{E}_\theta NB(j,\theta)}_{\text{II}}$$

The second term of the equation for EVPI is the expected NB of the optimal treatment based on current evidence. The first term is the expected NB of the optimal treatment choice given perfect knowledge of θ. Information from future research only has value if it changes the optimal adoption decision. So, for this example, those values of θ for which we would choose treatments that do not have

the highest expected NB based on current evidence generate positive value, whereas those that do not change our decision generate zero value. Total EVPI represents the sum of these values over the expected realisations of θ. This formula for per patient EVPI can then be multiplied by the number of patients expected to benefit over the expected lifetime of the technology. Collecting additional information can reduce the size, and expected cost, of decision uncertainty. A potential gain in NB can be made by conducting further research where the expected cost of decision uncertainty exceeds the cost of collecting additional information.

The Bayesian decision theoretic approach that emerges from the above considerations views decision-making as an iterative process in which two conceptually distinct decisions are made simultaneously: i) the decision about which alternative to implement is made on the basis of expected NB, and ii) the decision is taken about whether to gather additional information. If more evidence is acquired, both decisions are then revised in the light the new information. Clearly this framework can only be put into practice if decision-makers can address the adoption decision and the decision about acquiring additional information simultaneously. This would be possible if the decision-maker:

i. Has the remit to make decisions about both adoption/reimbursement and the remit to prioritise and commission research;
ii. Has the remit and legal standing to issue and enforce conditional approval; where technologies are adopted or reimbursed, now or in the future, only if the required research is conducted.

In both cases, an adoption decision on the basis of expected NB is optimal because any research for which the value of additional information exceeds the costs of obtaining that information would be conducted. In this 'first-best' world it would be possible to obtain maximum expected value for both current and future patients. This is the context in which the original irrelevance of inference argument was formulated. However, decision-makers that can simultaneously address the allocation of healthcare resources and the funding of additional research may not exist in practice.

Option value

If there are sunk costs associated with implementing a technology then adoption may be delayed until any additional research reports. This may also apply if there is an irreversible element to the decision to reimburse. The economic value in deferring an

adoption decision in this way has been explored with option-pricing techniques.[2] The value of delaying a decision until additional evidence is available can be measured by EVPI. A decision to proceed with an irreversible decision removes an option, and the option value increases with the level of uncertainty and the time horizon over which a decision may be deferred. The implications of this approach is that the expected NB of any treatment option must exceed zero by some additional premium to account for the option value in order to make the decision to adopt immediately worthwhile.

2.2 Decision-making: how it tends to work

For the most part the authorities charged with making the adoption decision typically do not have control of health care services research because: they cannot or do not control the funding and commissioning of research; and/or they cannot issue or cannot enforce conditional approval.

For example, NICE was set up to issue guidance about the use of licensed treatments in the NHS in England and Wales. The decisions made by NICE are informed by the ICERs of relevant alternatives, which are calculated based on a systematic review of current evidence. The Institute can make recommendations about future research, but it does not directly fund research and it cannot instruct research funders or manufacturers to commission or even prioritise research. NICE also lacks a formal mechanism for issuing conditional approval that has legal sanction for the enforcement of conditions.[6]

In practice, funding and initiation of future research will be undertaken by other bodies, which may not have the same objective functions as the authority charged with making the adoption decision. For this reason the research that is conducted may not meet the needs of the decision-maker. One could argue that if decision-makers cannot in practice control the production of future research, they could omit any consideration of decision uncertainty when taking adoption decisions. In the presence of sunk costs or irreversibility, one might like to consider the option value of the adoption decision. However, this approach characterises a situation in which the decision-maker plays a passive role in the emergence of new information. In practice, the completion of future research is not independent of the adoption decision. A decision to adopt or reimburse a particular health care technology, particularly if mandatory (as in the UK), will impact future research in numerous ways:

i. The incentive for the sponsor to conduct further research is removed (in the absence of a new competitor).
ii. The approval decision eradicates the pretence of clinical equipoise, so that it becomes unethical to enrol patients into new trials.
iii. The change in practice following an adoption decision may halt or damage existing trials.

For example, the decision to approve the use of paclitaxel as first-line therapy for ovarian cancer reduced the number of patients available for enrolment into clinical trials to assess its effectiveness as a second-line therapy. An ongoing trial comparing paclitaxel to an alternative treatment for second-line treatment of ovarian cancer was consequently stopped early. Paclitaxel remained a relevant comparator in the second-line treatment of ovarian cancer, but the decision about its cost-effectiveness in this setting was based on reduced evidence as a result of the previous adoption decision.[7]

Even though they may not be able to directly commission or require future research, decision-makers have control over the amount of evidence available in the future through their ability to grant or withhold approval. Thus the decision to issue immediate approval can remove not only an option to defer that decision, but also an option for future research. This additional element (over and above traditional sunk costs or irreversibility) represented by the opportunity loss of forgone research is the focus of this paper.

3. The costs of omission

The adoption or rejection of a technology may be the only policy instrument available to a decision maker concerned with the allocation of scarce health care resources. Under these circumstances decision makers should not ignore the effect of the adoption decision on the potential for future research, and must therefore consider more than expected NB. In this section we calculate the opportunity losses associated with the adoption or rejection of technologies that would be judged cost-effective on the basis of expected NB. We then use this information to formulate decision rules that can be applied to the results of a CEA and that reflect any opportunity loss of forgone research.

3.1 The opportunity loss of adoption decisions

The opportunity loss of rejection

The treatment strategy that would be optimal based on all current available evidence can be identified on the basis of expected NB. In other words the treatment with the maximum expected NB is optimal, as indicated by the second part of equation (2). If any other strategy is selected, the opportunity loss to current patients can be measured by the difference in NB between the optimal strategy and the strategy selected. So, basing adoption decisions on expected NB minimises expected opportunity loss to current patients.

The opportunity loss of adoption

The opportunity loss of the decision to approve a technology is measured by the value of information which could have been generated by any research forgone as a result of approval being granted. By reducing the amount of information available for future decisions, the probability of selecting a sub-optimal decision is increased, which would therefore result in an opportunity loss in terms of NB for future patients. If decision-makers take account of the opportunity loss of approval, the optimal adoption decision cannot be based solely on expected NB. If decision-makers ignore the impact of expected-value decision-making on the potential for future research, the objective to maximise health benefits over time will not be achieved. In the following sections we demonstrate, using stylised examples, why decision-making based only on expected NB is sub-optimal and can damage the evidence base for current and future clinical practice.

Calculating opportunity loss

Suppose we consider a decision-maker whose role is limited to granting approval for the reimbursement of health-care programmes. When choosing between a set of mutually exclusive alternative programmes, j, they have two options: approve the treatment with the highest expected NB, that is the optimal treatment j_o; or withhold approval of the optimal treatment, in which case patients receive current practice, j_c. There are costs and consequences to each option, as illustrated in Table 1.

Table 1. Consequences from granting or withholding approval

	Approve optimal treatment on the basis of current evidence	Withhold approval (leaving current practice unchanged)
Benefits	**B_A** Patients receive treatment with highest expected net benefit now.	**B_{WA}** Future research on A proceeds, reducing decision uncertainty for a future decision.
Costs	**C_A** Future research on A is deterred and the future benefits from that research are forgone.	**C_{WA}** Patients denied treatment with highest expected net benefit now.

The same probabilistic decision model used to estimate the NB of each treatment can be used to quantify the expected value of the benefits and costs associated with each option (although we need only consider one option as each is the complement of the other). This can be done by calculating EVPI.

Immediate approval of the new technology results in a gain equal to the expected INB of the optimal strategy, INB_o, for patients, current and future. If immediate approval deters all research, the (upper bound of) opportunity loss will be measured by EVPI forgone. For now we will ignore the issue of the timing and probability of future research so that we can express the net benefits of approval, NB_A, very simply as:

(3) $$NB_A = INB_o - EVPI$$

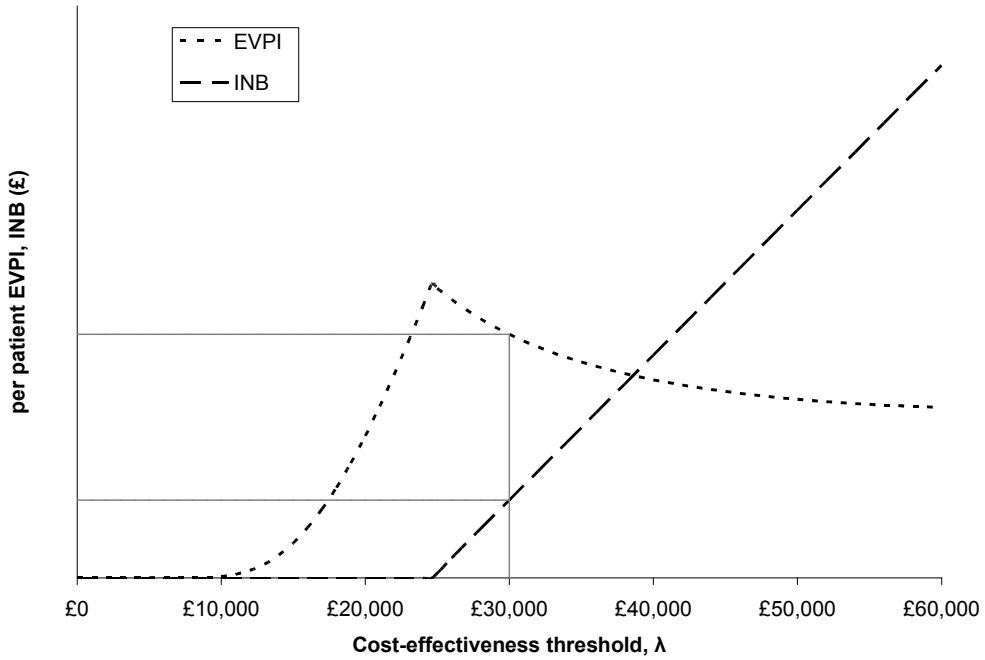
If EVPI is small (i.e. the per patient EVPI is less than the per patient INB of the optimal strategy based on current evidence) we know that there will not be much opportunity loss associated with approval now, even if it deters future research. For example, an assessment of long term antibiotics for the prevention of urinary tract infections in children found that cotrimoxazole was expected to be cost-effective in boys aged 3 with no VUR, with an ICER of £20,476. The per patient EVPI was so small that the total population EVPI for this decision problem was only £22,547.[8] However, if the EVPI is high (i.e. the per patient EVPI is greater than the per patient INB) then we may wish to explore further to discover whether approval based on current evidence could result in an overall loss of NB. For example, a comparison of

clopidogrel and aspirin for the secondary prevention of occlusive vascular events in patients who had experience myocardial infarction estimated the per patient INB of clopidogrel to be £304 for a 2 year treatment duration. The estimated per patient EVPI was £387 at this cost-effectiveness threshold of £30,000 per QALY, reflecting the large amount of decision uncertainty.[9]

3.2 Opportunity loss and the cost-effectiveness threshold

The INB of a treatment strategy will tend to zero as the ICER approaches the threshold for cost-effectiveness, λ. In other words, as the ICER approaches λ, there is little difference between strategies in terms of expected NB, and so little consequence in terms of benefits forgone if the second best strategy is selected. In contrast, a graph plotting EVPI against the cost-effectiveness threshold will display a peak or inflection at the point where the cost-effectiveness threshold is equal to the ICER of an optimal treatment strategy. When the ICER is equal to λ the decision about which treatment is preferred is most uncertain, and the likelihood of making the wrong choice is at its greatest. Figure 1 illustrates this relationship for an example where the ICER of a new technology compared to current practice is £25,000.

Figure 1. Relationship between ICER, EVPI and λ



At a cost-effectiveness threshold of £30,000 per QALY the technology would be adopted under a decision rule based on expected cost-effectiveness. Indeed the decision to reject the technology under these circumstances would incur an expected opportunity loss, in terms of NB forgone, of £160 per patient for current and future

patients. However, the decision to approve this technology would also incur an opportunity loss if that decision deterred future research. The EVPI of £280 per patient represents the upper bound of this opportunity loss. In the example shown in Figure 1 the EVPI exceeds the INB at a threshold of £30,000 per QALY, and the maximum opportunity loss from adoption exceeds the expected opportunity loss of rejection. This means that the decision to approve on current evidence would carry a positive opportunity loss (NB_A<0). Only for values of λ greater than £38,000 would the opportunity loss of rejecting the new technology exceed the EVPI, and the NB_A be positive. This demonstrates that decisions cannot simply be based on expected NB if approval deters research. In this example the sufficient condition for adoption is not λ > £25,000 but λ > £38,000.

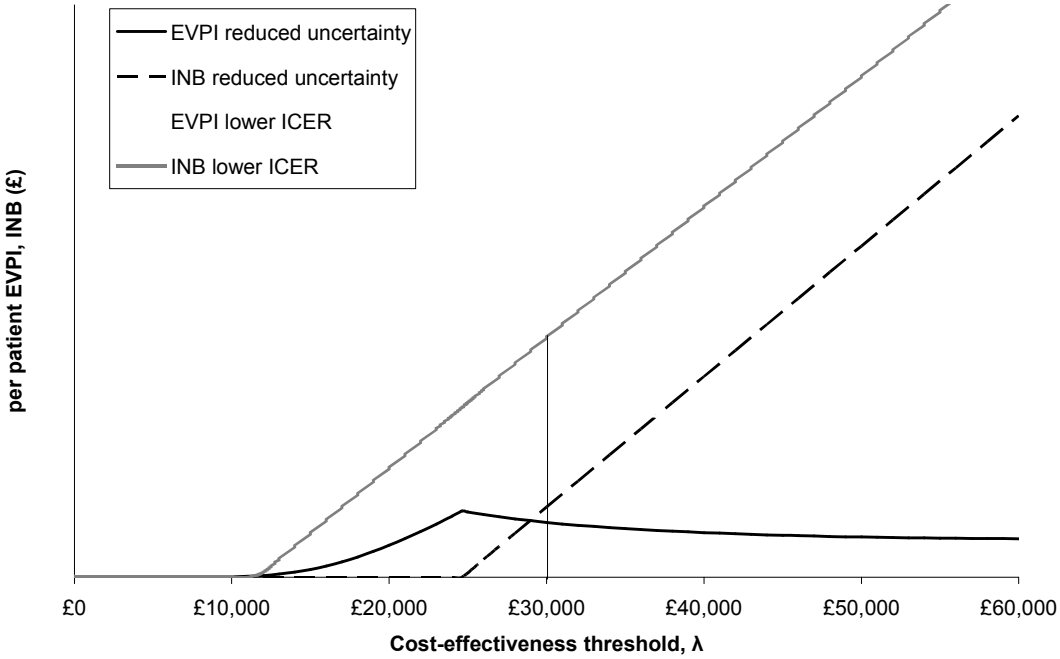
Incentives to manufacturers

If manufacturers believe that decision makers approve technology solely on the basis of expected NB, they have no incentive to provide evidence other than that required for licensing, and they also have an incentive to price their technology such that the ICER comes in just under the cost-effectiveness threshold. By doing so they can minimise research and development costs and fully capture consumer surplus to maximise profits. In contrast, decision rules that consider the opportunity loss of approval do provide incentives for manufacturers to either provide more evidence to support adoption or to reduce price. Indeed we can show the trade off for manufacturers between price and evidence.

Reducing uncertainty

The decision problem can be modified by reducing the uncertainty around the model parameters. This could be achieved if, for example, the manufacturer of the new technology provides additional evidence. Figure 2 demonstrates the case where additional information has been collected, reducing decision uncertainty but leaving the ICER unchanged. In this instance, given a cost-effectiveness threshold of £30,000 per QALY we would accept the new treatment based on current evidence because the opportunity loss from rejecting is greater than the EVPI (NB_A>0). So for the same ICER below the threshold for cost-effectiveness, the decision whether to accept or reject is dependent on the level of uncertainty, that is the opportunity loss associated with an approval decision based on current evidence.

Figure 2. Reducing uncertainty or reducing price



Reducing price

Suppose instead of collecting additional information, the manufacturer reduces the price of the new technology, thereby reducing the ICER. At a threshold of £30,000 per QALY this will reduce decision uncertainty but it will also increase the opportunity loss of rejection. This is also shown in Figure 2. The EVPI is a little lower than that shown in Figure 1, but the opportunity loss of approval is shifted to the left and NB_A would be positive. Now the same technology with the same evidence as that shown in Figure 1 but with a lower price should be accepted on the basis of current evidence.

If decision-makers were to formally consider the costs of decision uncertainty, the number of new technologies approved would be reduced in comparison to a decision rule based solely on expected NB. The decision to reject technologies with ICERs higher than the threshold would be unaffected, but some technologies with ICERs below the threshold would be rejected. The most affected technologies would be those with ICERs close to the threshold. Following a decision to reject a new technology on the basis of positive NB_A, manufacturers could alter the decision in two ways: they could collect additional information or they could lower the cost of the new technology, thereby reducing the ICER.

3.3 Timing and probability of future research

The comparison between per patient EVPI and per patient INB is relevant if we have to choose either INB or EVPI over the lifetime of the technology. In reality, the trade off will be more complex. There is likely to be a delay before additional information is available, and hence the EVPI would be valued over a period shorter than the time between the decision and the lifetime of the technology. Additionally, once new information is available, the adoption decision may be revised. Hence the opportunity loss, in terms of INB, from rejecting a cost-effective technology may only impact up until the time at which additional information became available. In a world where the decision-maker does not control future research, there is uncertainty over whether the future research will be conducted and when it will report. Thus calculating the benefits of withholding approval features two additional components, the probability that future research will be conducted, P_R, and the expected time that evidence from this research would be available, t_R. Both INB and EVPI must be multiplied by the incident number of patients in each year, I, discounted by some appropriate rate, r. To simplify the equations we will define T_x as the total discounted patient population at time t_x.

$$T_x = \sum_{t=1}^{t_x} \frac{I_t}{(1+r)^t} \qquad \text{; where } x = R, L \tag{4}$$

For simplicity, we assume that approval reduces the probability of future research, P_R, to zero. In addition, we can assume that t_R is less than or equal to the lifetime of the technology, t_L, as there is no incentive to conduct research once a technology is obsolete. The benefits of approving the optimal treatment on the basis of current evidence (costs of rejecting the optimal treatment) are then:

$$B_A = T_L . \max_j \mathrm{E}_\theta NB(j,\theta) \tag{5}$$

If we assume that future research on θ will report at time T_R, the costs of approval (benefits of withholding approval) can be expressed as:

$$C_A = T_R . \mathrm{E}_\theta NB(j_c,\theta) + (T_L - T_R).\left[P_R . \mathrm{E}_\theta \max_j NB(j,\theta) + (1-P_R).\mathrm{E}_\theta NB(j_o,\theta)\right] \tag{6}$$

The NB of approval of a treatment on the basis of current evidence, NB_A, is therefore equation (5) - equation (6), which can be expressed as:

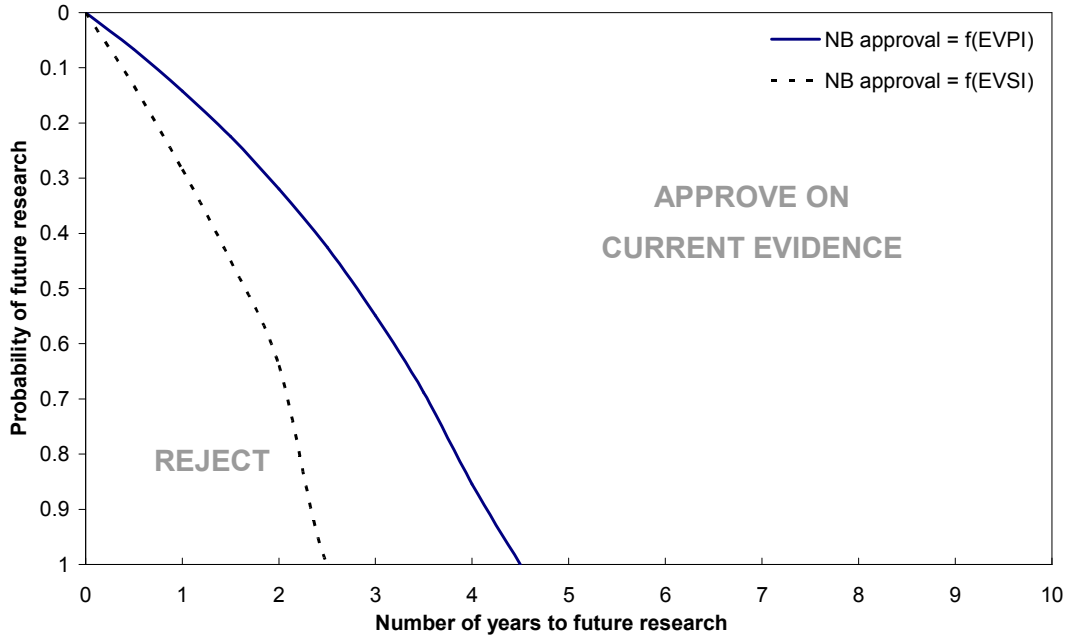
$$(7) \qquad NB_A = B_A - C_A = T_R.\left[\mathrm{E}_\theta NB(j_o,\theta) - \mathrm{E}_\theta NB(j_c,\theta)\right] - (T_L - T_R).P_R.EVPI$$

In the case a comparison between two treatments, the first term on the right-hand side (R.H.S) of (7) is INB_{jo} multiplied by T_R. If the probability of future research is negligible, or the expected lifetime of the technology is close to the expected time at which future research evidence will be made available, then we would expect NB_A to be positive.

Uncertainty about future research

So far we have considered the case where T_R and P_R are known. We can now consider the decision problem If T_R and P_R are allowed to vary. For a given value of λ we can calculate the combinations of T_R and P_R for which the expected NB_A are zero. This represents our indifference curve where the expected opportunity loss from rejection is equal to the expected opportunity loss from adoption (there is zero expected opportunity loss associated with immediate adoption or rejection). Figure 3 plots this line of indifference for the example from Figure 1 (with ICER = £25,000, T_L = 10, annual population = 6,000, discount rate = 3.5% and λ = £30,000).

Figure 3. Indifference curve for approval based on current evidence, λ = £30,000

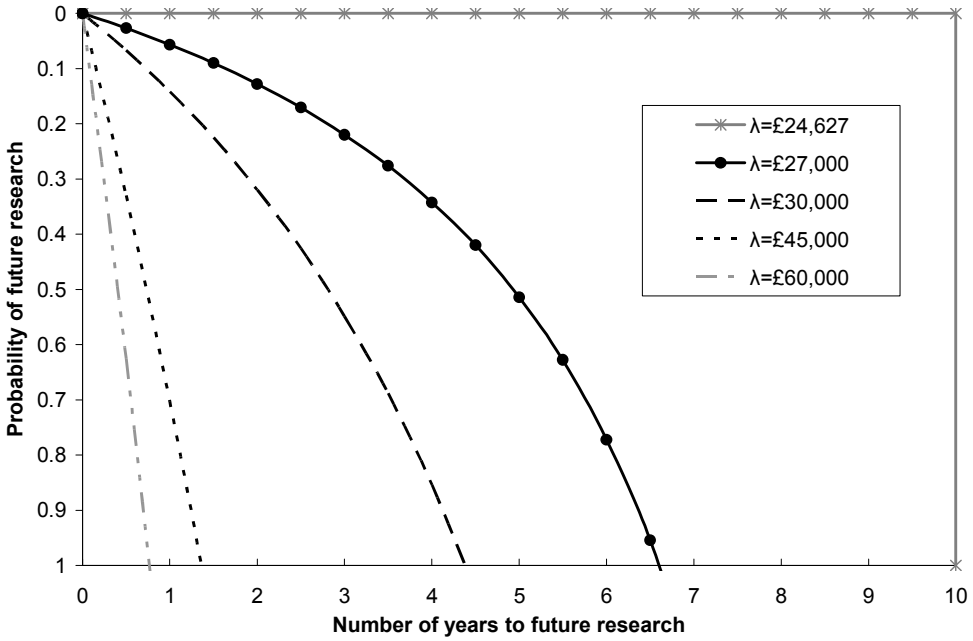


Above this line of zero NB_A, we would always choose to approve the new treatment on the basis of current evidence (it meets the sufficient condition for adoption). This is because EVPI represents the maximum value of future research, and if NB_A is positive with perfect information it will also be positive with less than perfect (sample) information. The region in which we would always reject the optimal strategy based on current evidence is less clear. The indifference curve for approval calculated using expected value of sample information (EVSI)[10] will be lower than that calculated using EVPI. This results in a region where NB_A may be negative based on perfect information, but is positive based on sample information. For any given point below the line of zero NB_A we could calculate the threshold value of EVSI below which we would choose to accept on the basis of current evidence. Of course as P_R approaches 1 and T_R approaches 0 below the indifference curve we would be increasingly likely to reject on the basis of current evidence.

In this example we would not be willing to wait more than 4.5 years for the results of future research. Likewise, to wait even 1 year for research the probability of research reporting over that next year would need to be at least 0.15, increasing to a constant annual probability of 0.38 if we expected to wait 4 years.

As λ approaches the ICER, this line of indifference will move further up and to the right, until where λ=ICER there is no region of acceptance based on current evidence. This is because at this point there is no opportunity loss to rejecting the new technology, and the opportunity loss of approval will be high. As λ moves further away from the ICER the line of indifference will move down and to the left, and we become more likely to accept on the basis of current evidence. Figure 4 illustrates this by showing the line of zero NB_A for a range of values of λ.

Figure 4. Indifference curve for approval for a range of values of λ



The expected value of NB_A will vary between a maximum gain equal to INB (where P_R = 0 and/or T_R >= T_L and/or EVPI = 0) and a maximum loss equal to EVPI (where P_R = 1 and T_R = 0, and/or INB = 0). For example, an assessment of antibiotic prophylaxis may demonstrate large decision uncertainty around the impact of antibiotic resistance, but it may be considered infeasible to design a trial to reduce this uncertainty (P_R = 0) or the time scale for any possible trial design may exceed the expected lifetime of the technology (T_R >= T_L).

If we can characterise the uncertainty around P_R and T_R we can calculate expected NB_A. For example, at the time the adoption decision is taken, it may be known that there is a new registered trial that is recruiting patients. Information about the expected rate of patient accrual and expected time at which the results will be available should already have been calculated in setting up the trial. We could then calculate the expected NB_A, integrating over the uncertainty in P_R and T_R. We can plot expected NB_A for different values of λ, as shown in Figure 5.

Figure 5. Expected net benefits of immediate adoption based on expected INB

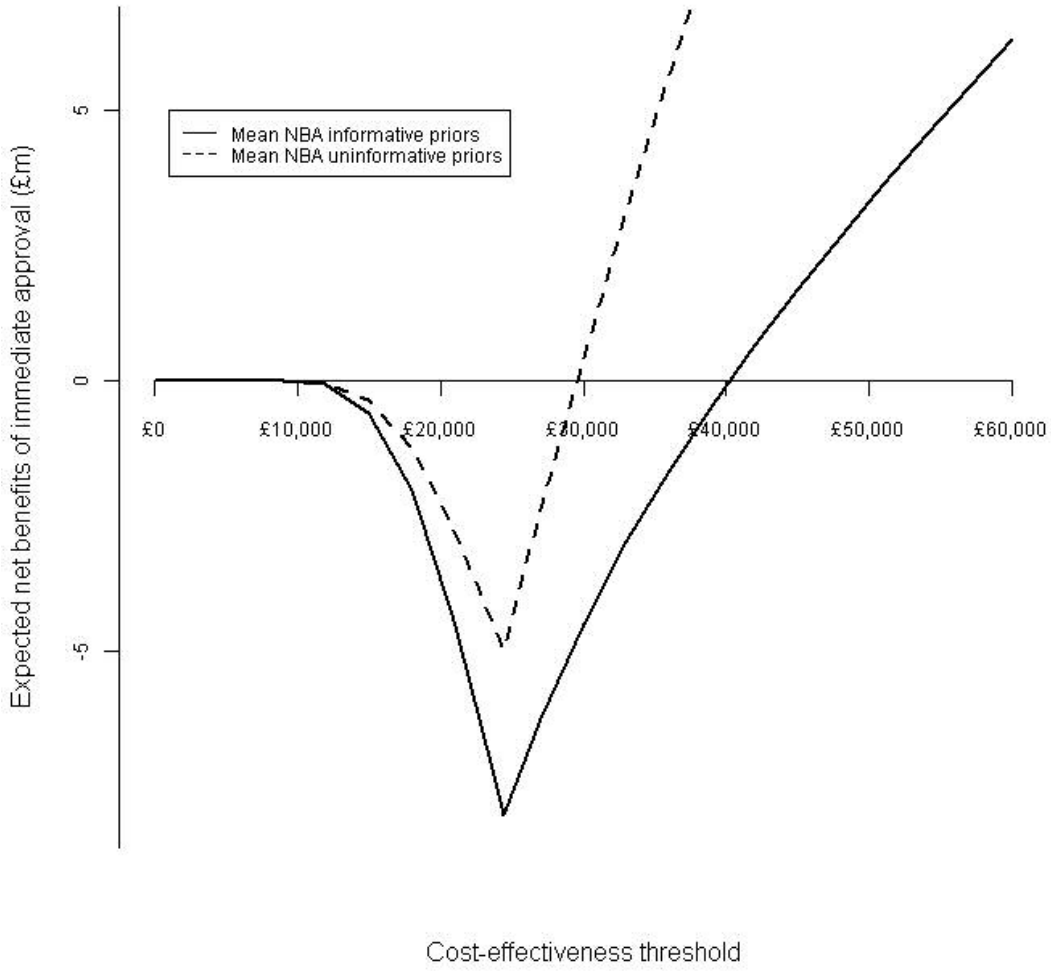


Figure 5 shows the expected net benefits of adoption for the example shown in Figure 1, where the per patient INB was £160 and the per patient EVPI was £280 at a threshold of £30,000 per QALY. We can calculate expected NB_A for uninformative uniform priors on T_R and P_R, in which case the expected net benefits of adoption are positive at a threshold of £30,000 per QALY. However, suppose we knew that a trial was in progress that was expected to report in 2 years (plus or minus 6 months), and we were 50% certain the trial would complete and the results be published. By using this information to specify informative priors for T_R and P_R, we see that although the ICER remains less than £30,000 we would not necessarily accept the new technology on the basis of current evidence because the expected NB_A is negative (on the basis of perfect information). In other words, the technology does not meet the sufficient condition for immediate adoption. Since future research will not provide

perfect information, a necessary condition for rejection requires estimates of the EVSI. This may be computationally expensive, but given this prior information about T_R and P_R we can calculate the threshold for the per patient EVSI would have to be less than £70 for the technology to be acceptable at a threshold of £30,000 per QALY.

4. Discussion

In a first-best world it would be possible to base adoption decisions on expected NB because any future research that would result in a net gain for the health care system would still be undertaken. In practice we are in a second-best world where a large proportion of research is conducted merely to obtain licensing approval. There are a number of reasons why potentially valuable research may cease following an positive adoption decision due to the affect this has on the ability to recruit patients to clinical trials, both in terms of numbers and ethics, and the fact that once reimbursement is secured the manufacturer has no incentive to conduct further research. In this second-best world adoption decisions based on expected NB without consideration of decision uncertainty forgo potential NB of future patients in favour of maximising the NB of current patients. We have shown that if current and future patients are considered equal, this can result in an expected loss of net benefit. The likelihood of a net benefit loss is particularly high if the estimated ICER is close to the threshold for cost-effectiveness, which may be the case with technologies approved by NICE if they have an ICER in the range £20-30,000 per QALY. The opportunity loss of withholding adoption of a technology which appears cost-effect based on current evidence may be necessary to ensure that additional information is obtained. This is in addition to any deferral value conferred by other sunk costs associated with approval, such as the purchase of specialised capital equipment with little resale value, or the effort required to change clinical practice.

Although the formal consideration of decision uncertainty described in this paper is not explicitly used by decision-makers, it is possible that some informally consider decision uncertainty when making an adoption decision. Formalising the approach to considering decision uncertainty has a number of advantages:

i. It ensures consistency and transparency in decision-making within and between technology appraisal since the estimates of opportunity loss are based on the same analysis which is used to provide estimates of cost-effectiveness;

ii. it discourages manufacturers from attempting to fully capture consumer surplus by pricing new technologies so that the ICER is just under threshold for cost-effectiveness;
iii. by being explicit it provides clear incentives to manufacturers in the case of rejection to either invest in providing sufficient evidence or reducing prices.

Future costs of omission

So far we have considered the opportunity loss of failing to get additional information for the current decision problem. In fact, the true value of additional information may exceed that based on the current decision problem if that information can be used in future decisions. For example, if a new comparator were to emerge, evidence on existing comparators feeds into the network used to inform the new decision problem. Methodological work in the area of VOI may allow such future events to be incorporated in the calculation of EVPI. This issue becomes more critical as adoption decisions are made close to the time at which new technologies are licensed. There is a danger that early adoption decisions could undermine the network of evidence for future technologies.

Partial information and sample information

Our discussions so far have focused on the EVPI for the whole (current) decision. Clearly this represents an upper limit for the opportunity loss of forgoing future research for two reasons. Firstly, we have also ignored the costs of obtaining additional information. Secondly the information which is forgone will not be perfect and would not resolve all the uncertainties in the decision problem. The decision problem becomes more complex as we move to consider the expected value of partial perfect information (EVPPI) and EVSI but the principle of including these opportunity losses remains the same. Clearly, the likelihood, timing and cost of future research could differ between parameters. For example, additional information on treatment efficacy may be obtained from a large randomised controlled trial (RCT), whereas additional information on the utility values associated with health states in the model could be obtained by postal survey from a representative sample of patients. These separate items of research will differ greatly in terms of timescale and cost. Even if P_R and T_R were known for each parameter, it is not possible to sum across the separate EVPPI for each parameter to obtain the total opportunity loss of forgoing research on all those parameters. Another level of complexity is introduced when we consider that future research will not report perfect information, only sample

information. The informational requirements of using the formal approach described in this paper with EVPPI or EVSI instead of EVPI would be large.

If NB_A is positive based on perfect information, we have a clear indication that we should accept the optimal treatment based on current evidence. Until methodological work proceeds on EVPPI and on simplifying EVSI calculations the formal methods described in this paper are limited to calculating expected NB_A as a function of EVPI. In certain circumstances where NB_A is negative based on perfect information it would be positive based on sample information (Figure 3). Currently we can only calculate the threshold value of EVSI or combined EVPPI below which we would choose to accept on the basis of current evidence. The decision to reject on the basis of current evidence is therefore not as clear cut, with the exception of the point where ICER=λ.

5. Conclusions

If we accept that the decision to reimburse a health care programme affects the likelihood of future research, then there is a demonstrable and calculable opportunity loss associated with an adoption decision. In order to prevent a net opportunity loss, decision-makers must be able to reject treatments that appear cost-effective based on current evidence. The decision to reject an apparently cost-effective treatment on the basis of the decision uncertainty will be justified if the potential opportunity loss to future patients exceeds the NB forgone by current patients.

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