OPTIMAL CLINICAL TRIAL DESIGN USING VALUE OF INFORMATION METHODS WITH IMPERFECT IMPLEMENTATION

By Andrew Willan and Simon Eckermann
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ABSTRACT

Traditional sample size calculations for randomized clinical trials are based on tests of hypotheses and depend on somewhat arbitrarily chosen factors, such as type I and II errors rates and the smallest clinically important difference. In response to this, many authors have proposed the use of methods based on the value of information, as an alternative. Previous attempts have assumed perfect implementation, *i.e.* if current evidence favours the new intervention and no new information is sought or expected, all future patients will receive it. A framework is proposed to allow for this assumption to be relaxed. The profound effect that this can have on the optimal sample size and expected net gain is illustrated on two recent examples. In addition, a model for assessing the value of implementation strategies is proposed and illustrated.
1. INTRODUCTION

Recently, methods based on the value of information (VOI) have been proposed for determining optimal sample size for clinical trials designed to compare a new intervention with a standard (Hornberger, Brown Jr and Halpern, 1995; Claxton and Posnett, 1996; Hornberger and Eghtesady, 1998; Claxton, 1999; Claxton and Thompson, 2001; Halpern, Brown Jr and Hornberger, 2001; Willan and Pinto, 2005; Willan, 2007; Eckermann and Willan, 2007; Eckermann and Willan, 2008a, 2008b, 2009; Kikuchi, Pezeshk and Gittins, 2008; Willan and Kowgier, 2008, Willan, 2008). These methods are proposed as an alternative to more traditional methods, which are based on the test of a null hypothesis and rely on somewhat arbitrarily determined quantities, such as the type I and II error rates and the smallest clinically important difference. VOI methods determine the sample size that maximizes the expected net gain (ENG). The ENG is the difference between the expected value of sample information (EVSI) provided by the trial and the trial’s expected total cost (ETC). Willan and Pinto (2005) provide a solution under the following assumptions:

1. all patients in the jurisdiction of interest are recruited into the trial;
2. the results are available immediately after the last patient is randomized;
3. perfect implementation, *i.e.* if current evidence favours the new intervention and no new information is sought or expected, then the new intervention will be adopted for all future patients;
4. patients outside the trial receive the standard intervention while the trial is performed;
5. no research is planned outside the jurisdiction of interest; and,
6. the trial is a single-stage design, \( i.e. \) no interim “looks” at the data.

Eckermann and Willan provide solutions relaxing Assumptions 1, 2 and 4 (2007) (2008a) (2008b) and relaxing Assumption 5 (2009). Willan and Kowgier (2008) provide solutions relaxing Assumption 6. The purpose of this paper is to provide solutions relaxing Assumptions 1, 2 and 3 while assuming that Assumptions 4, 5 and 6 hold. Fenwick, Claxton and Sculpher (2008) have recently proposed a VOI-based framework to address the issue of imperfect implementation (Assumption 3). Their framework determines an upper bound for the value of implementation strategies (EVPIM) which combined with the expected value of perfect information (EVPI) gives the expected value of perfection (EVP) in moving from current to perfect information and implementation. However, in modeling value of information this framework:

(i) assumes there is no interaction between level of evidence and implementation in defining and estimating EVPI;

(ii) is restricted to considering EVPI with current information, rather than EVSI and expected total costs (ETC) for identifying optimal trial design (sample size);

and,

(iii) does not relax any other assumptions.

In this paper we relax Assumption 3 to allow for the expected effect of imperfect implementation on EVSI, ETC and ENG, while also relaxing Assumptions 1 and 2.

Our model is developed in the Methods Sections, followed by two examples from the recent literature. We also discuss the expected value of implementation strategies.
2. METHODS

2.1 The Model

In this section and all empirical applications in this paper we assume that Assumptions 4, 5 and 6 hold. Consider the problem of choosing a sample size for a two-arm clinical trial in which patients are to be randomized between the current standard ($S$) and a new intervention ($T$) for the usual case of interest where current information suggest a positive, though uncertain, incremental net benefit in favour of $T$. The treatment arms $T$ and $S$ will be compared with respect to effectiveness and cost. The total cost for each patient will be determined by collecting data on the units of health care resources consumed, multiplied by the appropriate unit prices. Statistical methods for the analysis of data from cost-effectiveness trials have undergone rapid development over the past ten years (Willan and Briggs, 2006). Early development focused on making inferences about the incremental cost-effectiveness ratio, but more recently, due to the problems associated with ratio statistics, attention has shifted to incremental net benefit (INB). The analysis of INB requires the specification of the decision maker’s budget constrained threshold value for an additional unit of effectiveness, often denoted as $\lambda$.

Let $\Delta e$ be the between-treatment difference ($T - S$) of mean effectiveness, where effectiveness is scaled so that a larger value represents a better patient outcome. Also, let $\Delta c$ be the between-treatment difference ($T - S$) of mean cost. INB is defined as

$$b \equiv \Delta e \lambda - \Delta c.$$  

The term $\Delta e \lambda$ is the expected increase in the value of effectiveness, expressed in monetary terms, and the term $-\Delta c$ subtracts off the expected increase in cost, yielding the incremental net benefit of adopting $T$ over $S$. If $b$ is positive, either because $\Delta e$ is sufficiently positive or $\Delta c$ sufficiently negative, or both, then in the
absence of considering additional evidence, adopting \( T \) is optimal in terms of maximizing net benefit for future patients.

Consider a trial in which a fixed number of patients, \( n \), are to be allocated to each arm. Let the prior distribution for \( b \) be normal with mean \( b_0 \) and variance \( v_0 \) and let the posterior distribution following the trial be normal with mean \( b_1 \) and variance \( v_1 \). If \( \hat{b} \) is the sample mean-based estimator of incremental net benefit using the data from the trial, and assuming normality for \( \hat{b} \), we have \( \hat{b} \sim N(b_0, v_0 + 2\sigma^2/n) \), where \( \sigma^2 \) is the between-patient variance of INB, which is assumed known. Therefore,

\[
b_1 = v_1 \left[ \left( b_0/v_0 \right) + \left( nb/2\sigma^2 \right) \right] \quad \text{and} \quad v_1 = \left[ \left( 1/v_0 \right) + \left( n/2\sigma^2 \right) \right]^{-1}.
\]

In decision theory, the expected value of sample information (EVSI) is the expected amount by which additional information reduces the expected opportunity loss (EOL) of making a decision given current knowledge. Ignoring discounting for future benefits, the EVSI is given by \( \text{EVSI} = N \left[ \text{EOL}_{pp0} - E_b \text{EOL}_{pp1} \right] \), where \( \text{EOL}_{pp0} \) and \( \text{EOL}_{pp1} \) are the EOL per patient before and after the trial, respectively, \( E_b \) is the expectation with respect to the data observed in the trial, and \( N \) is the number of patients that will benefit from the information from the trial.

Under Assumption 3 (perfect implementation), \( N = (h-t)k \), where \( h \) is the time horizon for the decision, \( k \) is the annual incidence and \( t = \tau + 2n/a \) is the duration of the trial, where \( a \) is the annual patient accrual rate and \( \tau \) is the duration of time between when the last patient is randomized and the results are available. Under Assumptions 1 and 2, \( a = k \) and \( \tau = 0 \), respectively, and \( N = hk - 2n \). Since \( hk - 2n > (h-t)k \), if either
Under Assumption 3,
\[
EQL_{pp_0} = \left[\frac{v_0}{(2\pi)^{\frac{1}{2}}} \exp\left(-\frac{b_0^2}{2v_0}\right)\right] - b_0 \left[\Phi\left(-\frac{b_0}{\sqrt{v_0}}\right) - I(b_0 \leq 0)\right] = \Phi(b_0, v_0) \quad \text{and}
\]
\[
EQL_{pp_1} = \Phi(b_1, v_1),
\]
where \(\Phi(\cdot)\) is the cumulative distribution function for a standard normal random variable and \(I(\cdot)\) is the indicator function. (See Willan and Pinto (2005) for a close form solution for \(EQL_{pp_1}\).)

For \(b_0 > 0\), the expected total cost is given by \(ETC = C_f + 2nC_v + \tilde{n}b_0\), where \(C_f\) is the fixed cost of the trial, \(C_v\) is the variable cost per patient and \(\tilde{n}\) is the number of patients who, while the trial is conducted, receive \(S\), who otherwise would have received \(T\), had the trial not been conducted. These patients incur an opportunity cost of \(b_0\). Under Assumption 3 all future patients would receive \(T\) if the trial is not performed. Therefore, under Assumption 3, \(\tilde{n} = tk - n\), that is, \(\tilde{n} = [\text{the } tk \text{ patients who contract the health condition while the trial is conducted}] \text{ minus } [\text{the } n \text{ patients who received } T \text{ in the trial}].\)

Under Assumptions 1 and 2, \(a = k\) and \(\tau = 0\), and therefore, \(t = 2n/k\) and \(\tilde{n} = n\). Since \(n < tk - n\), if either \(a < k\) or \(\tau > 0\), relaxing Assumptions 1 and 2 will increase the number of patients that incur an opportunity cost and thereby will increase the ETC.

### 2.2 Relaxing Assumption 3

Under Assumptions 3, if \(b_0 > 0\), and no new information is sought or expected, then all future patients would receive \(T\). In practice this is unlikely to be the case, and the
degree of implementation will most probably depend on the strength of the evidence in favour of T, which \textit{a priori} can be expected to increase with the additional information from a new trial. Let \( p_0 \) be the probability that a future patient would receive T, given evidence characterized by \((b_0, v_0)\), assuming no new information is sought or expected, and let \( p_1 \) be the post-trial probability that a future patient would receive T, given evidence characterized by \((b_1, v_1)\), again assuming no further information is sought or expected. Assumptions 3 can be relaxed by allowing \( p_i < 1 \), in which case it can be shown, see Appendix A, that EVSI becomes

\[
\text{EVSI} = N \left\{ \mathcal{D}(b_0, v_0) + (1 - p_0) b_0 - \left[ E_b \mathcal{D}(b_1, v_1) + E_b \left\{ (1 - p_1) b_1 \right\} \right] \right\},
\]

Thus, the EOLpp\(_0\) increases by \( (1 - p_0) b_0 \) and the EOLpp\(_1\) increases by \( E_b \left\{ (1 - p_1) b_1 \right\} \).

However the increase in EOLpp\(_0\) is greater since implementation is expected to improve with additional evidence. That is, if we assume that \( p_i, i = 0,1 \), is an non-decreasing function of the strength of the evidence, then \( (1 - p_0) b_0 > E_b \left\{ (1 - p_1) b_1 \right\} \). Therefore, relaxing Assumption 3 increases the EVSI. The term \( E_b \mathcal{D}(b_1, v_1) \) has a closed form solution, see Willan and Pinto (2005). However, the term \( E_b \left\{ (1 - p_1) b_1 \right\} \) must be evaluated using numerical integration.

Now we consider the impact of relaxing assumption 3 on expected total cost (ETC) while 4, 5 and 6 hold. Relaxing assumption 3, the number of patients who incur an opportunity cost becomes \( \tilde{n} = p_0 tk - n \), where \( p_0 tk \) is the number of patients who would have received T during the trial period, if the trial had not be undertaken, and \( n \) is the number of patients within the trial receiving T. Since \( p_0 tk - n < tk - n \), relaxing
Assumption 3 reduces the number of patients that incur an opportunity cost, and thereby reduces the ETC.

In summary, relaxing Assumptions 1 and 2 decreases EVSI and increases ETC, while relaxing Assumption 3 increases EVSI and decreases ETC. The optimal sample size is the one that maximizes EVSI – ETC, and if EVSI < ETC, regardless of sample size, then basing the decision regarding the adoption of \( T \) on current information is optimal. Therefore, relaxing Assumptions 1 and 2 increases the chance that current information is sufficient for optimal decision making, while relaxing Assumption 3 increases the chance that more information (a new trial) is required.

3. EXAMPLES

3.1 The early EECV trial

In a pilot study (Hutton, 2003), 232 pregnant women presenting in the breech position were randomized between early (\( T \)) versus late (\( S \)) external cephalic version (ECV). ECV is an attempt to manipulate the fetus into a cephalic presentation. Elective caesarean section is accepted practice for breech presentation, and the primary outcome for the trial was a non-caesarean delivery. In the early ECV arm 41 of 116 (35.3%) patients had a non-caesarean delivery and in the late ECV arm the corresponding numbers were 33 of 116 (28.4%). Based on this data the investigators designed a larger trial of 730 patients per arm to have an 80% probability of rejecting the null hypothesis of no treatment effect, if the treatments differed by eight percentage points, using a two-sided type I error of 0.05. This trial has been funded by the Canadian Institutes for Health Research (CIHR) and is currently recruiting patients.
Suppose, for sake of argument, that society is willing to pay $1000 to achieve a non-caesarean delivery in these patients. This amount reflects the cost savings and the preference for a non-caesarean birth. Suppose further that, apart from the possible cost savings from preventing a caesarean delivery, there is no difference in cost between early and late ECV. Therefore, \( b = \Delta_e \cdot 1000 \), where \( \Delta_e \) is the [probability of a non-caesarean delivery for early ECV] minus [the probability of a non-caesarean delivery for late ECV], which, based on the pilot data, is estimated as \( \hat{\Delta_e} = \frac{41}{116} - \frac{33}{116} = 0.06897 \). The prior distribution for \( b \), given the pilot data, is assumed normal with mean

\[
b_0 = 0.06897 \cdot 1000 = 68.97
\]

and variance

\[
v_0 = \left\{ \frac{\frac{41}{116}(1-\frac{41}{116})}{116} + \frac{\frac{33}{116}(1-\frac{33}{116})}{116} \right\} 1000^2 = 3724.78.
\]

The normal assumption is based on the Central Limit Theorem, which is typically invoked for the distributions of proportions. The z-statistic for the testing the null hypothesis that \( b \leq 0 \) is

\[
z = b_0 / \sqrt{v_0} = 68.97 / \sqrt{3724.78} = 1.130 ,
\]

with associated p-value of 0.13. Using the overall proportion of non-caesarean delivery \( (41 + 33)/(116 + 116) = 0.3189655 \), an estimate of the between-patient variance of incremental net benefit is given by

\[
\sigma^2 = 0.3189655(1 - 0.3189655)1000^2 = 217,227.
\]

Consider a time horizon \( (h) \) of 20 years and assume that the annual North American incidence \( (k) \) is approximately 50,000. Based on the total budget for the CIHR funded trial of $2,836,000, we determined that \( C_f = $500,000 \) and \( C_v = $1,600 \). Under
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Assumptions 1 to 6 and using the above values for \( b_0, v_0, \sigma^2, k, h, C_f \) and \( C_v \), the sample size \( (n^*) \) that maximizes expected net gain is 345 per arm, and corresponds to a financial cost of $1,604,000 and an expected opportunity cost of $23,793. The expected net gain is $736,391, yielding a 45% return on investment. By contrast, the planned sample size of 730 per arm for the CIHR funded trial corresponds to a financial cost of $2,836,000 and an opportunity cost of $50,345. The expected net gain for the CIHR funded trial is $179,657, yielding a 6.2% return on investment. This demonstrates a clear advantage to the EVI approach. A plot of EVSI and ETC, as a function of \( n \), is given in Figure 1.

Relaxing Assumptions 1 and 2 by setting \( a = 1000 \) and \( \tau = 0.5 \) yields an optimal sample size of 0. That is, there is no sample size for which EVSI > ETC. The ENG for the CIHR funded trial of 730 patients per arm is $-6,774,699 with a total cost of $9,544,276, yielding a -71% return on investment. A plot of EVSI and ETC, as a function of \( n \), is given in Figure 2. Relaxing Assumptions 1 and 2 increases the opportunity costs, for \( n = 345 \), from \( nb_0 = 23,793 \) to \( [(\tau + 2n/a)k - n]b_0 = 4,079,655 \) and decreases the number of patients who would benefit, for \( n = 345 \), from \( hk - 2n = 999,310 \) to \( [h - (\tau + 2n/a)]k = 940,500 \), resulting in a reduction of EVSI of $139,134. Thus an apparent dilemma exists whereby assuming a reasonable accrual rate and follow-up duration, a VOI approach leads to the conclusion that the current information is sufficient to support the decision to adopt \( T \), while taking a traditional test of hypothesis approach would lead to the opposite conclusion. The dilemma is primarily due to the huge opportunity costs incurred by those patients receiving \( S \) while the trial is conducted under Assumptions 3 and 4. Assumption 3 states that if \( b_0 > 0 \) and the trial is not done, all
future patients would receive T. On the other hand, if the trial is performed, then under Assumption 4, all patients incident during the trial will receive S, except the $n$ patients randomized to $T$ in the trial itself.

To relax Assumption 3 a functional relationship between the strength of evidence and the probability that a future patient receives $T$ needs to be hypothesized. Assuming that the strength of the evidence can be characterized by the $z$-statistic $z_i = b_i / \sqrt{v_i}$, $i = 0, 1$, let $g(\cdot)$ be a non-decreasing function such that $g(z) = 0$ for $z < \gamma$ and $g(z)$ either equals or approaches 1 as $z$ increases above $\gamma$. Consider the “sliding-step” function given by $g(z) = \min(1, \max(0, (z-\gamma)/(\beta-\gamma)))$. The “sliding-step” function is 0 for $z < \gamma$, 1 for $z > \beta$, and linear for $\gamma \leq z \leq \beta$, see Figure 3. If $\gamma = \beta$ then $g(z) = I(z > \beta)$. Assumption 3 implies $\gamma = \beta = 0$. The “sliding-step” function has been used previously to relate strength of evidence to the probability of regulatory approval and the probability of the adoption of a new intervention, see Kikuchi, Pezeshk and Gittins (2008), Willan and Pinto (2005) and Willan (2008).

For the EVC trial, suppose as the base case we set $\gamma = \Phi^{-1}(0.75) = 0.674$ and $\beta = \Phi^{-1}(0.99) = 2.33$. These settings can be interpreted as follows: if the hypothesis that $b \leq 0$ cannot be rejected at the 0.25 level, then no future patients would receive $T$, while, on the other hand, if $b \leq 0$ can be rejected at the 0.01 level, then all future patients will receive $T$. Applying this function to the EECV data, the probability that a future patient receives $T$ if the trial is not performed, is $p_0 = g(z_0) = g(68.97/\sqrt{3724.78}) = g(1.130) = 0.2758$, and therefore, relaxing Assumption 3 increases the EOLpp0 from
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\[ \mathcal{D}(h_0, \nu_0) = 3.945 \text{ to } \mathcal{D}(b_0, \nu_0) + (1 - p_0) b_0 = 53.89. \]

Consequently, there is a dramatic, almost 14-fold, increase in the potential value of additional information as a result of relaxing Assumptions 3. The optimal sample size is now 489 per arm, yielding an expected net gain of $38,168,737 with a financial cost of $2,064,800 and an opportunity cost of $1,371,707, yielding a return on investment of 1111%. (The opportunity cost for entering 489 patients per arm under Assumption 3 is $5,035,516.) A plot of EVSI and ETC as a function of \( n \) is given in Figure 4. The expected net gain for the CIHR funded trial of 730 patients per arm is $37,386,369 with a total cost of $4,649,420, yielding an 804% return on investment. This example demonstrates the profound effect that relaxing Assumption 3 can have. Where assumptions 3-6 hold the ENG is negative for all sample sizes. However, relaxing Assumption 3 yields an optimum ENG of over $38 million.

A sensitivity analysis regarding the values of \( \gamma \) and \( \beta \) is provided in Table 1. For each combination for the values of \( \gamma = \Phi^{-1}(0.5), \Phi^{-1}(0.75) \) and \( \Phi^{-1}(0.95) \) and \( \beta = \Phi^{-1}(0.95), \Phi^{-1}(0.99) \text{ and } \Phi^{-1}(0.999) \), the optimal sample size and corresponding ENG is provided. In addition, we report the ENG from entering 489 patients per arm (the optimum trial size in the base case of \( \gamma = \Phi^{-1}(0.75), \beta = \Phi^{-1}(0.99) \)), and the percentage reduction relative to the optimal solution this represents. Although the optimal sample size varies considerably with \( \gamma \) and \( \beta \), the per cent reduction in ENG from entering 489 patients per arm is quite small, reaching a maximum of 7.41% for \( \gamma = \Phi^{-1}(0.5) \) and \( \beta = \Phi^{-1}(0.95) \), and is less than 2% in six of the eight cases considered.
3.2 The CADET-Hp Trial

The CADET-Hp Trial was a double-blind, placebo-controlled, parallel-group, multi-centre, randomized controlled trial, performed in 36 family practitioner centres across Canada, see Chiba et al. (2002). Patients 18 years and over with uninvestigated dyspepsia of at least moderate severity presenting to their family physicians were eligible, provided they did not have any alarm symptoms and were eligible for empiric drug therapy.

Patients were randomized between

\[ T: \text{Omeprazole 20 mg, metronidazole 500 mg and clarithromycin 250 mg, and } \]
\[ S: \text{Omeprazole 20 mg, placebo metronidazole and placebo clarithromycin. } \]

Both regimens were given twice daily for seven days. Treatment success was defined as no or minimal dyspepsia symptoms at one year. Total costs were determined from the societal perspective and are given in Canadian dollars. Of the 142 patients randomized to \( T \), 72 (50.70%) achieved success, compared to 54 (36.99%) of the 146 patients randomized to \( S \). Therefore, \( \hat{\Delta} = 0.5070 - 0.3699 = 0.1371 \).

The average cost on \( T \) was $476.97, compared to $529.98, yielding \( \hat{\Delta}_c = 476.97 - 529.98 = -53.01 \). In addition,

\[ \hat{v}(\hat{\Delta}_c) = 0.003356, \hat{V}(\hat{\Delta}_e) = 4792 \text{ and } \hat{C}(\hat{\Delta}_e, \hat{\Delta}_c) = -0.7129, \text{ where } V(\cdot) \text{ and } C(\cdot) \text{ are the variance and covariance functions, respectively, see Willan (2004) for detailed calculations. } \]

Note that \( T \) is observed to be more effective and less costly. If a success is valued at $1000, then \( b_0 = 1000\hat{\Delta}_e - \hat{\Delta}_c = 190.11 \) and

\[ v_0 = 1000^2V(\hat{\Delta}_e) + V(\hat{\Delta}_c) - 2*1000C(\hat{\Delta}_e, \hat{\Delta}_c) = 9575. \text{ The z-statistic } \]
\[ z_0 = b_0/\sqrt{v_0} = 1.943, \text{ and statistical significance is achieved at the level 0.026. } \]
Suppose as the base case we again set $\gamma = \Phi^{-1}(0.75) = 0.6744$ and $\beta = \Phi^{-1}(0.99) = 2.326$, then $p^* = g(z^*) = g(1.943) = 0.7679$. Using the parameters as shown in Table 2, the optimal sample size is 109 patients per arm. The optimum ENG is $\$8,077,377$ on a financial cost of $\$1,045,000$ and an opportunity cost of $\$1,7293,204$, for return on investment of 44.1%. A sensitivity analysis regarding the values of $\gamma$ and $\beta$ is provided in Table 3. For each combination of $\gamma$, $\beta$ values for $\gamma = \Phi^{-1}(0.5), \Phi^{-1}(0.75)$ and $\Phi^{-1}(0.95)$ and $\beta = \Phi^{-1}(0.95), \Phi^{-1}(0.99)$ and $\Phi^{-1}(0.999)$, the optimal sample size and expected net gain is reported. In addition, the ENG and the per cent reduction from optimum of entering 109 patients per arm (the base case) is given. In this example the optimal solution is sensitive to the choice of $\gamma$ and $\beta$. For some combinations of $\gamma$ and $\beta$ the optimal sample size is zero. For example, if $\beta = \Phi^{-1}(0.95)$, $p^* = 1$ with current information (regardless of $\gamma$), and all future patients would receive $T$. Consequently, if $\beta < z^*$, further evidence cannot improve (and could potentially lower) implementation, which when combined with limited scope for reducing uncertainty, could result in a negative EVSI. For the assumption that $\gamma = \Phi^{-1}(0.5)$ and $\beta = \Phi^{-1}(0.99)$, $p^* < 1$, but any increase in EVSI is more than off-set by the trial costs.

The sensitivity analysis for the CADET-Hp trial demonstrates that optimal trial design can be sensitive to assumptions about the extent to which practice changes with levels of evidence implicit in $\alpha$ and $\beta$. For a situation with a very large return on investment, such as the EECV trial, where the solution is located on a relatively flat part
of the ENG curve, one can expect very robust solutions, but caution should be exercised for situations with low returns of investment.

4. PERFECTING IMPLEMENTATION

As discussed by Fenwick, Claxton and Sculpher (2008), strategies that promote implementation of health interventions with positive incremental net benefit (otherwise known as knowledge transfer) can increase the net benefit for future patients. Consider an implementation strategy of duration \( t_{IS} \) that increases the probability that a future patient receives the new intervention from \( p_0 \) to \( p_1 \), linearly in time. That is, the probability that a future patient receives the new intervention, as a function of time \( t \), is given by

\[
p(t) = \min\left( p_1, \max\left( p_0, p_1 \frac{t}{t_{IS}} \right) \right),
\]

where the strategy begins at \( t = 0 \) and ends at \( t = t_{IS} \).

The expected value of the implementation strategy (EVIS) over the time horizon \( h \) is given by

\[
EVIS = k \left( h - t_{IS} / 2 \right) \left( p_1 - p_0 \right) b_0,
\]

see Appendix B.

Contained in Table 4, as a function of \( t_{IS} \), are the values of EVIS for a ten percentage point increase (i.e. \( p_1 - p_0 = 0.1 \)) in implementation for the EECV and CADET-Hp examples. These values indicate that there are large potential gains in net benefit from effective implementation strategies, although any gains in net benefit need to exceed the associated cost of the strategy to be viable. By comparing the values of ENG in Table 1 to the values of EVIS in Table 4 for the EECV example, it can be seen that a new trial would provide a larger ENG than an implementation strategy, even if the strategy were costless and increased the probability that a future patient receives the new intervention by as much as 20 percentage points. On the other hand, comparing the base
5. DISCUSSION AND CONCLUSIONS

Value of information methods allow efficient as well as robust trial design to inform decision making in health technology assessment (HTA), following a principle of maximizing the expected net gain. However, until recently restrictive assumptions made in the determination of EVSI have limited the usefulness of these methods to decision makers, since they failed to reflect trial constraints and decision contexts in which trials are designed and performed. Eckermann and Willan (2007, 2008a, 2008b, 2009) develop a framework that provides solutions while relaxing a number of these assumptions.

In this paper we have extended this framework to relax the assumption that decisions to either adopt T or retain S are perfectly implemented. We have shown that allowing for imperfect implementation:

(i) increases the expected opportunity loss;

(ii) increases the expected value of sample information where trial information is expected to improve implementation; and,

(iii) decreases the expected opportunity cost.

The expected opportunity loss increases because patients receiving S realize a higher opportunity loss that those receiving T and because, without further information, the proportion of patients receiving S increases from 0 to \((1 - p_o)\) under imperfect implementation. EVSI increases when allowing for imperfect implementation because of
the higher adoption rate expected with stronger evidence provided by the trial. The reduction in opportunity cost results because, with imperfect, rather than perfect implementation, fewer patients would receive T if the trial is not performed.

Consequently, relaxing the assumption of perfect implementation increases the likelihood that the optimal sample size for a new trial is greater than 0, which is to say, that a new trial is expected to increase the net benefit for future patients.

These findings regarding the impact on expected opportunity loss and EVSI of allowing for imperfect implementation have not been pointed to or discussed previously. Previous research considering the impact from relaxing assumptions of perfect implementation on value of information by Fenwick, Claxton and Sculpher (2008) has been limited to considering impact on ‘realisable EVPI’ with a base case assumption that the level of evidence has no impact on level of implementation. Our work has allowed the level of evidence to have an impact on the level of implementation in estimating the upper bound for future research that EVPI represents. We have also taken the further step of evaluating the effect of imperfect implementation on the expected value of sample information and costs of trials and the implication that has on optimal sample size calculations. Hence the methods we propose provide the necessary and sufficient conditions to inform optimal research decisions allowing for imperfect implementation. In addition, we proposed methods for evaluating the expected value of implementation strategies, which allow one to consider, as demonstrated by the examples, whether further investment is best directed towards gathering more evidence or promoting implementation.
The methods and empirical results presented in this paper have assumed positive prior INB and that Assumptions 4, 5 and 6 hold. However, these assumptions could also be relaxed to extend the framework provided in this paper, as we now discuss. The usual case of interest within a jurisdiction is where prior INB is positive, while uncertain. Where prior INB is negative retaining the standard intervention is optimal in the absence of further evidence. However, EVSI from delaying the decision and undertaking a trial relative to rejecting with no trial can still be estimated within and across jurisdictions as discussed in Eckermann and Willan (2008b, 2009). Where prior INB is negative, EVSI can be estimated as expected opportunity loss from making a bad decision under uncertainty to reject the new intervention, while expected opportunity costs will arise from placing trial patients on the new intervention rather than standard outside the trial setting.

In considering relaxing of assumption 4, a primary factor which needs to be considered is whether trials are feasible where patients are treated with the new intervention outside the trial setting. As discussed in Eckermann and Willan (2008b, 2009), where there is current evidence of net clinical benefit of the new intervention, a trial undertaken within a jurisdiction while adopting is infeasible if there is perfect implementation, as all informed patients would prefer to remain outside of the trial setting. However, a trial may become feasible (and ethical) within jurisdiction with imperfect implementation for informed patients where the chances of getting the new intervention inside the trial setting are still greater than the chances outside the trial setting. For example, trials with equal allocation by arm may be considered feasible and ethical if the chance of getting the new intervention outside the trial setting is less than
50%. The opportunity cost of delay for patients in such a trial setting would be reduced, however EVSI would also be reduced in allowing for costs of reversal, see Eckermann and Willan (2007, 2008a). A trial with patients recruited from another jurisdiction where adoption has not taken place and evidence is translatable would also be feasible, an advantage of designing an optimal global trial across jurisdictions rather than a local trial, as discussed in Eckermann and Willan (2009).

Assumptions 5 and 6 have been made to simplify analysis, and could additionally be relaxed in future research combining methods developed here with those demonstrated in Eckermann and Willan (2009) and Willan and Kowiger (2008). That is, optimal global trial design and multiple stage trial design could be undertaken allowing for imperfect implementation applying the methods developed in this paper. Consequently, the methods presented in this paper provide a general framework to inform optimal trial design and decision making accounting for imperfect implementation, where each of the previously restrictive assumptions (1 to 6) can be relaxed.
Table 1. Optimal sample size and optimum expected net gain, and the expected net gain and the per cent reduction from optimum of entering 485 patients per arm (base case) for the ECV trial, as a function of $\gamma$ and $\beta$.

<table>
<thead>
<tr>
<th>$\gamma = \Phi^{-1}(0.5)$</th>
<th>$\beta = \Phi^{-1}(0.95)$</th>
<th>$\beta = \Phi^{-1}(0.99)$</th>
<th>$\beta = \Phi^{-1}(0.999)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>254</td>
<td>$14,000,165$</td>
<td>$25,100,532$</td>
<td>$30,301,150$</td>
</tr>
<tr>
<td>$12,962,599$</td>
<td>$24,977,507$</td>
<td>$30,152,568$</td>
<td></td>
</tr>
<tr>
<td>7.41%</td>
<td>0.490%</td>
<td>0.490%</td>
<td></td>
</tr>
<tr>
<td>337</td>
<td>$27,515,791$</td>
<td>$38,168,737$</td>
<td>$41147983$</td>
</tr>
<tr>
<td>$27,066,698$</td>
<td>(base case)</td>
<td>$4,061,7494$</td>
<td></td>
</tr>
<tr>
<td>1.63%</td>
<td></td>
<td>1.29%</td>
<td></td>
</tr>
<tr>
<td>506</td>
<td>$56,871,611$</td>
<td>$54,446,668$</td>
<td>$51,617,903$</td>
</tr>
<tr>
<td>$56,865,482$</td>
<td>$53,976,672$</td>
<td>$49,714,904$</td>
<td></td>
</tr>
<tr>
<td>0.0108%</td>
<td>0.863%</td>
<td>3.69%</td>
<td></td>
</tr>
</tbody>
</table>

Note: DOI:10.1002/hec.1493

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Table 2. Parameters values used for the CADET-Hp trial example.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Incidence ((k))</td>
<td>50,000</td>
</tr>
<tr>
<td>Time Horizon ((h))</td>
<td>20</td>
</tr>
<tr>
<td>Annual Accrual Rate ((a))</td>
<td>1000</td>
</tr>
<tr>
<td>Fixed Cost ((C_f))</td>
<td>500,000</td>
</tr>
<tr>
<td>Variable Cost ((C_v))</td>
<td>2500</td>
</tr>
<tr>
<td>Duration of Follow-up ((\tau))</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Table 3. Optimal sample size and optimum expected net gain, and the expected net gain and the per cent reduction from optimum of entering 109 patients per arm (base case) for the CADET-Hp trial, as a function of $\gamma$ and $\beta$.

<table>
<thead>
<tr>
<th>$\gamma = \Phi^{-1} (0.5)$</th>
<th>$\beta = \Phi^{-1} (0.95)$</th>
<th>$\beta = \Phi^{-1} (0.99)$</th>
<th>$\beta = \Phi^{-1} (0.999)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>187</td>
<td>25,532,229</td>
</tr>
<tr>
<td>$$0$</td>
<td>$$0$</td>
<td>undefined</td>
<td>undefined</td>
</tr>
<tr>
<td>$$-25,796,185$</td>
<td>$$-11,17,609$</td>
<td>undefined</td>
<td>$$22,524,755$</td>
</tr>
<tr>
<td>undefined</td>
<td>undefined</td>
<td></td>
<td>11.8%</td>
</tr>
</tbody>
</table>

$\gamma = \Phi^{-1} (0.75)$

| 0                           | 109                         | 217                         | $\$41,355,942$             |
| $\$0$                       | $\$8,077,377$              | undefined                   | $\$35,420,113$             |
| $\$-27,280,284$             | $\$8,077,377$              | (base case)                 | 14.4%                       |

$\gamma = \Phi^{-1} (0.95)$

| 0                           | 186                         | 283                         | $\$93,956,998$             |
| $\$0$                       | $\$61,549,137$             | undefined                   | $\$77,514,411$             |
| $\$-34,710,744$             | $\$58,446,572$             | 5.04%                       | 17.5%                       |
Table 4. EVIS for a ten percentage point increase
\( (i.e. p_1 - p_0 = 0.1) \) in implementation.

<table>
<thead>
<tr>
<th>Duration of Initiative ( (t_{IS}) )</th>
<th>EECV</th>
<th>CADET-Hp</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6,724,575</td>
<td>18,535,725</td>
</tr>
<tr>
<td>2</td>
<td>6,552,150</td>
<td>18,060,450</td>
</tr>
<tr>
<td>3</td>
<td>6,379,725</td>
<td>17,585,175</td>
</tr>
<tr>
<td>4</td>
<td>6,207,300</td>
<td>17,109,900</td>
</tr>
<tr>
<td>5</td>
<td>6,034,875</td>
<td>16,634,625</td>
</tr>
</tbody>
</table>
Figure 1. Expected value and costs of trial designs for the EECV example under Assumptions 1-6.
Figure 2. Expected value and costs of trial designs for the EECV example under Assumptions 3-6 (1 and 2 relaxed).
Figure 3. The probability that a future patient receives $T$ as a function of $z$. 
Figure 4. Expected value and costs of trial designs for the EECV example under Assumptions 5-6 (1 to 4 relaxed).
Figure 5. Expected value and costs of trial designs for the CADET-Hp example under Assumptions 5-6 (1 to 4 relaxed).
REFERENCES


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**Appendix A**

Given the evidence \((b_i, v_i)\), for \(i = 0, 1\), the EOLpp\(_i\) of adopting \(T\) is \(\int_{-\infty}^{0} -b f_i(b) \, db\) and the EOLpp\(_i\) of retaining \(S\) is \(\int_{0}^{\infty} b f_i(b) \, db\). Therefore,

\[
\text{EVSI} = N \left\{ p_0 \int_{-\infty}^{0} -b f_0(b) \, db + (1 - p_0) \int_{0}^{\infty} b f_0(b) \, db - E_{\bar{b}} \left( p_1 \int_{-\infty}^{0} -b f_1(b) \, db + (1 - p_1) \int_{0}^{\infty} b f_1(b) \, db \right) \right\}
\]

\[
= N \left\{ p_0 \mathcal{D}(b_0, v_0) + (1 - p_0) \left[ \mathcal{D}(b_0, v_0) + b_0 \right] \right. \\
- E_{\bar{b}} \left. \left( p_1 \mathcal{D}(b_1, v_1) + (1 - p_1) \left[ \mathcal{D}(b_1, v_1) + b_1 (I(b_1 > 0) - I(b_1 \leq 0)) \right] \right) \right\}
\]

\[
= N \left\{ \mathcal{D}(b_0, v_0) + (1 - p_0) b_0 - E_{\bar{b}} \left( \mathcal{D}(b_1, v_1) + (1 - p_1) b_1 (I(b_1 > 0) - I(b_1 \leq 0)) \right) \right\}
\]

\[
= N \left\{ \mathcal{D}(b_0, v_0) + (1 - p_0) b_0 - E_{\bar{b}} \mathcal{D}(b_1, v_1) - E_{\bar{b}} \left( (1 - p_1) b_1 \right) \right\}.
\]
Appendix B

The expected value of the implementation strategy (EVIS) over the time horizon $h$ is the increase in expected total incremental net benefit of $T$ from the increase in implementation. Therefore,

$$EVIS = k b_0 \left[ \int_0^h [p(t) - p_0] dt \right]$$

$$= k b_0 \left[ \int_0^h p(t) dt - p_0 h \right]$$

$$= k b_0 \left[ \int_0^{t_{IS}} \frac{1}{t_{IS}} \left[ t_{IS} p_0 + (p_1 - p_0) t \right] dt + \int_{t_{IS}}^h p_0 dt - p_0 h \right]$$

$$= k b_0 \left[ \int_0^{t_{IS}} \frac{1}{t_{IS}} \left[ t_{IS} p_0 + (p_1 - p_0) t \right] dt + p_1 (h - t_{IS}) - p_0 h \right]$$

$$= k b_0 \left[ \frac{1}{t_{IS}} \left[ p_0 t_{IS}^2 + (p_1 - p_0) t_{IS}^2 / 2 \right] + p_1 (h - t_{IS}) - p_0 h \right]$$

$$= k b_0 \left[ p_0 t_{IS} + (p_1 - p_0) t_{IS} / 2 + p_1 (h - t_{IS}) - p_0 h \right]$$

$$= k \left( h - t_{IS} / 2 \right) (p_1 - p_0) b_0.$$