2

Randomized Clinical Trials I

2.0 INTRODUCTION

The frequentist approach for designing and analyzing randomized clinical trials is outlined briefly in Section 2.1. This is the standard approach taken in most randomized clinical trials for comparing a new health care intervention to a standard one, where inference and probabilities are conditioned on a null hypothesis rather than current evidence. Criticisms leveled at the frequentist approach include the use of arbitrarily determined probabilities for the Type I and II errors and the fact that the same error probabilities are used in almost all clinical trials regardless of the seriousness of the errors which vary between trials. A full critique of the frequentist approach is given in Section 2.1. If the results of trials are meant to inform decision making regarding the adoption of new interventions, then Bayesian decision theory, which conditions inference and probabilities on current evidence, provides the appropriate and optimal framework for doing so. In Section 2.2 an introduction is given for using decision theory and expected value of information methods for determining optimal sample sizes for randomized clinical trials. The optimal sample size is that which maximizes the difference between the value of information provided by the trial and the cost of performing it. A societal perspective is taken, in which health care costs are covered through public expenditure and trial research is funded by government or donation-based philanthropic agencies. A solution is provided under simplifying assumptions which are relaxed in later chapters.

Value of information methods require the identification of the threshold value for a unit of health outcome, the incidence of the health condition being examined and the time horizon (or shelf-life) of the new intervention and, although there maybe uncertainty regarding these parameters, none are arbitrary.

In Section 2.3 value of information methods for determining sample size are applied to the CADET-Hp example from Chapter 1 and two other examples. Contrasts with the frequentist approach are given for the same examples. Value of information methods can be used to determine if current information regarding the new health care intervention is sufficient for decision making. This is illustrated using the same examples with graphs for demonstrating robustness with respect to the incidence, time horizon and threshold value. A brief review of previous work on decision-theoretic approaches for determining sample size in clinical trials is given in Section 2.4, followed by a summary discussion in Secion 2.5.

2.1 THE FREQUENTIST APPROACH

Consider a randomized clinical trial in which a new health care intervention, referred to as *Treatment* and labeled *T*, is compared to an existing intervention, referred to as *Standard* and labeled as *S*, for the purpose of considering the adoption of *Treatment* if it is superior to *Standard*. This type of trial is often referred to as a superiority trial. Let Y be the random variable representing the primary outcome where larger values of Y are preferred, such as survival (where $Y = 1$ if the patient survives, 0 otherwise), survival time, quality-adjusted survival time or net benefit. Let $\mathrm{E}(Y \mid i), i = T, S$ be the expected

value of the outcome for a patient randomized to *i*, and let $\theta = \mathrm{E}(Y \mid T) - \mathrm{E}(Y \mid S)$. Thus, larger values of θ favour *Treatment*. Typically, in a superiority trial the data is used to test the null hypothesis $H : \theta \leq 0$ versus the alternative hypothesis $A : \theta > 0$. *Treatment* is considered for adoption if, and only if, *H* is rejected in favour of *A*. If the estimate of θ is sufficiently large so that, if *H* were true, the probability of observing an estimate of θ as large or even larger is sufficiently small, say α, then *H* is rejected in favour of *A*. Rejecting *H* when it is true is a Type I error, so the probability of committing a Type I error is α, also referred to as the level or size of the test. However, recall from Chapter 1 that the frequentist definition of the probability of an event is the limiting relative frequency of its occurrence in a series of repeated observations of a chance outcome in which it could occur. So α is actually the proportion of times a Type I error is committed in a very large series of tests of hypotheses. Nothing can be said of regarding the probability of committing a Type I error for a particular trial.

Consider a simple situation where the estimate of θ, denoted $\hat{\theta}$, is the difference of the sample means and that the sample size is sufficiently large to apply the central limit theorem and assume that $\hat{\theta}$ is normally distributed. Consider the z-statistic $Z = \hat{\theta} \Big/ \sqrt{\sigma_+^2 / n}$, where *n* is the number of patients randomized to each treatment group and $\sigma_+^2 = \sigma_T^2 + \sigma_S^2$, where σ_i^2 is the between-patient variance of *Y* for a patient randomized to receive *i*, for *i* = *T*, *S*. Under the null hypothesis, *Z* is a standard normal random variable. To limit the Type I error to α, *H* is rejected in favour of *A* if, and only if,

$Z \geq z_{1-\alpha}$, where $z_{1-\alpha}$ is the $100(1-\alpha)$ percentile for the standard normal random variable, since under the null hypothesis *Z* will exceed $z_{1-\alpha}$ with probability α.

The Type I error is limited to α regardless of the sample size. Given the need to limit the Type I error, the sample size is determined by limiting the probability of the Type II error to β, where the Type II error is the failure to reject *H* in favour of *A* when the treatment difference is equal to or greater than a specified smallest clinically important (positive) difference (SCID), denoted as θ_{SCID}. The interpretation of the SCID varies significantly, but it probably best described as the smallest amount of improvement in mean outcome that would justify adopting *Treatment*. Limiting Type II error to β requires that

$$\Pr\left(\text{not reject } H \mid \theta = \theta_{SCID}\right) < \beta$$

$$\Leftrightarrow \Pr\left(Z < z_{1-\alpha} \mid \theta = \theta_{SCID}\right) < \beta$$

$$\Leftrightarrow \Pr\left(\frac{\hat{\theta} - \theta_{SCID}}{\sqrt{\sigma_+^2/n}} < \frac{z_{1-\alpha}\sqrt{\sigma_+^2/n} - \theta_{SCID}}{\sqrt{\sigma_+^2/n}} \mid \theta = \theta_{SCID}\right) < \beta .$$

Since $\left(\hat{\theta} - \theta_{SCID}\right)\Big/\sqrt{\sigma_+^2/n}$ is a standard normal random variable when $\theta = \theta_{SCID}$, limiting Type II error β requires that $\dfrac{z_{1-\alpha}\sqrt{\sigma_+^2/n} - \theta_{SCID}}{\sqrt{\sigma_+^2/n}} = z_\beta = -z_{1-\beta}$.

Solving for *n*, the required sample size per treatment group is given by

$$n = \sigma_+^2\left[(z_{1-\alpha} + z_{1-\beta})\big/\theta_{SCID}\right]^2 . \qquad (2.1)$$

The quantity $1-\beta$ is the probability of rejecting *H* when $\theta = \theta_{SCID}$ and is referred to as the power of the test. By rearranging Equation 2.1 and replacing θ_{SCID} by θ, the power can be expressed as a function of the true mean difference, as given in Equation 2.2, where $\Phi(\cdot)$ is cumulative distribution function (*cdf*) for a standard normal random variable.

$$1-\beta = \Phi\left(\theta\sqrt{n/\sigma_{+}^{2}} - z_{1-\alpha}\right) \tag{2.2}$$

Equation 2.2 is referred to as the power curve and is the probability of rejecting the null hypothesis as a function of θ, the true difference in mean outcome. An example is shown in Figure 2.1. The power curve will always pass through α at the null hypothesis, *i.e.* at $\theta = 0$, since the probability of rejecting the null hypothesis *H*, when it is true, is limited to α. In addition, the power curve will pass through $1-\beta$ at θ_{SCID}. Essentially, the power curve represents the product or the value of an randomized clinical trial, because for any value of the true mean difference it provides the probability of the result of the trial, *i.e.* the probability of rejecting the null hypothesis.

There are many problems with this approach to designing and analyzing randomized clinical trials. Firstly, the value selected for α, the probability of a Type I error, is somewhat arbitrary and is almost always set to 0.05. Using the same value for the probability of a Type I error for every trial ignores the seriousness of the error, which clearly varies from trial to trial. Thus, a trial that randomizes patients with age-related macular degeneration between two different wavelengths of laser coagulation, see Willan *et al*. (1996), uses the same probability of falsely declaring *Treatment* superior, as does a

trial of Caesarean section versus vaginal delivery for women presenting in the breech position, see Hanna *et al*. (2000). In the former, declaring one wavelength superior to another when they are the same is not a serious error since selecting the wavelength is simply dialing the appropriate frequency and the only difference to patients is the colour of the light observed during the procedure. However, in the latter, declaring Caesarean section superior, when it is the same as vaginal delivery, is a serious error. Assigning the same probability to the two errors makes no sense, quite apart from the fact that the value of 0.05 is somewhat arbitrary in the first place. Also somewhat arbitrary is the typical choice of 0.2 for the probability of a Type II error. It means that there is a 20 per cent chance that the effort and money invested in the trial will be wasted, even if there is a clinically important difference between the treatments. Again, it fails to reflect the seriousness of making the error. The choice of θ_{SCID} can be less arbitrary and can be estimated by polling clinicians and decision makers. However, in practice it is often back-solved from the Equation 2.1 after substituting in a convenient sample size that reflects constraints relating to patient recruitment and budget. Even if θ_{SCID} is a reasonable, clinically determined estimate of the smallest clinically important difference, there is a range of values for the true treatment difference that is less than the smallest clinically important difference, for which the probability of rejecting the null hypothesis and adopting *Treatment* is greater than 50 per cent. This range is shown in Figure 2.1 as lying between $\theta_{0.5}$ and θ_{SCID}. The point $(\theta_{0.5}, 0.5)$ is the only truly non-arbitrary point on the power curve, since $\theta_{0.5}$ should represent the value of the true difference for which we are indifferent, because if $\theta = \theta_{0.5}$, there is a 50% probability of rejecting the null hypothesis and potentially adopting *Treatment*. If $\theta > \theta_{0.5}$, the probability of rejecting the

null hypothesis is greater than 0.5, whereas if $\theta < \theta_{0.5}$, the probability of rejecting the null hypothesis is less than 0.5. Since one could argue for incremental net benefit that $\theta_{0.5} = 0$, the level of the test, α, should be set to 0.5, so that the probability of adopting *Treatment* is greater than 0.5 if incremental net benefit is positive and less that 0.5 if incremental net benefit is negative. This could be considered appropriate, since incremental net benefit is defined as the value of improvement in mean net clinical benefit (allowing for harms as well as benefits) *minus* the additional mean cost.

It is often argued for a superiority trial that the appropriate null hypothesis is $H' : \theta = 0$ versus $A' : \theta \neq 0$, and that H' be rejected if, and only if, $|Z| \geq z_{1-\alpha/2}$ using a two-sided test. The argument usually put forward is that *Treatment* may be inferior to *Standard* (*i.e.* $\theta < 0$) and so it might. But the use of a two-sided, rather than one-sided, test in this situation is based on a misunderstanding of the purpose of limiting the probability of a Type I error in a superiority trial. The purpose is to limit the probability of adopting *Treatment* when it is equivalent or inferior to *Standard*, (*i.e.* $\theta \leq 0$), which is the original null hypothesis, *H*. The hypothesis H' is rejected in favour of A' if either a significantly negative difference or a significantly positive difference is observed. These two findings have totally different health care policy implications (retain *Standard* for the former or adopt *Treatment* in the latter) and should not be lumped together, as in the alternative hypothesis A'. Since the health care policy implication for *Treatment* being inferior to *Standard* (*i.e.* $\theta < 0$) and *Treatment* being equivalent to *Standard* (*i.e.* $\theta = 0$) are the same (namely retain *Standard*) they should be lumped together, as they are in the null hypothesis *H*. Testing $H' : \theta = 0$ versus $A' : \theta \neq 0$ requires a larger sample size, thereby

subjecting some patients to unnecessary experimentation and raising an ethics issue, particularly if the main purpose of the trial, as explained to the patients during the consent procedure, is to determine if the new intervention is superior. If a two-sided test is proposed then patients must understand that the main purpose of the trial is to determine if the new intervention is either superior or inferior to the standard intervention, *i.e.* the one they would receive if they refused entry into the trial. Consequently, in a superiority trial the question of *Treatment* being inferior is not part of the primary analysis and should be addressed, if at all, as a secondary analysis by testing the null hypothesis $H'': \theta \geq 0$ versus $A'': \theta < 0$, with a separate, one-sided Type I error probability.

2.2 OPTIMAL SAMPLE SIZE BASED ON THE EXPECTED VALUE OF SAMPLE INFORMATION

In response to the problems associated with sample size determinations based on tests of hypotheses and power arguments, many authors have proposed alternatives, see Section 2.4 for a complete review. In particular, Willan and Pinto (2005) and Eckermann and Willan (2007) (2008a) propose methods based on decision theory and the expected value of information (EVI) that determines the sample size for maximizing the difference between the expected cost of the trial and the expected value of information provided by the results. Fixed, variable and opportunity trial costs are considered. In addition to providing optimal sample sizes, these methods can identify circumstances when the current information is sufficient for decision making, see Willan (2007). Details of the approach, including a solution under simplifying assumptions, are given in the remainder of this section.

Consider the problem of determining the sample size for a randomized clinical trial designed to examine the cost-effectiveness of a new health care intervention, referred to as *Treatment*, labeled *T*, in comparison to an existing health care intervention, referred to as *Standard*, labeled *S*. The trial is conducted with the purpose of adopting *Treatment* if it is found to be cost-effective. *Treatment* is cost-effective if the incremental net benefit (INB) is greater that zero. Recall from Chapter 1 that the incremental net benefit is defined as $b(\lambda) \equiv \Delta_e \lambda - \Delta_c$, where λ is the threshold value for a unit of health outcome (effectiveness); $\Delta_e = e_T - e_S$, where e_j, for $j = T, S$, is the mean effectiveness for intervention j; and $\Delta_e = c_T - c_S$, where c_j, for $j = T, S$, is the mean cost for intervention j. Note that $b(\lambda) = e_T \lambda - c_T - \left(e_S \lambda - c_S\right)$, so that INB = $\text{NB}_T - \text{NB}_S$, where $\text{NB}_j (\equiv e_j \lambda - c_j)$ is the mean net benefit for intervention j.

2.2.1 The Expected Value of Sample Information

In the following, the threshold value is initially considered fixed for ease of notation but can be conditioned on where required, as demonstrated later in examining robustness. Let the current information regarding incremental net benefit be characterized by a normal prior *pdf* with mean b_0 and variance v_0, where $b_0 > 0$ and $v_0 > 0$. Since the prior mean incremental net benefit (b_0) is positive, adopting *Treatment*, rather than retaining *Standard*, maximizes the expected net benefit for future patients. However, since the prior variance of incremental net benefit (v_0) is positive, adopting *Treatment* is not necessarily the optimum decision facing a decision maker. Consideration must be given to collecting more information, *i.e.* conducting another trial. Decision uncertainty

resulting from a positive v_0 implies that a decision maker faces an opportunity loss when adopting *Treatment*, even though doing so is the decision that maximizes expected net benefit for future patients. The opportunity loss per patient associated with the decision to adopt *Treatment* is defined as the utility of the best decision *minus* the utility of the decision taken, which in this case, because b_0 is positive, is adopting *Treatment*. Since, in this context, utility equals net benefit, the opportunity loss becomes the maximum of (NB_T, NB_S) *minus* NB_T. The maximum of (NB_T, NB_S) depends on INB. If INB is positive, then $NB_T > NB_S$, and NB_T is the maximum. On the other hand, if INB is not positive, then $NB_T \leq NB_S$, and NB_S is the maximum. Thus, in denoting INB by *b*, the opportunity loss per patient (OLpp) associated with adopting *Treatment*, as a function of incremental net benefit, is given by:

$$\mathrm{OLpp}_T(b) = \begin{Bmatrix} \mathrm{Max}(\mathrm{NB}_T, \mathrm{NB}_S) - \mathrm{NB}_T = \mathrm{NB}_S - \mathrm{NB}_T = -b : b \leq 0 \\ \mathrm{Max}(\mathrm{NB}_T, \mathrm{NB}_S) - \mathrm{NB}_T = \mathrm{NB}_T - \mathrm{NB}_T = 0 \quad : b > 0 \end{Bmatrix}.$$

When incremental net benefit is positive there is no opportunity loss associated with adopting *Treatment* since future patients would receive the net benefit-maximizing intervention. However, if *Treatment* is adopted when incremental net benefit is negative, future patients would not receive the net benefit-maximizing intervention and each patient would experience a reduction in net benefit equal to the absolute value of incremental net benefit. A plot of $\mathrm{OLpp}_T(b)$ is given in Figure 2.2.

Taking the expected value of $\mathrm{OLpp}_T(b)$ with respect to the current information regarding incremental net benefit, which, as assumed above, is characterized by a normal prior *pdf* with mean b_0 and variance v_0, yields the prior expected opportunity loss per patient (EOLpp_{T0}). Letting $f(x;\mu,v)$ be the *pdf* for normal random variable with mean μ and

variance v, then $\text{EOLpp}_{T0} = \int_{-\infty}^{\infty} \text{OLpp}_T(b)\, f(b; b_0, v_0)\, \text{d}b = \int_{-\infty}^{0} -b\, f(b; b_0, v_0)\, \text{d}b = \mathcal{D}(b_0, v_0)$,

where $\mathcal{D}(\mu, v) = \left[v/(2\pi)\right]^{\frac{1}{2}} \exp\left[-\mu^2/(2v)\right] - \mu\left[\Phi(-\mu/v^{\frac{1}{2}}) - I(\mu \le 0)\right]$; $\Phi(\cdot)$ is the *cdf* for the standard normal random variable; and, $I(\cdot)$ is the indicator function. The expected opportunity loss per patient, multiplied by the number of future patients, is the total expected opportunity loss and is also known as the expected value of perfect information, since if the decision maker had perfect information (*i.e.* $v_0 = 0$), the opportunity loss could be avoided by adopting *Treatment* if b_0 is positive and retaining *Standard* otherwise. Applying decision theory, as illustrated in Chapter 1, Section 1.3, the expected value of sample information (EVSI) of a new trial is the amount by which the information from the new trial reduces the total expected opportunity loss.

Suppose a new trial of n patients per arm is conducted where the observations of effectiveness and cost on each patient is denoted by e_{ji} and c_{ji} respectively, where $j = T, S$ indexes treatment arm and $i = 1, 2, \ldots n$ indexes patient within treatment arm. Let $\overline{e}_j$ and $\overline{c}_j$ be the within-treatment arm sample means. Further, let $\hat{\Delta}_e = \overline{e}_T - \overline{e}_S$ and $\hat{\Delta}_c = \overline{c}_T - \overline{c}_S$. Thus, the estimate of incremental net benefit based on the trial data is $\hat{b} = \hat{\Delta}_e \lambda - \hat{\Delta}_c$ and relying on the central limit theorem regarding the distribution of $\hat{b}$ the posterior mean and variance for incremental net benefit are given by:

$$b_1 = v_1\left(\frac{b_0}{v_0} + \frac{n\hat{b}}{\sigma_+^2}\right) \text{ and } v_1 = \left(\frac{1}{v_0} + \frac{n}{\sigma_+^2}\right)^{-1},$$

where $\sigma_+^2 = \mathrm{V}(e_{Ti}\lambda - c_{Ti}) + \mathrm{V}(e_{Si}\lambda - c_{Si})$, *i.e.* the sum over treatment arm of the between-patient variances of incremental net benefit, and is assumed known or determinable from prior data. The posterior (*i.e.* post trial) expected opportunity cost per patient is given by $\mathrm{EOLpp}_1 = \mathcal{D}(b_1, v_1)$. EOLpp_1 is a function of the random variable $\hat{b}$ and to determine the expected reduction in per-patient opportunity loss before conducting the new trial, with the purpose of identifying the optimal sample size, the expectation of EOLpp_1 must be taken with respect to $\hat{b}$. Applying the central limit theorem, the predictive distribution for $\hat{b}$ is $N(b_0, v_{\hat{b}})$, where $v_{\hat{b}} = v_0 + \sigma_+^2 / n$, and the expected value of EOLpp_1 with respect to $\hat{b}$ becomes, see Willan and Pinto (2005),

$$\mathrm{E}_{\hat{b}}\mathrm{EOLpp}_1 = \mathrm{E}_{\hat{b}}\mathcal{D}(b_1, v_1) = \int_{-\infty}^{\infty} \mathcal{D}(b_1, v_1)\, f(\hat{b}; b_0, v_{\hat{b}})\mathrm{d}\hat{b} = I_1 + I_2 + I_3, \text{ where}$$

$$I_1 = \sqrt{v_0/(2\pi)}\,\sigma_+^2 \exp\left(-b_0^2/2v_0\right)\Big/(nv_{\hat{b}}),$$

$$I_2 = -b_0\Phi\left(-b_0/\sqrt{v_0}\right) + v_0^{3/2}\exp\left(-b_0^2/2v_0\right)\Big/\left(v_{\hat{b}}\sqrt{2\pi}\right) \text{ and}$$

$$I_3 = b_0\Phi\left(-b_0\sqrt{v_{\hat{b}}}/v_0\right) - v_0\exp\left(-b_0^2 v_{\hat{b}}/(2v_0^2)\right)\Big/\sqrt{2\pi v_{\hat{b}}}\,.$$

Thus, the expected value of sample information of a trial of *n* patients per arm is given by $\mathrm{EVSI}(n) = N(n)\left\{\mathcal{D}(b_0, v_0) - \mathrm{E}_{\hat{b}}\mathcal{D}(b_1, v_1)\right\}$, where $N(n)$ refers to the post-trial patient horizon, defined as the number of patients who could potentially receive the new intervention at the end of the trial. For an incidence rate of *k*, a time horizon of *h* and a trial duration of *t*, $N(n; h, k, t) = k(h - t)$. The time horizon is the duration for which the decision to either adopt *Treatment* or perform another trial is relevant. If we make the

simplifying assumptions that all patients are recruited into the trial and that the results of the trial are available immediately after the last patient is randomized, then $N(n) = kh - 2n$. The patient horizon at the point in time when the decision to adopt *Treatment* or perform another trial has to be made is *kh*. If the trial is performed, then 2*n* of these patients will be recruited into the trial. The trial results will not have value for these 2*n* patients, consequently the patient horizon at the end of the trial is $kh - 2n$.

2.2.2 Expected Total Cost

The cost of a trial is assumed to have two components, one financial and the other reflecting opportunity costs. Let C_f be the fixed financial cost of setting up a trial and let C_v be the financial cost per patient. Then the total financial cost of a trial with *n* patients per arm is $C_f + 2nC_v$.

Since b_0 is positive, and assuming perfect implementation, if the trial is not performed all future patients would receive *Treatment*, since adopting *Treatment* maximizes expected net benefit for future patients. If the trial is performed, all patients who receive *Standard* until trial evidence is updated pay an expected opportunity cost equal to b_0. The decision to perform the trial means that these patients have an expected reduction in net benefit equal to b_0 because they will receive *Standard* rather than *Treatment* due to delaying the adoption decision and performing the trial. Under the simplifying assumptions that all patients are recruited into the trial and that the results of the trial are available immediately after the last patient is randomized, the number of patients who receive *Standard* while the trial is performed is simply the *n* patients who receive *Standard* in the

trial. Therefore the expected total costs (ETC) of delaying the decision and performing the trial are $\text{ETC}(n) = C_f + 2nC_v + nb_0$.

2.2.3 The Expected Net Gain and Optimal Sample Size

Given b_0, v_0, σ_+^2, *h* and *k*, the expected value of sample information is a function of the sample size *n*, given as $\text{EVSI}(n) = (hk - 2n)\left\{\mathcal{D}\left(b_0, v_0\right) - \text{E}_{\hat{b}}\mathcal{D}\left(b_1, v_1\right)\right\}$. Likewise, given b_0, C_f and C_v, the expected total cost is a function of the sample size *n*, given as $\text{ETC}(n) = C_f + 2nC_v + nb_0$. Considering the trial in isolation, and being free of budget constraints, the optimal sample size, denoted *n**, is that value of *n* that maximizes the expected net gain (ENG), which is the expected value of sample information *minus* expected total cost. That is, $\text{ENG}(n^*) \geq \text{ENG}(n)$ for all positive integers *n*, where

$$\text{ENG}(n) = \text{EVSI}(n) - \text{ETC}(n) = (hk - 2n)\left\{\mathcal{D}(b_0, v_0) - \text{E}_{\hat{b}}\mathcal{D}(b_1, v_1)\right\} - (C_f + 2nC_v + nb_0).$$

If $\text{ENG}(n) \leq 0$ for all positive integers *n*, then optimal sample size is zero and the current information, *i.e.* b_0 and v_0, is sufficient for decision making. In this case no trial is necessary, since the expected value of the information from the trial is less than the expected total cost, regardless of the sample size. On the other hand, if $\text{ENG}(n^*) > 0$, the decision maker is in a state of equipoise and the optimal decision is to delay adopting *Treatment*, even though $b_0 > 0$, and perform a trial with *n** patients per arm.

2.3 EXAMPLES

2.3.1 The CADET-Hp Trial

As described in Chapter 1, Section 1.3.1, the CADET-Hp Trial is a randomized controlled trial performed in Canada. The results are published in Chiba *et al*. (2002) and Willan (2004). Patients with uninvestigated dyspepsia were randomized between

T: Omeprazole 20 mg, metronidazole 500 mg and clarithromycin 250 mg, and

S: Omeprazole 20 mg, placebo metronidazole and placebo clarithromycin.

A total of 188 patients were randomized, 142 (= n_T) to *Treatment* and 146 (= n_S) to *Standard*. The binary measure of effectiveness was treatment success and defined as the presence of no or minimal dyspepsia symptoms at one year. Total costs were determined from the societal perspective and are given in Canadian dollars.

In this example, e_{ji} equals 1 if patient *i* on treatment arm *j* has a successful outcome, *i.e.* has no or minimal dyspepsia at one year, and 0 if not. Thus, the sample average $\bar{e}_j$ is simply the proportion of success observed on arm *j*. A summary of the parameter estimates is given in Table 2.1. Assuming no prior information and invoking the central limit theorem, the posterior *pdf* for incremental net benefit is normal with mean $b_0(\lambda) = \hat{\Delta}_e\lambda - \hat{\Delta}_c = 0.1371\lambda + 53.01$ and variance $v_0(\lambda) = \hat{\mathrm{V}}(\hat{\Delta}_e)\lambda^2 + \hat{\mathrm{V}}(\hat{\Delta}_c) - 2\hat{\mathrm{C}}(\hat{\Delta}_e, \hat{\Delta}_c)\lambda = 0.003356\lambda^2 + 4782 + 1.426\lambda$, where λ is the threshold value for a treatment success. The posterior *pdf* for the CADET-Hp trial given above serves as the prior *pdf* for the consideration of any future trial. For a threshold value of \$250, and dropping λ in the notation as before, the prior *pdf* for incremental net benefit for any future trial is normal with mean $b_0 = 87.29$ and variance $v_0 = 5358.20$. The sum over treatment arm of the between-patient variances can be estimated as

$$\hat{\sigma}_{+}^{2} = \sum_{j=T,S} \left\{ \lambda^2 \hat{V}(e_{ji}) + \hat{V}(c_{ji}) - 2\lambda \hat{C}(e_{ji}, c_{ji}) \right\}$$

$$= \sum_{j=T,S} \left\{ \lambda^2 \overline{e}_j (1 - \overline{e}_j) + \sum_i (c_{ji} - \overline{c}_j)^2 \Big/ (n_j - 1) - 2\lambda \sum_i (e_{ji} c_{ji} - \overline{e}_j \overline{c}_j) \Big/ (n_j - 1) \right\}$$

$$= \sum_{j=T,S} n_j \left(\lambda^2 \hat{V}(\overline{e}_j) + \hat{V}(\overline{c}_j) - 2\lambda \hat{C}(\overline{e}_j, \overline{c}_j) \right) = 772,596.$$

Assuming an incidence (*k*) of 80,000 per year, a time horizon (*h*) of 20 years, a fixed cost (C_f) of $800,000 and a variable cost (C_v) of $2000, the optimal sample size per arm (*n**) is 465. An optimal sample size of 465 per arm corresponds to an expected value of sample information of $4,049,912, a financial cost of 2,660,000, an expected opportunity cost of $40,588 and an expected net gain of $1,349,325. Plots of expected value of sample information, expected total cost and expected net gain, as functions of *n*, are given if Figure 2.3.

The specific values used above for the threshold value for a unit of health outcome, incidence, time horizon and financial costs will be referred to as the base case. It is reasonable to investigate the sensitivity regarding departures from the base case. For this example, the solution is reasonably robust to 25% departures from the base case. As shown in Panel A of Table 2.2, if the incidence is 100,000 per year (*i.e.* 25% larger), or equivalently if the time horizon is 25 years (*i.e.* 25% longer), then the optimal sample size is 541. However, entering 465 patients per arm (the optimal sample size if the incidence is 80,000) yields a mere 1.54% reduction in the expected net gain. The largest reduction in ENG for 25% departures from the base case is for incidence of 60,000 (*i.e.* 25% smaller), or equivalently a time horizon of 15 years (*i.e.* 25% shorter), where the

reduction is 12.6%. For 25% deviation from the base case in threshold value and financial cost the reduction in expected net gain is less than 5%.

Table 2.2 provides a one-way sensitivity analysis. Multi-way sensitivity can be examined by considering the following. The plots of expected value of sample information for three different values for the incidence are given in Figure 2.4, together with the plot of expected total cost. For an incidence of 80,000 per year we have the solution given above. For an incidence of 30,000 the expected value of sample information is always less than ETC, regardless of sample size, and the optimal sample size is 0. This means that for an incidence of 30,000 there is sufficient evidence for decision making, since the cost of any new trial will exceed the value of the information provided by it. The plot of EVSI for an incidence of 51,280 is just tangent to the plot of expected total cost, implying that for value of the incidence less that 51,280 the optimal sample size is zero and the evidence is sufficient for decision making. On the other hand, for levels of incidence greater than 51,280, the optimal sample size is greater than zero and the optimal decision is to delay the decision regarding the adoption of *Treatment* and perform another trial. We will refer to 51,280 as the "threshold incidence" and denote it as $\tilde{k}$. Since the expected value of sample information also depends on λ (*i.e.* the threshold value for unit of health outcome), we can determine the threshold incidence for various values of λ, and by plotting these values, as in Figure 2.5, examine two-way sensitivity. The plot in Figure 2.5 represent the combinations of k and λ for which ENG = 0. Above the line, where ENG > 0, lies the Region of "Equipoise", for which the optimal sample size is greater than zero. The term "equipoise" is used because, given the value placed on health

outcome, the number of patients that could benefit from additional information and the cost of acquiring it, the current evidence is insufficient for decision making, in the sense that there exists sample sizes for which the value of additional information exceeds the cost of acquiring it. The region below this equipoise line, where ENG < 0, is referred to as the Region of Adoption, since for combination of k and λ in this region the evidence is sufficient for decision making, in the sense that the cost of any additional information exceeds its value, again given the value placed on health outcome, the number of patients that could benefit from additional information and the cost of acquiring it. To additionally consider cost of trials, three-way sensitivity analyses are facilitated by plotting the "ENG = 0" lines for alternative trial costs. Such plots are given in Figure 2.6 for the three trial cost configurations given in Table 2.2.

To consider potential variation in optimal sample size, two-way sensitivity analyses can also be undertaken by plotting combinations of the incidence and threshold value for a unit of health outcome that have the same optimal sample size. Such "contours" are shown in Figure 2.7 for various values for the optimal sample size. One such contour is presented for the base case optimal sample size of 465, where $k = 80{,}000$ and $\lambda = 250$ contributes one point. Departures from the base case optimal sample size of 25% are also shown in Figure 2.7 with contours for optimal sample sizes of 325 and 600. This illustrates that if the investigators are quite sure that the incidence is between 60,000 and 100,000 and that the threshold value for a unit of health outcome is between 187.50 and 312.50, then the optimal sample size lies between 325 and 600.

As illustrated in Section 2.1 the sample size based on the frequentist approach is given by

$$n = \sigma_+^2 \left[(z_{1-\alpha} + z_{1-\beta}) \big/ \theta_{\text{SCID}} \right]^2, \qquad (2.1)$$

where α and β are the Type I and II error probabilities, respectively; $z_{1-\gamma}$ is the $100(1-\gamma)$ percentile for the standard normal random variable; $\sigma_+^2 = \sigma_T^2 + \sigma_S^2$, where σ_i^2 is the between-patient variance of an observation for a patient randomized to receive *i*, for *i* = *T, S*; and θ_{SCID} is the smallest clinically important difference. Using Equation 2.1 to determine *n* as a function of θ_{SCID}, a plot of ENG as function of θ_{SCID} is given in Figure 2.8. The values of α and β were set to 0.05 and 0.2, respectively. Thus Figure 2.8 illustrates, as a function of θ_{SCID}, the ENG realized by a trial designed using frequentist principles. ENG is positive for θ_{SCID} values between 66 and 194, with respective sample size of 1097 and 127, and attains its optimum value of 1,349,325 at the optimal sample size of 465 (*n**), corresponding to a θ_{SCID} of 101.

2.3.2 The Prostate Trial

In a multi-site randomized trial of symptomatic, hormone resistant prostate cancer, 161 patients were randomized between prednisone alone (*Standard*) and prednisone plus mitoxantrone (*Treatment*). The clinical results are published in Tannock *et al*. (1996) and the economics analysis in Bloomfield *et al*. (1998). Although there was no statistically significant difference in survival, patients experienced a better quality of life with *Treatment*. Cost data, including hospital admissions, outpatient visits, investigations, therapies and palliative care, were collected retrospectively on the 114 patients from the three largest clinical sites and are given in Canadian dollars (CAD$). Survival was quality-adjusted using the EORTC quality of life questionnaire QLQ-C30. All patients

were followed until death. In this example, e_{ji} is the quality-adjusted survival time for patient *i* from treatment arm *j*, given in quality-adjusted life-weeks (QALWs), and was determined using the area under the curve from repeated measurements.

A summary of the parameter estimates is given in Table 2.3. The sample mean quality-adjusted survival for patients randomized to prednisone plus mitoxantrone was 40.9 QALWs, compared to 28.1 QALWs for patients randomized to prednisone alone, with corresponding sample variance of 24.10 and 16.42. The treatment groups did not differ with respect to overall survival. The sample mean cost for those on *Treatment* and *Standard* was $27,322 and $29,039 respectively. Since *Treatment* is observed to increase quality-adjusted survival and decrease costs, the estimated incremental net benefit $\hat{b}(\lambda)$ is positive for all positive values for the threshold value for a quality-adjusted life-week (λ). For a threshold value of $300 per QALW ($\simeq$ $15,000 per quality-adjust life-year), the current estimate of incremental net benefit (b_0) and its variance (v_0) are 5551 and 14,597,242, respectively. Note that a traditional test of the hypothesis of $b(300) \leq 0$ versus $b(300) > 0$ yields a p-value of 0.073. The sum over treatment arm of the between-patient variances can be estimated as

$$\hat{\sigma}^2_{+} = \sum_{j=T,S} \left\{ \lambda^2 \hat{\mathrm{V}}(e_{ji}) + \hat{\mathrm{V}}(c_{ji}) - 2\lambda \hat{\mathrm{C}}(e_{ji}, c_{ji}) \right\}$$

$$= \sum_{j=T,S} \left\{ \lambda^2 \sum_i (e_{ji} - \overline{e}_j)^2 \Big/ (n_j - 1) + \sum_i (c_{ji} - \overline{c}_j)^2 \Big/ (n_j - 1) - 2\lambda \sum_i (c_{ji} - \overline{c}_j)(e_{ji} - \overline{e}_j) \Big/ (n_j - 1) \right\}$$

$$= \sum_{j=T,S} n_j \left(\lambda^2 \hat{\mathrm{V}}(\overline{e}_j) + \hat{\mathrm{V}}(\overline{c}_j) - 2\lambda \hat{\mathrm{C}}(\overline{e}_j, \overline{c}_j) \right) = 829,435,498.$$

For a time horizon of 20 years, an incidence of 2500 per year and fixed and variable per patient trial costs set at 1,000,000 and 2000, respectively, the optimal sample size in 197 per arm. Thus, the optimal decision is to delay the decision regarding the adoption of *Treatment* and perform a trial of 197 patients per arm. Associated with this optimal solution is an expected value of sample information of $3,452,226, an expected total cost of $2,881,575 and an expected net gain of $570,651. Plots of expected value of sample information, expected total cost and expected net gain, as functions of sample size, are given in Figure 2.9.

Robustness to 25% departures from the base case with respect to incidence, time horizon, threshold value for a QALW and financial costs is illustrated in Table 2.4. For situations where optimal sample size is none-zero the optimal solution is seen to be fairly robust with respect to 25% deviations in incidence, time horizon and cost. For these situations the largest reduction in expected net gain is 5.14%%, which occurs for a 25% increase in trial financial costs. So that if the true fixed and variable cost were $1,250,000 and $2500 and 197 patients per arm were entered into a new trial, the ENG would only be 5.14% less than if the optimal sample size of 184 per arm were entered. However, if the incidence was 1875 (or equivalently the time horizon was 15 years) or if threshold value was 375, the optimal sample size is zero. In these cases entering 197 patients per arm would lead to suboptimal solutions. These situations are illustrated in Figure 2.10, where the combination of incidence and threshold value (λ) for which expected net gain is zero are plotted for the three cost configuration given in Panel D of Table 2.4. For $\lambda = 300$, base case trial cost, and an incidence of 1875, the optimal decision is to adopt *Treatment*

without performing another trial. This corresponds to the first column of Panel A in Table 2.4, where the optimal sample size is zero, and Point 1 in Figure 2.10 which falls under the base case curve. Similarly, for $\lambda = 375$, base case trial cost, and an incidence of 2500 the optimal decision is to adopt *Treatment* without performing another trial. This corresponds to the third column of Panel C in Table 2.4, where the optimal sample size is zero, and Point 2 in Figure 2.10 which falls under the base case curve.

The expected net gain realized by a trial designed using frequentist principles, as a function of θ_{SCID}, is illustrated in Figure 2.12. The values of α and β were set to 0.05 and 0.2, respectively. Expected net gain is positive for θ_{SCID} values between 3810 and 7532, with respective sample size of 358 and 91, and attains its optimum value of $570,651 at the optimal sample size of 197 (n^*), corresponding to a θ_{SCID} of 5103.

2.3.3 The Early ECV Trial

In a pilot study (see Hutton *et al*., 2003), 232 pregnant women presenting in the breech position were randomized between early (*Treatment*) versus late (*Standard*) external cephalic version (ECV). External cephalic version 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. The trial was funded by the Canadian Institutes for Health Research (CIHR) and finished recruiting patients in 2008.

Suppose, for sake of argument, that the threshold value to achieve a non-Caesarean delivery in these patients is $1000. (All costs are given in Canadian dollars.) This amount reflects both 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, $b(1000) = \Delta_e 1000$, where $\Delta_e = e_T - e_S$ is the probability of a non-Caesarean delivery for early ECV (e_T) *minus* the probability of a non-Caesarean delivery for late ECV (e_S), which, based on the pilot data, is estimated as $\bar{e}_T - \bar{e}_S = 41/116 - 33/116 = 0.06897$. The prior distribution for incremental net benefit, given the pilot data, is assumed normal with mean $b_0 = (\bar{e}_T - \bar{e}_S)1000 = 0.06897 * 1000 = 68.97$ and variance

$$v_0 = \left\{ \frac{\bar{e}_T(1-\bar{e}_T)}{n_T} + \frac{\bar{e}_S(1-\bar{e}_S)}{n_S} \right\} 1000^2$$

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

The normal assumption is based on the Central Limit Theorem, which is typically invoked for the distributions of proportions. The sum over treatment arm of the between-patient variances can be estimated as

$$\hat{\sigma}_+^2 = \sum_{j=T,S} \bar{e}_j(1-\bar{e}_j)1000^2 = \left\{ \frac{41}{116}\left(1-\frac{41}{116}\right) + \frac{33}{116}\left(1-\frac{33}{116}\right) \right\} 1000^2 = 432,075 .$$

Consider a time horizon (h) of 20 years and assume that the annual North American incidence is approximately 100,000. If we further assume that 50% of the patients would receive *Treatment* if it were observed to be superior, then the effective incidence (k) is 50,000. Based on the total budget for the CIHR funded trial of $2,836,000, it was determined that the fixed cost (C_f) is $500,000 and the cost per patient (C_v) is $1600. Using the above values for b_0, v_0, σ_+^2, k, h, C_f, and C_v, the sample size (n*) that maximizes expected net gain is 345 per arm and corresponds to an expected value of sample information of 2,370,448 and an expected total cost of 1,627,793, yielding an expected net gain of 742,655. Plots of expected value of sample information, expected total cost and expected net gain, as functions of sample size, are given in Figure 2.13.

Robustness of optimal expected net gain to 25% departures from the base case with respect to incidence, time horizon, threshold value for a non-Caesarean delivery and financial costs is illustrated in Table 2.5. The optimal solution is seen to be fairly robust with respected to 25% deviations in costs and to 25% increases in incidence, time horizon and the threshold value. However, if the incidence or time horizon is 25% lower, entering 345 patients per arm (the optimal solution for the base case), will result in a 16.3% reduction in expected net gain compared to the optimal solution of entering 279 patients per arm. A similar reduction in expected net gain is associated with a 25% decrease in the threshold value.

Figure 2.14 illustrates, as a function of θ_{SCID}, the expected net gain realized by a trial designed using frequentist principles. The values of α and β were set to 0.05 and 0.2, respectively. ENG is positive for θ_{SCID} values between 58 and 165, with respective sample size of 795 and 99, and attains its optimum value of 742,655 at the optimal sample size of 345 (n^*), corresponding to a θ_{SCID} of 88.

2.4 REVIEW OF PREVIOUS WORK

Numerous authors have proposed Bayesian approaches for sample size determination, see Adcock (1997) for an overview and Lindley (1997) and Pezeshk (2003) for a general discussion with broad applications. The review provided here will focus on those approaches that are referred to as full Bayesian or decision-theoretic and will be restricted to applications for designing trials for comparing two or more interventions (treatments). Decision-theoretic approaches for sample size determination date back to the mid-twentieth century (Grundy, Healy, Rees, 1956; Raiffa and Schlaifer, 1961). They involve applying decision theory to determine which action maximizes the expected net gain, where expected net gain is defined as the difference between the expected utility and expected cost associated with the action. In the context of clinical trials, the actions consist of performing a clinical trial of size n/arm (possibly 0) and selecting an intervention for future patients based on the evidence updated with the trial data. A sample size of 0 implies that the decision will be made based on the current information alone. The optimum expected net gain associated with the unknown parameter of interest b can be written as

$$\max_n \left\{ \int_x \max_I \left[\int_b u_I(b)\, f_n(b \mid \boldsymbol{x}) \mathrm{d}b \right] f(\boldsymbol{x} \mid n) \mathrm{d}\boldsymbol{x} - C(n) \right\},$$

where $\boldsymbol{x}$ is the data observed in a trial of size n/arm, $C(n)$ is the total cost associated with the trial, $u_I(\theta)$ is the utility of selecting intervention I for a particular value of the parameter of interest, $f_n(b \mid \boldsymbol{x})$ is the posterior distribution of b, and $f(\boldsymbol{x} \mid n)$ is the predictive distribution of $\boldsymbol{x}$. For a more general discussion of the use of utility functions in clinical trials, see Tan and Smith (1998).

In relation to the work given in Section 2.2.1, the parameter of interest is incremental net benefit (b) and the utility of the trial is the reduction in opportunity loss, where the utility functions are given by

$$u_T(b) = (hk - 2n)\left\{\mathcal{D}(b_0, v_0) - \left(g(b) - b\right)\right\} \text{ and}$$

$$u_S(b) = (hk - 2n)\left\{\mathcal{D}(b_0, v_0) - g(b)\right\},$$

where $g(b) = b$ if $b > 0$, and 0 otherwise, so that $g(b)$ is the opportunity loss for choosing S and $g(b) - b$ is the opportunity loss for choosing T. Also, $f(\boldsymbol{x} \mid n)$ is the probability distribution function associated with a normal random variable with mean b_0 and variance $v_0 + \sigma_+^2 / n$ and $C(n) = C_f + (2C_v + b_0)n$. Under the assumption that the intervention with the largest mean net benefit based on the updated evidence is always selected, then

$$\max_I \left[\int_b u_I(b)\, f_n(b \mid \boldsymbol{x}) \mathrm{d}b\right] = (kh - 2n)\left\{\mathcal{D}(b_0, v_0) - \mathcal{D}(b_1, v_1)\right\} = \mathrm{EVSI}(n; b_0, \mathrm{v}_0, \sigma_+^2).$$

Claxton and Posnett (1996) take a decision-analytic approach for determining optimal sample size similar to that outlined in Section 2.2.1. They define the opportunity loss function as the difference between incremental net benefit of the best decision and the

incremental net benefit of the decision taken rather than the difference in net benefits, and consequently the formulation of opportunity loss function is twice that of the one given in Section 2.2.1. Further they define the per-patient post-trial expected opportunity loss as $\mathcal{D}(b_0, v_1)$ rather than $\mathrm{E}_{\hat{b}}\mathcal{D}(b_1, v_1)$. However, they discount expected opportunity loss by defining the population expected opportunity loss as $k\sum_{j=1}^{h} \mathrm{EOLpp}_i / (1+r)^j$, for $i = 0,1$, where *r* is the discount rate. They make the same simplifying assumptions regarding accrual rate and timing of results (*i.e.* that all patients are recruited into the trial and the results are available immediately) as made in Chapter 2, but do not include an opportunity cost in the cost function.

Claxton (1999) using the definition of opportunity loss as the difference between the net benefit of the best decision and the net benefit of the decision taken provides a solution for optimal sample size with discounted opportunity costs and unequal allocation between treatment arms. The argument for unequal allocation is based on the fact that health care costs and between-patient variance of net benefit may differ between treatment arms and therefore equal allocation is not optimal. Again, per-patient post-trial expected opportunity loss is calculated as $\mathcal{D}(b_0, v_1)$. The same simplifying assumptions are made regarding accrual rate and timing of results. The cost function includes the expected additional health care cost for patients allocated to the *Treatment* arm, and assuming these are positive, the optimal solution would have fewer patients in this arm than it would otherwise. However, if additional health care costs associated with *Treatment* are to be included as a cost, it could be argued the expected additional health

benefits associated with *Treatment* should be included as a benefit. Including both the additional expected costs and health benefits is accomplished by including opportunity cost as illustrated in Section 2.2.2. If the opportunity cost is included, and assuming pre-trial incremental net benefit is positive, the optimal solution would have more patients in *Treatment* arm than it would otherwise. Claxton and Thompson (2001) extend the methods of Claxton (1999) to include stages involving diagnostic testing.

Berry and Ho (1998) use a decision-theoretic model to determine stopping boundaries for industry-based clinical trials. In their model a trial, which only measures effectiveness, has *J* stages and is designed to compare an experimental drug to a control with the purpose of gathering evidence for seeking regulatory approval for marketing. At the end of each of the first $J-1$ stages a decision is made to either continue to the next stage, entering another $2n$ patients, or to stop the trial and abandon the experimental drug (decision d_1), concluding that $\Delta_e \leq 0$. At the end of the final stage a decision is made to either seek regulatory approval (decision d_2), concluding that $\Delta_e > 0$, or to abandon the experimental drug (decision d_1). Decision d_1 is available at the end of all stages, while decision d_2 is only available at the end of stage *J*. They define a loss function for decision d_1 as $L_1(\Delta_e) = 0$. This loss function reflects that there are no additional financial cost with decision d_1 and is not, strictly speaking, an opportunity loss function, since there would be positive opportunity lost for $\Delta_e > 0$. The loss function for decision d_2 is given by

$$L_2(\Delta_e) = \begin{cases} -K\Delta_e & \text{if } \Delta_e \geq 0 \\ L & \text{if } \Delta_e < 0 \end{cases}$$

where *K* and *L* are known positive constants. With the definition of $L_2(\cdot)$ the authors are assuming that if the drug is approved for marketing there will be a gain of *K* for each unit increase in effectiveness above zero and loss of *L* if $\Delta_e < 0$. The authors assume there is no fixed or opportunity cost associated with the trial.

Let the prior distribution for Δ_e be normal with mean Δ_{e0} and variance v_{e0}. Further, let the sample mean-based estimator of Δ_e using the data from stage *j* be denoted by $\hat{\Delta}_{ej}$ and let $\bar{\Delta}_{ej} = \sum_{i=1}^{j} \hat{\Delta}_{ej} \big/ j$. Therefore the posterior distribution for Δ_e at the end of stage *j* is normal with mean Δ_{ej} and variance v_{ej}, where

$$\Delta_{ej} = \frac{\Delta_{e0}\sigma_{e+}^2 + jnv_{e0}\bar{\Delta}_{ej}}{\sigma_{e+}^2 + jnv_{e0}},$$

$$v_{ej} = \frac{v_{e0}\sigma_{e+}^2}{\sigma_{e+}^2 + jnv_{e0}}$$

and σ_{e+}^2 is the sum across treatment groups of the between-patient variance of effectiveness. The authors use dynamic programming (backward induction) to determine $J+1$ threshold values, t_j, $j = 0, 1, 2 \ldots J$, such that d_1 (abandon the experimental drug) is optimal if, and only if, $\bar{\Delta}_{ej} < t_j$, where for convenience we set $\bar{\Delta}_{eo} = \Delta_{eo}$. If $\bar{\Delta}_{ej} \geq t_j$, it is optimal to enter another 2*n* patients for *j* < *J*, or seek regulatory approval for *j* = *J*. Optimality is defined as minimizing expected net loss.

Cheng, Su and Berry (2003) use a decision-theoretic approach to determine the optimal allocation of patients between two arms for each stage of a *J*-stage process where the measure of effectiveness is binary (*i.e.* success versus failure). They ignore financial costs, but their approach does account for opportunity costs. As we have done in Section 2.2.2, the authors have assumed that all eligible patients are recruited into the trial. Optimality is defined as maximizing utility, where utility is the number of expected successes for a fixed patient horizon of size *N*. In the final stage (stage *J*) all patients receive the treatment whose probability of success has the largest posterior mean as determined at the end of stage $J-1$. Let θ_S and θ_T be the probability of success for the two treatments, labeled *S* and *T*, respectively, and let $f_0(\theta_T, \theta_S)$ be the prior joint probability distribution (density) function for θ_S and θ_T. For $J = 2$ and the situation where θ_S is known (*i.e.* $\Pr(\theta_S = \pi) = 1$), the problem becomes one of maximizing the expected utility with respect to n_T and n_S, which are the sample sizes in the first stage for Treatments *T* and *S*, respectively. The expected utility is given as

$$n_T \mathrm{E}_0(\theta_T) + n_S \pi + (kh - n_T - n_S)\mathrm{E}_{\text{data}}\{E_1(\theta_T) \vee \pi\},$$

where *h* and *k* are the time horizon and incidence, respectively, and where $\mathrm{E}_0(\cdot)$, $\mathrm{E}_1(\cdot)$ and $\mathrm{E}_{\text{data}}(\cdot)$ are the expectation functions with respect to the prior distribution, the post distribution and the data observed in the trial, respectively. The symbol $\vee$ refers to the maximum. The authors show that it is optimal to allocate all patients in the first stage to Treatment *T* (*i.e.* $n_S^* = 0$), where the optimal number of patients in the first stage is given by

$$n_T^* = \left\{ \frac{0.5\pi(1-\pi) f_{T0}(\pi)}{\mathrm{E}_0(\theta_T \vee \pi) - \mathrm{E}_0(\theta_T)} N \right\}^{\frac{1}{2}} + o(N^{\frac{1}{2}}),$$

where $f_{T0}(\pi)$ is the prior marginal probability distribution function for θ_T and $o(N^{\frac{1}{2}})$ is defined to satisfy the condition $o(N^{\frac{1}{2}})N^{-\frac{1}{2}}$ approaches zero as *N* increases. For *J* = 2 where θ_S is not known, the expected utility to be maximized is given by

$$n_T \mathrm{E}_0(\theta_T) + n_S \mathrm{E}_0(\theta_S) + (hk - n_T - n_S)\mathrm{E}_{\text{data}}\{E_1(\theta_T) \vee E_1(\theta_S)\},$$

and the optimal allocation between treatment *T* and treatment *S* is n_T^* and n_S^*, respectively, where

$$n_T^* = \left\{ \frac{0.5c}{\mathrm{E}_0(\theta_T \vee \theta_S) - \mathrm{E}_0(\theta_T)} N \right\}^{\frac{1}{2}} + o(N^{\frac{1}{2}}),$$

$$n_S^* = \left\{ \frac{0.5c}{\mathrm{E}_0(\theta_T \vee \theta_S) - \mathrm{E}_0(\theta_S)} N \right\}^{\frac{1}{2}} + o(N^{\frac{1}{2}})$$

and

$$c = \int_0^1 x(1-x) f_0(x,x)\,\mathrm{d}x.$$

The trial costs and the between-treatment difference in health care cost are ignored in this model. Since maximizing expected utility is equivalent to maximizing expected net gain, as illustrated with the "What's in the Box?" example in Section 1.3.1, the solution given by Cheng, Su and Berry (2003) is the same as the one proposed in Section 2.2.3, depending on what assumptions are made. The comparable utility using net benefit is given by

$$n_T \mathrm{E}_0(B_T) + n_S \mathrm{E}_0(B_S) + (hk - n_T - n_S)\mathrm{E}_{\text{data}}\{E_1(B_T) \vee E_1(B_S)\} \qquad (3.1)$$

where B_i is the net benefit for treatment *i*. The utility expressed in (3.1) is close to EVSI minus opportunity cost as defined in Sections 2.2.1 and 2.2.2, and is identical under certain assumptions.

Consider as an example a two-stage procedure using the Early ECV Trial example given in Section 2.3.3. In this pilot trial pregnant women presenting in the breech position were randomized between early (*T*) versus late (*S*) external cephalic version (ECV). The measure of success was a non-Caesarean delivery. In a two-stage procedure patients are randomized between the two arms in the first stage, but in the second stage all patients receive the treatment that has the highest expected probability of success. 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%). Assuming flat prior distributions for θ_S and θ_T, *i.e.* $\theta_i \sim \text{Beta}(1,1)$, the posterior distributions after incorporating the pilot data, are $\theta_T \sim \text{Beta}(42,76)$ and $\theta_S \sim \text{Beta}(34,84)$. These are the prior distributions for a future trial. Assuming independence for θ_S and θ_T, the joint distribution is given by

$$f_0(\theta_T, \theta_S) = \frac{\theta_T^{41}(1-\theta_T)^{75}}{B(42,76)} \frac{\theta_S^{33}(1-\theta_S)^{83}}{B(34,84)},$$

where $B(\cdot,\cdot)$ is the beta function. It can be shown that

$$c = \int_0^1 f_0(x,x)\mathrm{d}x = \frac{B(42+76, 34+84)}{B(42,76)B(34,84)} = \frac{B(118,188)}{B(42,76)B(34,84)} = 0.79749.$$

Further, $\mathrm{E}_0\theta_T = 42/118$ and $\mathrm{E}_0\theta_S = 34/118$. The quantity $\mathrm{E}_0(\theta_T \vee \theta_S)$, which can be most easily be determined using sampling techniques as shown by the WinBUGS code given in Table 3.1, equals 0.3601. Assuming a patient horizon of 1,000,000, as in Section 2.3.3, the optimal sample sizes, to a first order approximation, are $n_T^* = 9781$ and $n_S^* = 2354$. Using value of information (VOI) methods with unequal allocation and trial cost equal to zero, the optimal sample sizes are 9940 and 2157 for arms *T* and *S*, respectively. The difference in health care cost in this example is essentially set to zero since they relate solely to the difference in the probability of success and can be thought of as part of the threshold value for a success, and when trial cost are set to zero the optimal solution does not depend on the threshold value. The VOI solution as given in this paragraph attempts to maximize net benefit over the patient horizon, which is achieved by maximizing the expected number of success, and so it is not surprising that the optimal solution concurs very closely with that of Cheng, Su and Berry (2003).

In a series of articles Hornberger, Brown and Halpern (1995), Hornberger and Eghtesady, (1998), Halpern, Brown and Hornberger (2001) take a decision-theoretic approach for determining sample size for a clinical trial. Their approach essentially determines the total sample size ($2n$) that minimizes the expected loss for a trial where the loss is defined as [the expected opportunity loss at the end of the trial] *plus* [the cost of the trial], given in our notation by $hk\mathrm{E}_{\hat{b}}\mathcal{D}\left(b_1, v_1\right) + 2nC_v$. This is equivalent to the approach given in Chapter 2 if opportunity costs and the fact that the patients in the trial cannot benefit from the results are ignored. That is, ignoring opportunity costs and the fact that the patients in the trial cannot benefit from the results, expected net gain becomes

$hk\{\mathcal{D}(b_0, v_0) - \mathrm{E}_{\hat{b}}\mathcal{D}(b_1, v_1)\} - (C_f + 2nC_v)$, and since $\mathcal{D}(b_0, v_0)$ and C_f do not depend of sample size, maximizing $hk\{\mathcal{D}(b_0, v_0) - \mathrm{E}_{\hat{b}}\mathcal{D}(b_1, v_1)\} - (C_f + 2nC_v)$ (expected net gain) is equivalent to minimizing $hk\mathrm{E}_{\hat{b}}\mathcal{D}\left(b_1, v_1\right) + 2nC_v$ (trial loss).

In a series of articles Gittins and Pezeshk (2000a)(2000b)(2002), Pezeshk (2003), and Pezeshk and Gittins (2006), use a decision theoretic approach to determine optimal sample size under the assumptions that the number of patients who receive the new intervention is a function of the size of the treatment effect and the associated statistical significance. The utility function the authors use is *wm*, where *w* is the additional utility received by a patient who switches from Standard to Treatment and *m* is the number of patients that, as a result of the trial, makes the switch. The number of patients who switch is a function of the size of the treatment effect and the associated statistical significance and is given by

$$m(\Delta_{e1}, v_{e1}) = \min\left(M, \max\left(0, M(\Delta_{e1} - (A + \Phi(1-\alpha)\sqrt{v_{e1}}))\big/(B - A)\right)\right),$$

where Δ_{e1} and v_{e1} are the posterior mean and variance for the difference in effectiveness; *M* is the maximum number of patients who would switch; *A* is the minimum difference in effectiveness for switches to occur in the absence of uncertainty; and, $B > A$ is that value of the difference in effectiveness at which *M* switches occur in the absence of uncertainty. The factor $\Phi(1-\alpha)$ accounts for the uncertainty, so that no switches occur if $\Delta_{e1} \le A + \Phi(1-\alpha)\sqrt{v_{e1}}$, meaning that switches occur only is the posterior mean is statistically significantly greater than *A* at the level α. Also, the maximum number of switches (*M*) is achieved for $\Delta_{e1} \ge B + \Phi(1-\alpha)\sqrt{v_{e1}}$. Thus the function $m(\Delta_{e1}, v_{e1})$ is 0

for $\Delta_{e1} \leq A + \Phi(1-\alpha)\sqrt{v_{e1}}$; M for $\Delta_{e1} \geq B + \Phi(1-\alpha)\sqrt{v_{e1}}$; and a straight line between the points $\left(A + \Phi(1-\alpha)\sqrt{v_{e1}}, 0\right)$ and $\left(B + \Phi(1-\alpha)\sqrt{v_{e1}}, M\right)$. The authors consider various perspectives, including that of the company who holds the patent on Treatment and commissions the trial, the regulator who has to approve Treatment for licensing and the public at large. They provide solutions for binomial, normal and Poisson models. However, they ignore treatment costs, fixed trial costs and opportunity costs.

2.5 DISCUSSION

In this chapter, a fully Bayesian approach for determining sample sizes for randomized clinical trials is given. A societal perspective is taken in which health care costs are covered through public expenditure and trial research is funded by government or donation-based philanthropic agencies. The approach is based on decision theory and the expected value of information and determines the sample size that maximizes the difference between the value of the information provided by the trial and the costs of performing it. It is proposed as an alternative to traditional frequentist's sample size determinations, which rely on somewhat arbitrary error rates and clinically important differences. Only a fully Bayesain approach guarantees an optimal sample size with respect to a given utility function based on the cost of the trial and the value of the information it provides. Sample sizes based on statistical tests of hypotheses will always be sub-optimal in this respect. Tests of hypotheses, while relevant for exploring scientific phenomena, are less useful for decision-making.

Speigelhalter (2004) outlines the arguments in favour of the role for decision theory in evaluating health-care interventions, stating that

> "[t]o maximize the health return from the limited resources available from a health budget, health-care purchasers should use [a] rational resource allocation procedure. Otherwise the resulting decisions could be considered as irrational, inefficient and unethical. Overall, a decision-theoretic framework provides a formal basis for designing trials, assessing whether to approve an intervention for use, deciding whether an intervention is cost-effective and commissioning further research."

Other authors, quoted by Speigelhalter (2004), support the role of decision theory. Lindley (2004) states that "clinical trials are not there for inference, but to make decisions," while Healy and Simon (1978) state that "the main objective of almost all trials on human subjects is (or should be) a decision concerning the treatment of future patients." Claxton, Lacey and Walker (2000), taking a step further, claim that "once a price per effectiveness unit has been determined, costs can be incorporated, and the decision can then be based on (posterior) mean incremental net benefit."

Although the fully Bayesian approach requires the specification of several parameters, such as trial costs, incidence rates, time horizon and the between-patient variance, these can be estimated and none are arbitrary. Even for a traditional frequentist's approach, some idea of the number of future patients (incidence *multiplied by* time horizon) is needed to justify performing the trial and the costs are needed for budgeting purposes. Traditional sample size determinations also require the between-patient variance. Several methods are available for exploring the robustness of the solution with respect to these assumptions, as shown in Tables 2.2, 2.4 and 2.5, and Figures 2.5, 2.6, 2.7, 2.9 and 2.10.

For simplification, a number of assumptions have been made in this chapter that are relaxed in later chapters. First, it is assumed that, faced with evidence of positive, but uncertain, incremental net benefit, decision makers have two actions from which to choose: (1) adopt *Treatment* now and not do another trial; or (2) delay the decision regarding the adoption of *Treatment* and do another trial. A third action, (3) adopt *Treatment* now and do another trial, is not considered. Action 3 is likely to be impractical or unethical within a single jurisdiction, since informed patients would prefer to be outside a trial setting where they would receive the new intervention with positive expected net clinical benefit. However, in considering options beyond a strictly within jurisdiction analysis, adopting while a trial is undertaken in another jurisdiction is feasible and, indeed, shown to be globally optimal in many cases by Eckermann and Willan (2009). Secondly, the cost of adoption is assumed to be zero. The expected value of sample information per patient is shown in Chapter 4 to increase with the cost of adoption. Thirdly, it is assumed that the decision to adopt *Treatment* is fully implemented, that is, if the decision to adopt *Treatment* is taken, then all future patients would receive it. Relaxing this assumption significantly increases the expected value of sample information per patient and reduces the opportunity costs, as shown in Willan and Eckermann (2010). Fourthly, assumptions affecting the trial durations are also made: namely, that all patients in the jurisdiction of interest are recruited into the trial and that the trial results are available immediately after the last patient is randomized. Relaxing these assumptions decreases the total expected value of sample information and increases opportunity costs, as shown in Eckermann and Willan (2008a, 2008b). Finally, the implicit assumption of a zero discount rate is also made. Positive discount rates reduce

the total expected value of sample information and the total expected costs, but since the value of the information is realized further into the future, it is reduced proportionally more. Each of these assumptions is relaxed in Chapter 4.

Table 2.1 Parameter estimates for the CADET-Hp Trial

	Treatment (n_T = 142)	*Standard* (n_S = 146)	
$\overline{e}_j$	0.5070	0.3699	difference = $\hat{\Delta}_e$ = 0.1371
$\overline{c}_j$	476.97	529.98	difference = $\hat{\Delta}_c$ = -53.01
$\hat{\mathrm{V}}(\overline{e}_j) = \overline{e}_j(1-\overline{e}_j)/n_j$	0.00176	0.001596	sum = $\hat{\mathrm{V}}\left(\hat{\Delta}_e\right)$ = 0.003356
$\hat{\mathrm{V}}(\overline{c}_j) = \sum_i \frac{(c_{ji}-\overline{c}_j)^2}{(n_j-1)n_j}$	2,167	2,625	sum = $\hat{\mathrm{V}}\left(\hat{\Delta}_c\right)$ = 4,792
$\hat{\mathrm{C}}(\overline{e}_j, \overline{c}_j) = \frac{\sum_i (e_{ji}c_{ji} - \overline{e}_j\overline{c}_j)}{(n_j-1)n_j}$	-0.2963	-0.4166	sum = $\hat{\mathrm{C}}\left(\hat{\Delta}_e, \hat{\Delta}_c\right)$ = -0.7129

Table 2.2 Optimal sample size (n*) and the per cent reduction in ENG for 25% departures from the base case, where for the base case incidence (k) = 80,000, time horizon (h) = 20, threshold value (λ) = 250, fixed cost (C_f) = 800,000, and variable cost (C_v) = 2000, for the CADET-Hp Trial

A	Incidence† (k)	60,000	80,000	1,000,000
	n*	377	465	541
	reduction in ENG	12.6%	0	1.54%
B	Time horizon† (h)	15	20	25
	n*	377	465	541
	reduction in ENG	12.6%	0	1.54%
C	Threshold Value (λ)	187.50	250	312.50
	n*	509	465	421
	reduction	0.506%	0	2.00%
D	C_f / C_v	600,000 / 1500	800,000 / 2000	1,000,000 / 2500
	n*	563	465	397
	reduction in ENG	2.20%	0	4.98%

†25% departures in incidence and time horizon have the identical effect on the optimal solution

Table 2.3 Parameter estimates for the Prostate Trial

	Treatment ($n_T = 61$)	*Standard* ($n_S = 53$)	
$\bar{e}_j$	40.89	28.11	difference = $\hat{\Delta}_e = 12.78$
$\bar{c}_j$	27,322	29,039	difference = $\hat{\Delta}_c = -1{,}717$
$\hat{\mathrm{V}}(\bar{e}_j) = \sum_i \frac{(e_{ji} - \bar{e}_j)^2}{(n_j - 1)n_j}$	24.10	16.42	sum = $\hat{\mathrm{V}}\left(\hat{\Delta}_e\right) = 40.52$
$\hat{\mathrm{V}}(\bar{c}_j) = \sum_i \frac{(c_{ji} - \bar{c}_j)^2}{(n_j - 1)n_j}$	6,466,456	7,872,874	sum = $\hat{\mathrm{V}}\left(\hat{\Delta}_c\right) = 14{,}339{,}330$
$\hat{\mathrm{C}}(\bar{e}_j, \bar{c}_j) = \sum_i \frac{(e_{ji} - \bar{e}_j)(c_{ji} - \bar{c}_j)}{(n_j - 1)n_j}$	2,771	2,876	sum = $\hat{\mathrm{C}}\left(\hat{\Delta}_e, \hat{\Delta}_c\right) = 5{,}647$

Table 2.4 Optimal sample size (n*) and the per cent reduction in ENG for 25% departures from the base case, where for the base case incidence (k) = 4000, time horizon (h) = 20, threshold value (λ) = 300, fixed cost (C_f) = 1,000,000, and variable cost (C_v) = 2000, for the Prostate Trial

A	Incidence† (k)	3000	4000	5000
	n*	225	273	315
	reduction in ENG	4.88%	0	1.07%
B	Time horizon† (h)	15	20	25
	n*	225	273	315
	reduction in ENG	4.88%	0	1.07%
C	Threshold Value (λ)	225	300	375
	n*	352	273	206
	reduction	2.14%	0	35.5%
D	C_f / C_v	750,000 / 1500	1,000,000 / 2000	1,250,000 / 2500
	n*	293	273	256
	reduction in ENG	0.284%	0	0.373%

†25% departures in incidence and time horizon have the identical effect on the optimal solution

Table 2.5 Optimal sample size (n*) and the per cent reduction in ENG for 25% departures from the base case, where for the base case incidence (k) = 50,000, time horizon (h) = 20, threshold value (λ) = 1000, fixed cost (C_f) = 500,000, and variable cost (C_v) = 1600, for the Early ECV Trial

A	Incidence† (k)	37,500	50,000	62,500
	n*	279	345	403
	reduction in ENG	16.3%	0	1.63%
B	Time horizon† (h)	15	20	25
	n*	279	345	403
	reduction in ENG	16.3%	0	1.63%
C	Threshold Value (λ)	750	1000	1250
	n*	279	345	401
	reduction	15.2%	0	1.56%
D	C_f / C_v	375,000 / 1200	500,000 / 1600	650,000 / 2000
	n*	417	345	293
	reduction in ENG	2.31%	0	5.95%

†25% departures in incidence and time horizon have the identical effect on the optimal solution

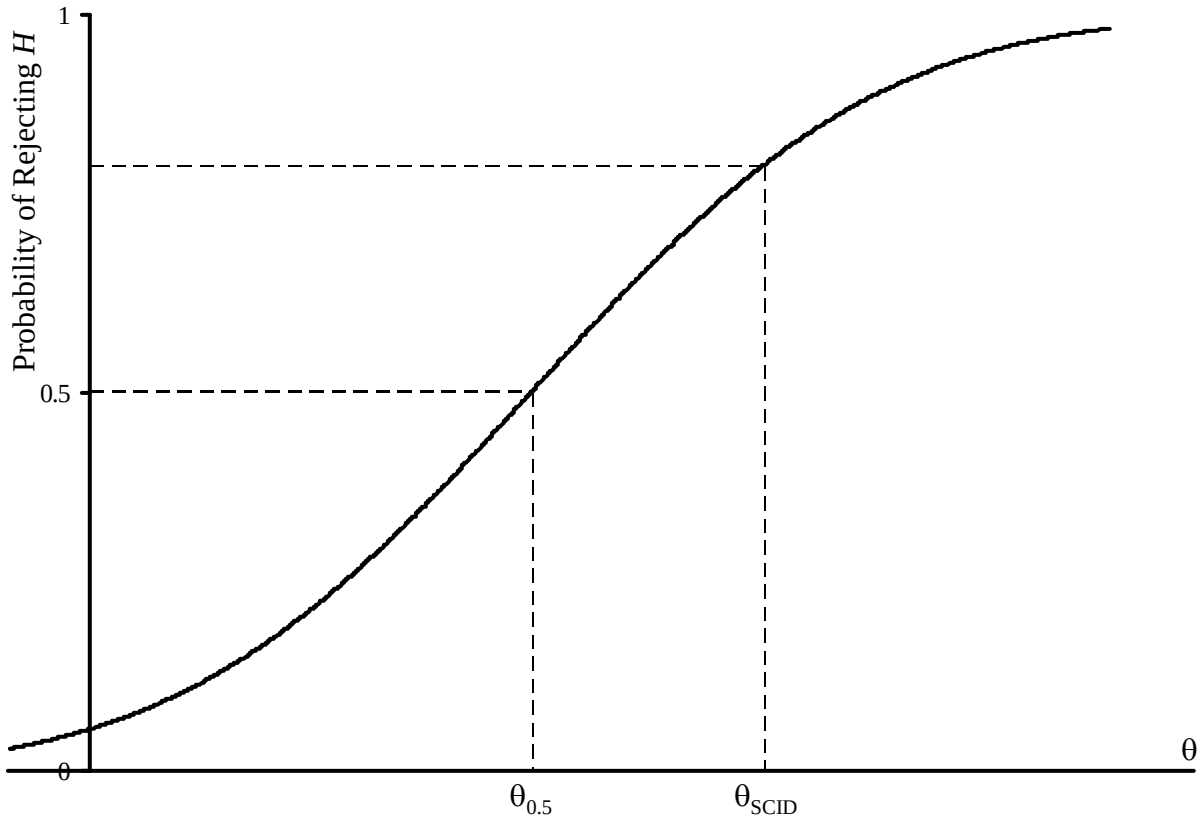

Figure 2.1 The probability of rejecting the null hypothesis as a function of the true mean difference

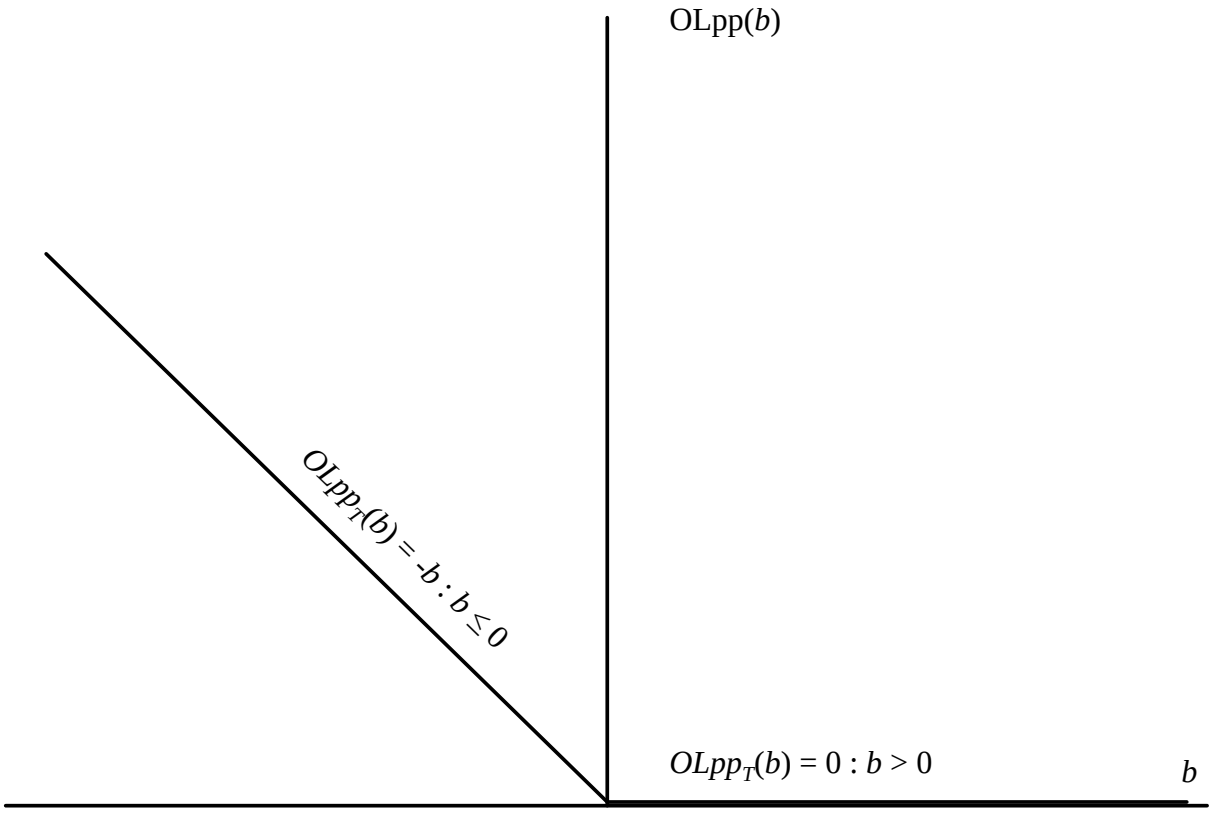

Figure 2.2 The opportunity loss function per patient

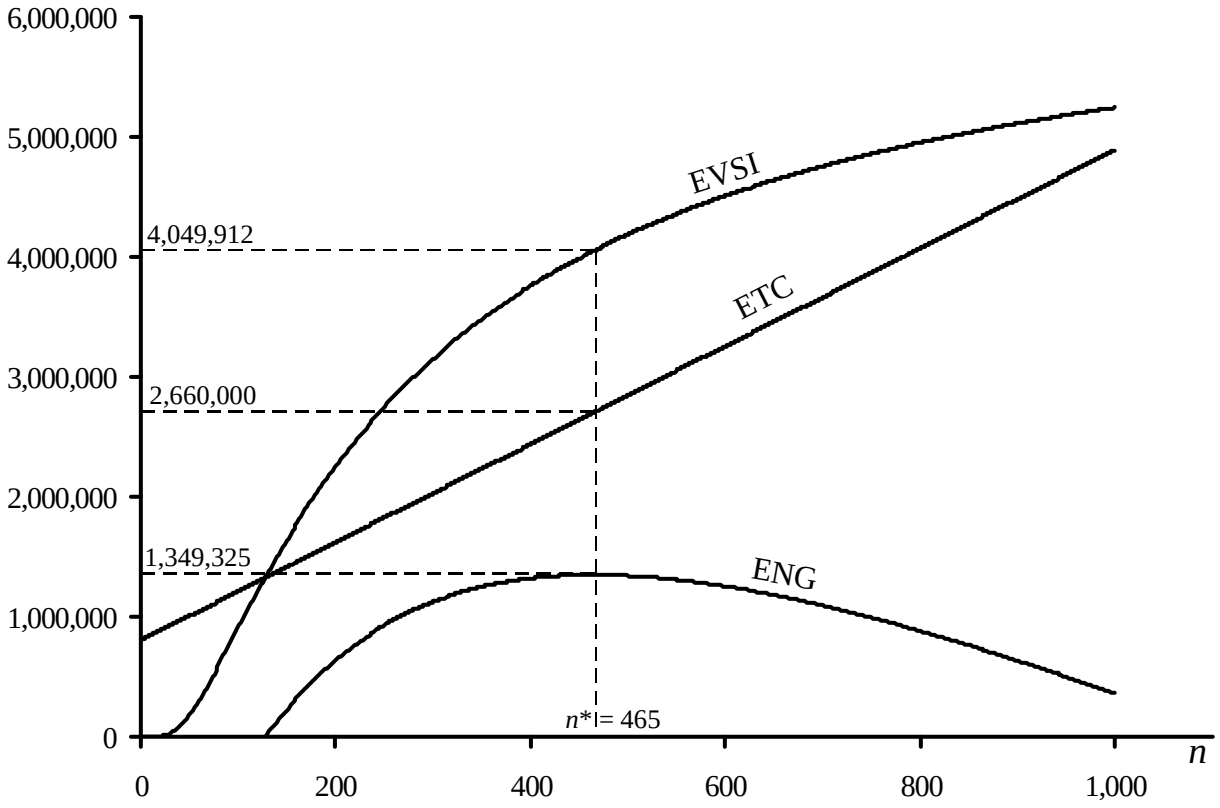

Figure 2.3 Expected value of sample information (EVSI), expected total cost (ETC) and expected net gain (ENG) as functions of sample size (n) for the CADET-Hp Trial

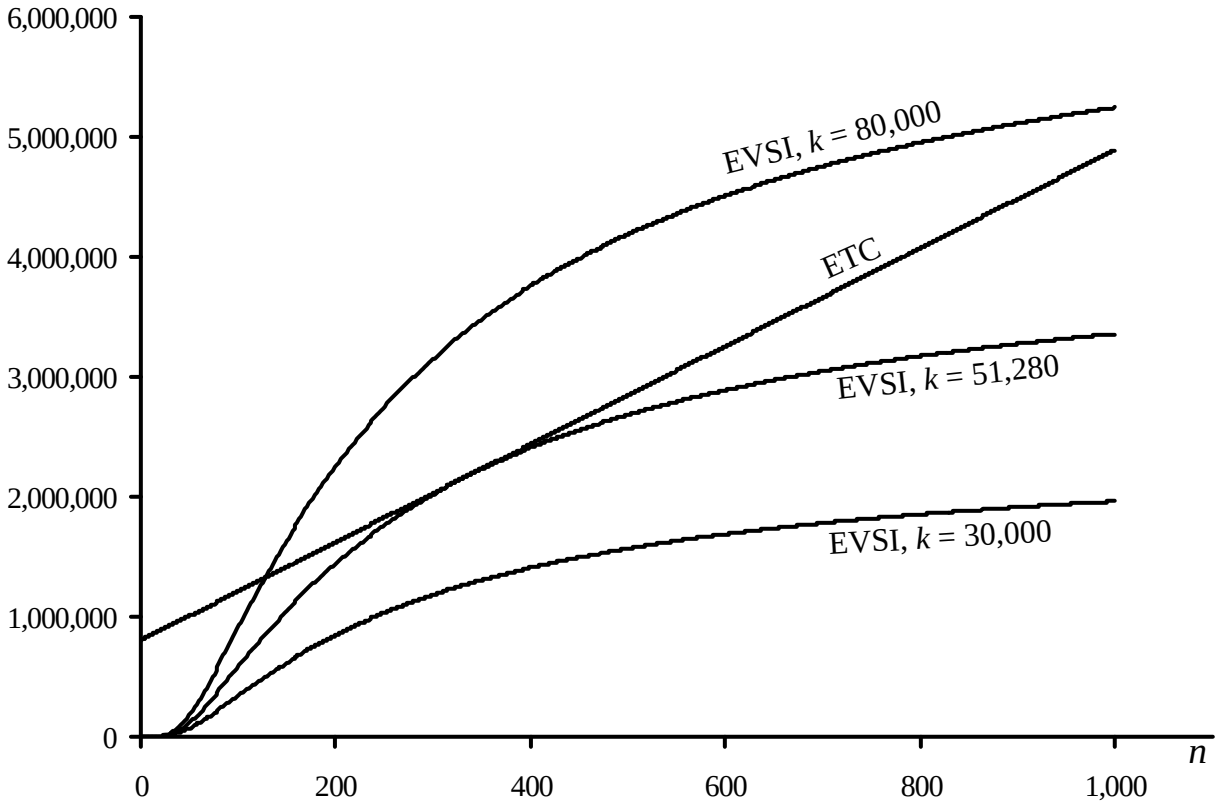

Figure 2.4 Expected value of sample information (EVSI) for various value of the incidence (k) and expected total cost (ETC) as functions of sample size (n) for the CADET-Hp Trial

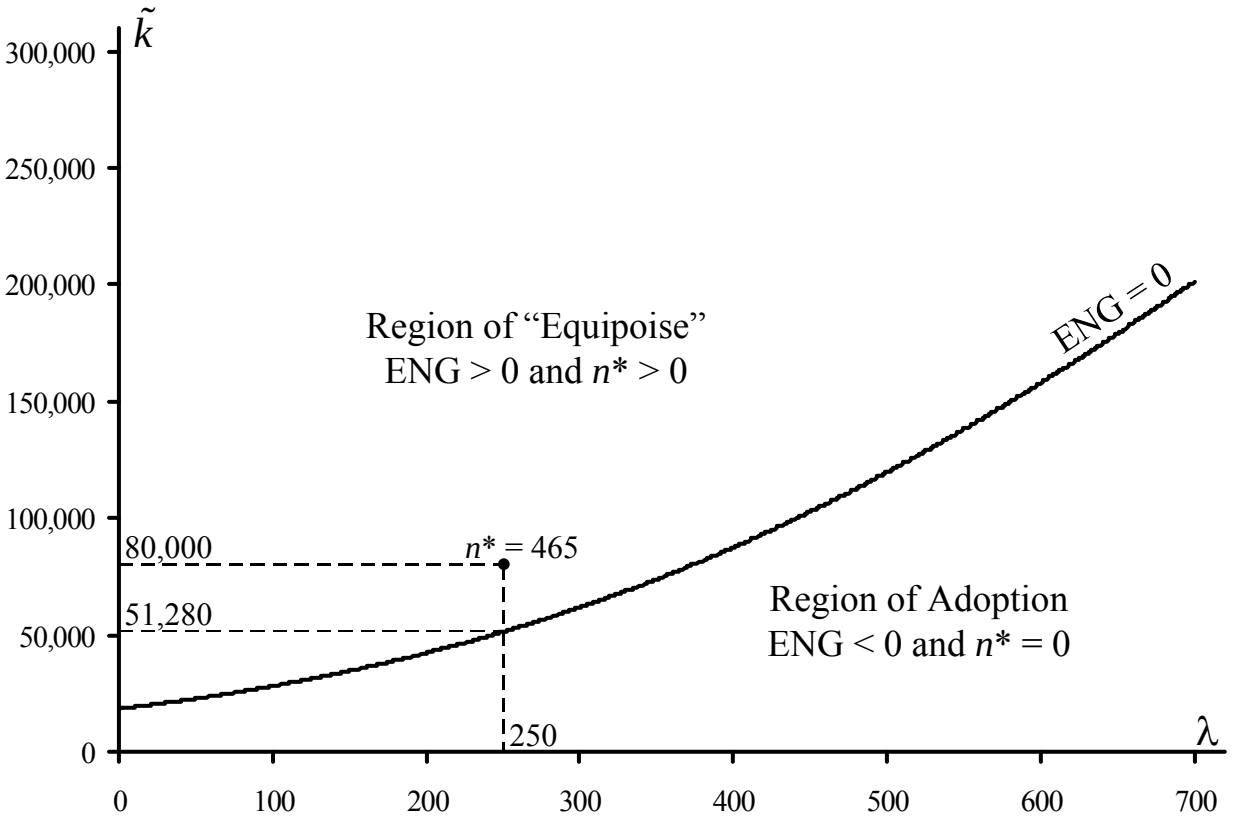

Figure 2.5 Threshold incidence ($\tilde{k}$) as a function of the threshold value for a unit of health outcome (λ) (*i.e.* those combinations of *k* and λ for which ENG = 0), for the CADET-Hp Trial

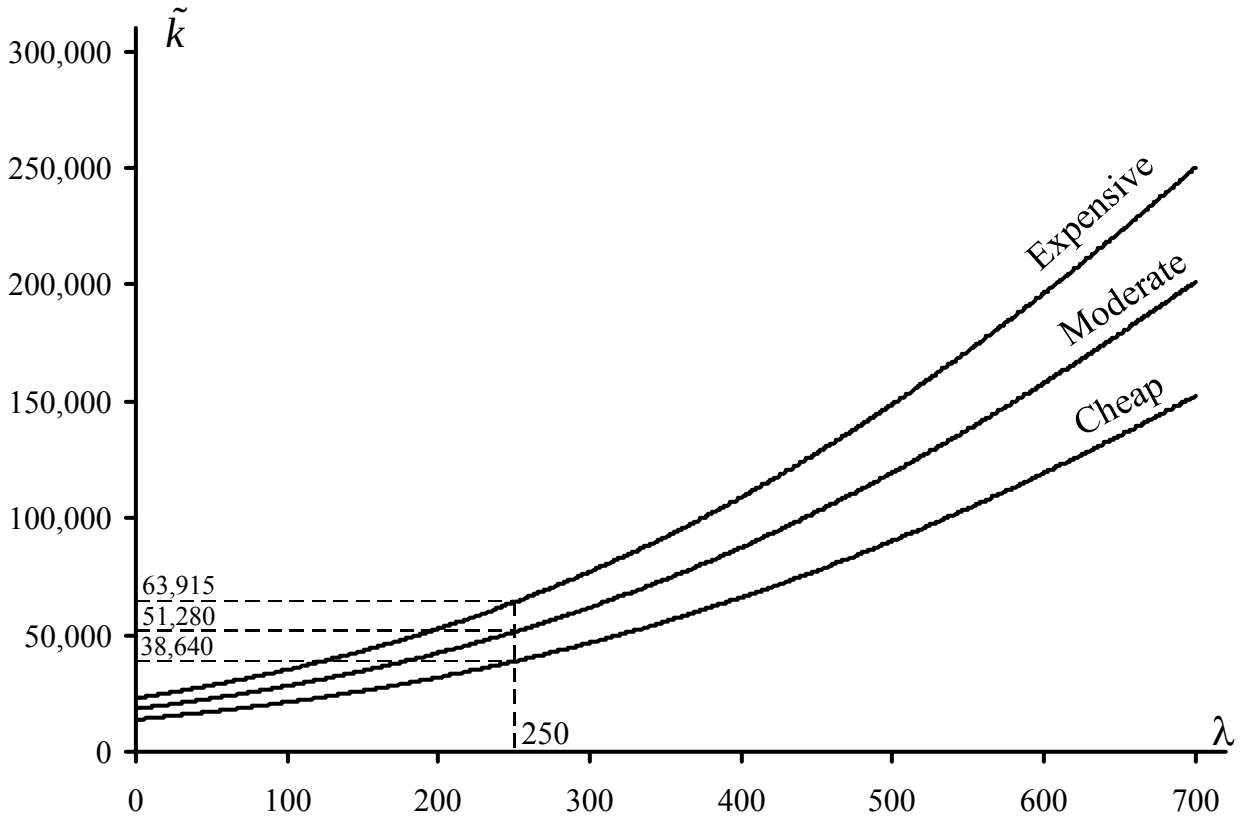

Figure 2.6 Threshold incidence $(\tilde{k})$ as a function of the threshold value for a unit of health outcome (λ) for the three configurations of trial cost given in Panel D of Table 2.2, for the CADET-Hp Trial

Cheap: $C_f = 600{,}000$; $C_v = 1500$.
Moderate: $C_f = 800{,}000$; $C_v = 2000$.
Expensive: $C_f = 1{,}000{,}000$; $C_v = 2500$

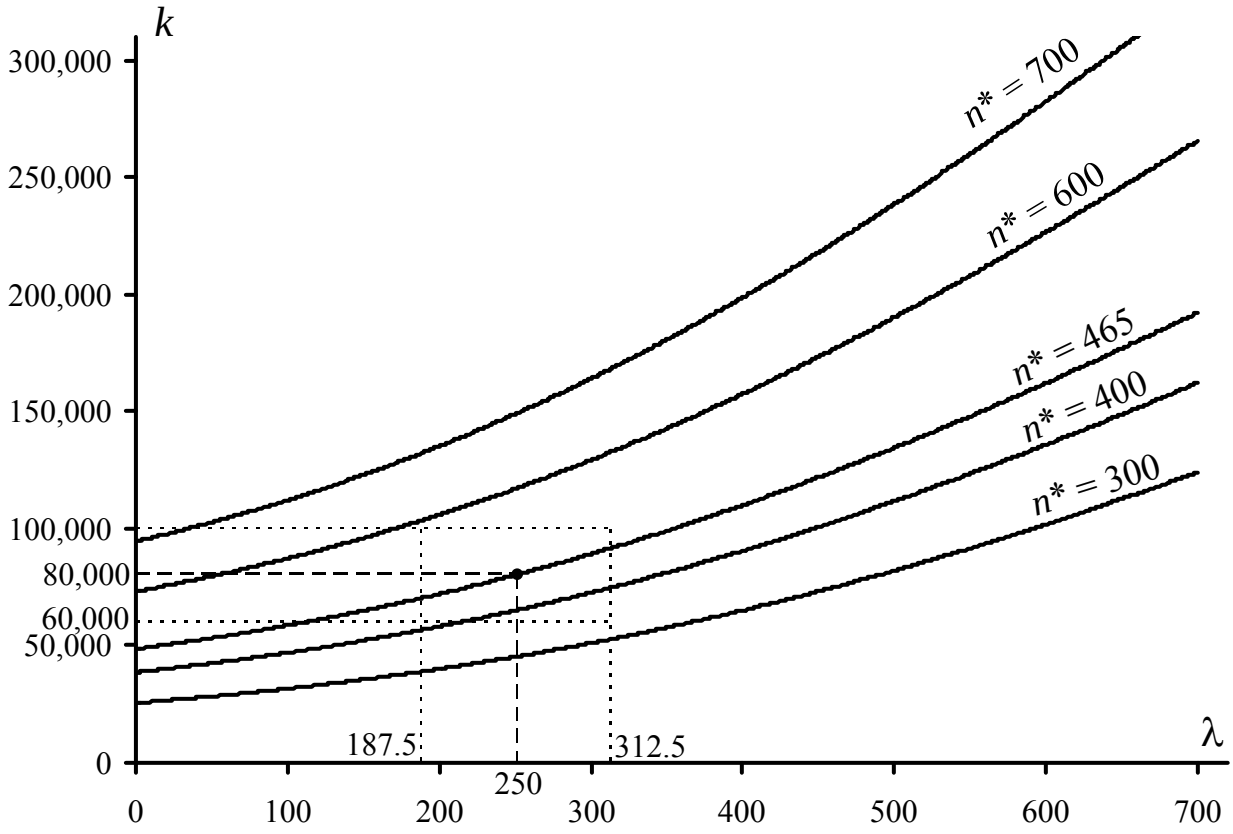

Figure 2.7 Combinations of k and λ that have the same optimal sample size for various optimal sample sizes, for the CADET-Hp Trial

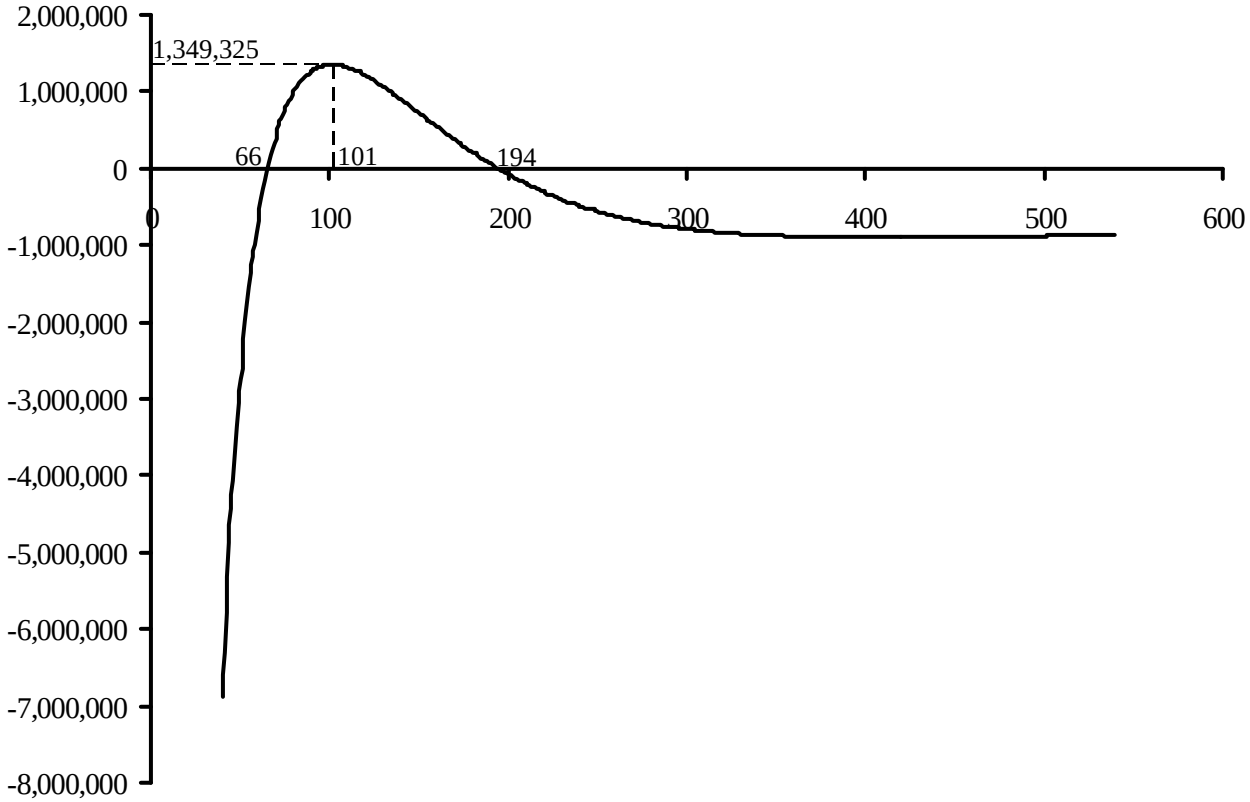

Figure 2.8 Expected net gain for trials design on frequentist principles as a function of the smallest clinically important difference, for the CADET-Hp Trial

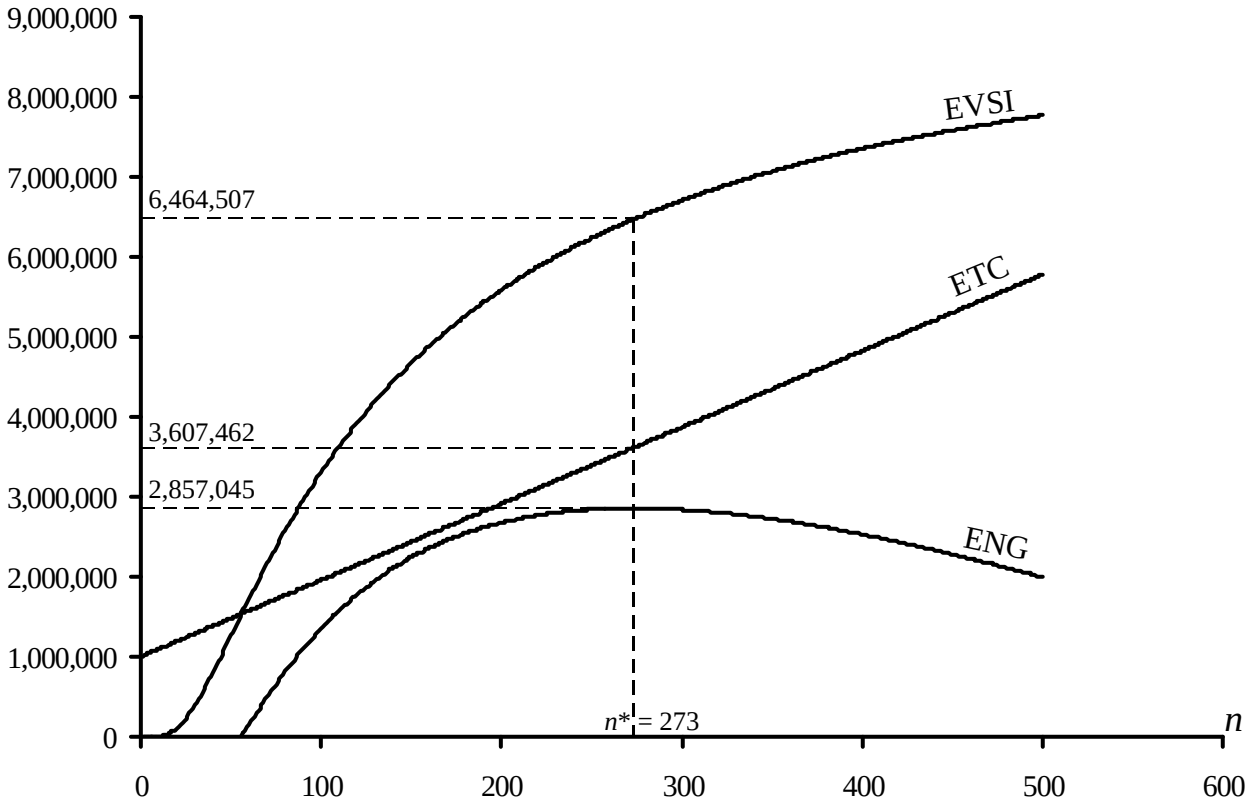

Figure 2.9 Expected value of sample information (EVSI), expected total cost (ETC) and expected net gain (ENG) as functions of sample size (n) for the Prostate Trial

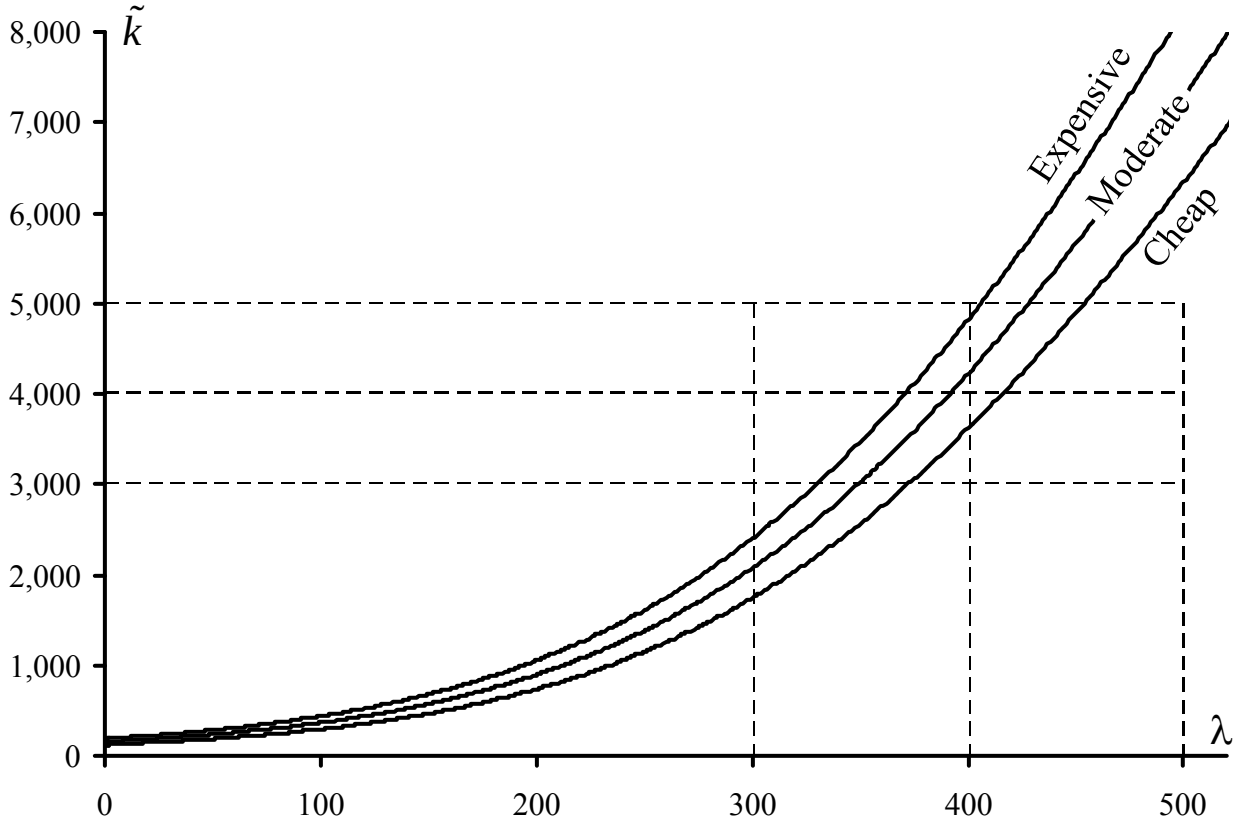

Figure 2.10 Threshold incidence $(\tilde{k})$ as a function of the threshold value for a unit of health outcome (λ) for the three configurations of trial cost given in Panel D of Table 2.4, for the Prostate Trial

Cheap: $C_f = 750{,}000$; $C_v = 1500$
Moderate: $C_f = 1{,}000{,}000$; $C_v = 2000$
Expensive: $C_f = 1{,}250{,}000$; $C_v = 2500$

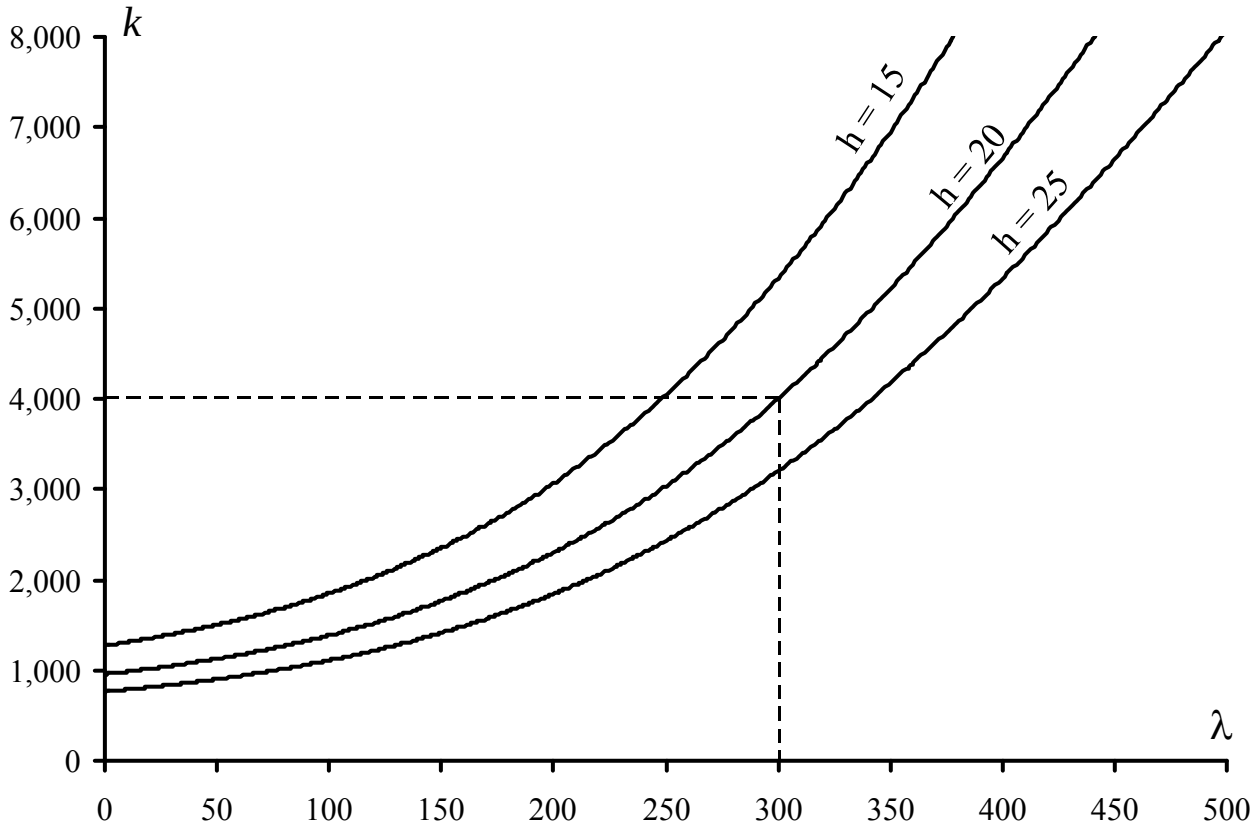

Figure 2.11 Combinations of incidence (k) and the threshold value for a unit of health outcome (λ) for which the optimal sample size is the same as the base case ($n^* = 273$) for the three time horizons given in Panel B of Table 2.4, for the Prostate Trial

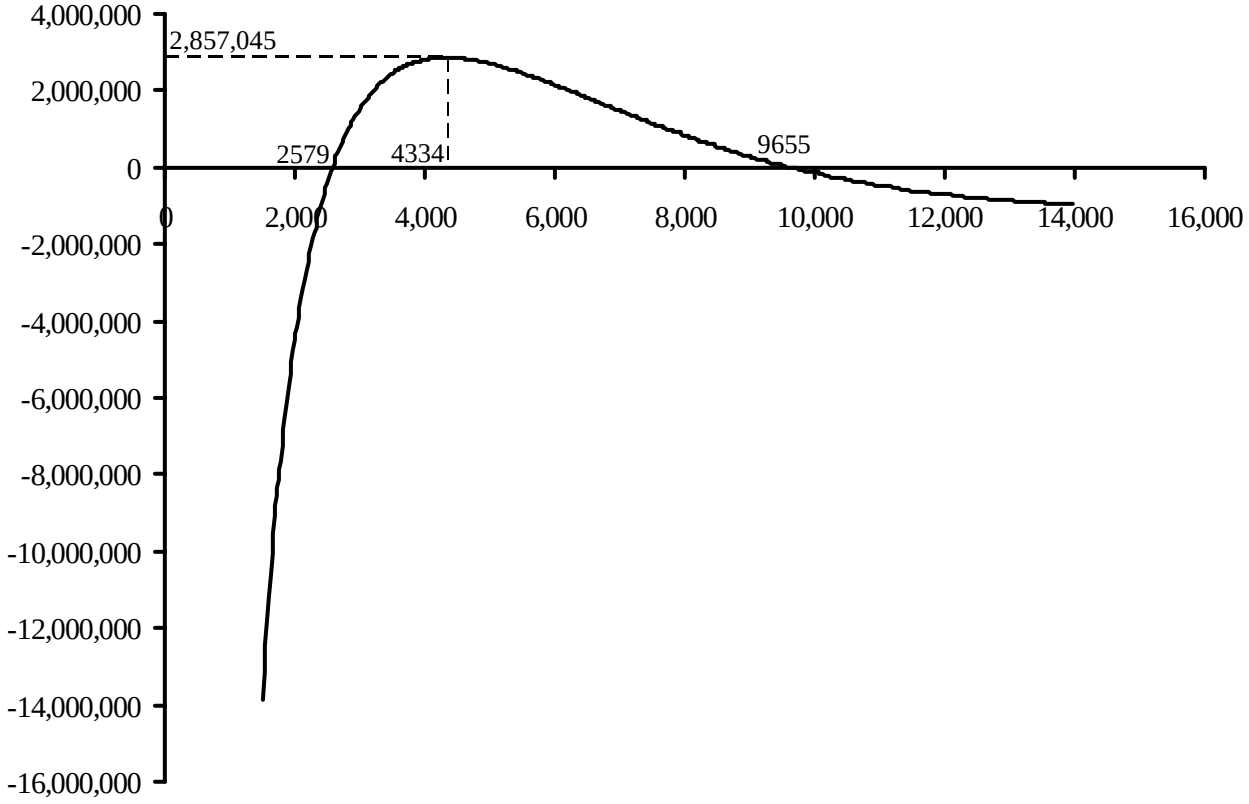

Figure 2.12 Expected net gain for trials design on frequentist principles as a function of the smallest clinically important difference, for the Prostate Trial

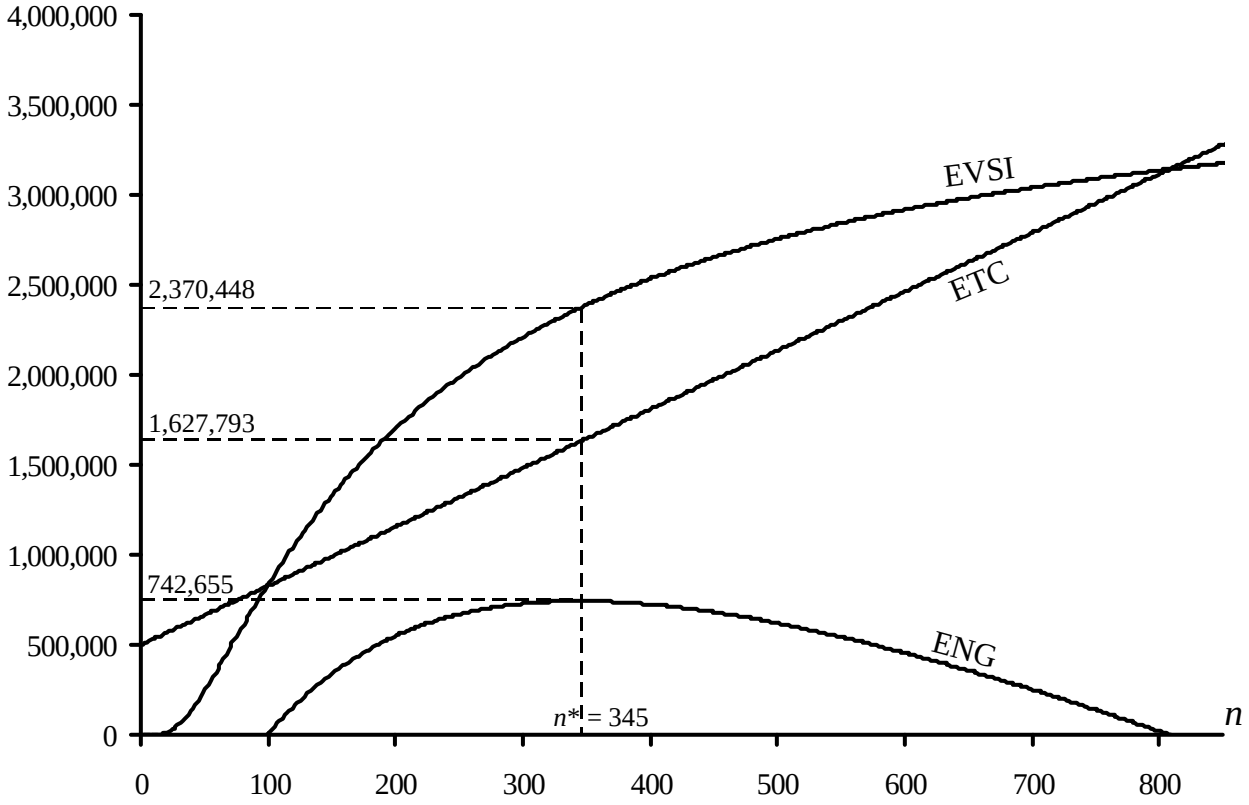

Figure 2.13 Expected value of sample information (EVSI), expected total cost (ETC) and expected net gain (ENG) as functions of sample size (*n*) for the Early ECV Trial

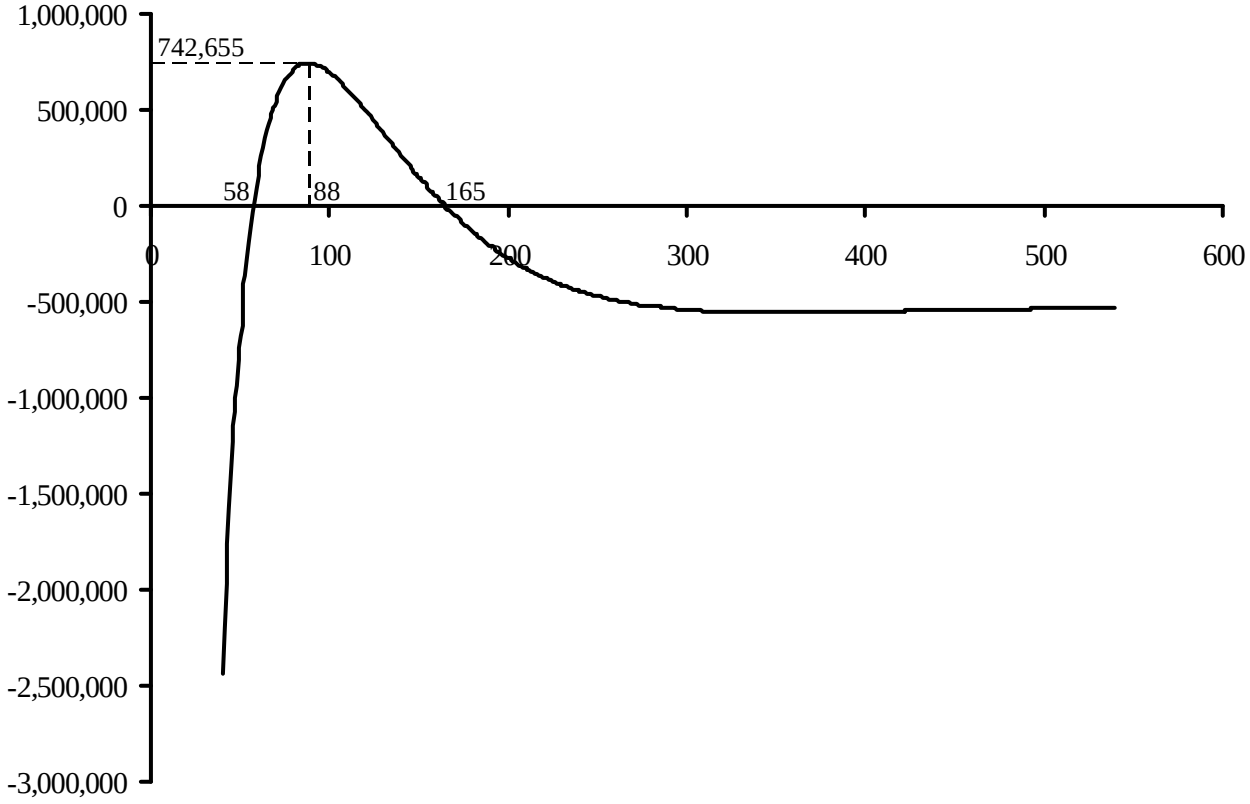

Figure 2.14 Expected net gain for trials design on frequentist principles as a function of the smallest clinically important difference, for the Early ECV Trial

3

Randomized Clinical Trials II

3.0 INTRODUCTION

In Chapter 2, value of information methods were used to provide optimal sample size determinations for randomized clinical trials under restrictive and unrealistic assumptions. In addition, it was shown that value of information methods can be used to determine whether current information is sufficient for decision making with regarding adoption of a new health care intervention, or if additional information is worthwhile. The current information is sufficient if the expected value of sample information (EVSI) of a new trial is less than its expected total cost (ETC), regardless of the sample size. On the other hand, if the expected value of sample information is greater than the expected total cost for some sample size, then additional information has a positive expected net gain. The solutions given in Chapter 2 were based on a number of simplifying assumptions. In this chapter value of information methods are extended to provide solutions with these assumptions relaxed. These solutions are illustrated on the same examples used in Chapter 2. The simplifying assumptions were:

1. the cost of adopting the new intervention is zero;
2. all patients in the jurisdiction of interest are recruited into the trial;
3. the results are available immediately after the last patient is randomized;

4. 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;
5. the discount rate is zero,
6. only research done within the jurisdiction of interest, has value; and,
7. the trial is a single-stage design, *i.e.* no interim "looks" at the data.

Eckermann and Willan (2007) (2008a) provide solutions with Assumptions 2 and 3 relaxed; Willan and Eckerman (2010) with Assumption 4 relaxed; Willan and Pinto (2005) with Assumption 5 relaxed; Eckermann and Willan (2009) with Assumption 6 relaxed; and Willan and Kowgier (2008) with Assumption 7 relaxed.

Solutions with Assumptions 1 through 3 relaxed are given in Section 3.1, with Assumption 4 relaxed in Section 3.2, with Assumption 5 relaxed in Section 3.3, and with Assumption 6 relaxed in Section 3.4. The relaxation of Assumption 7 is the topic of Chapter 8. All solutions are illustrating using examples from Chapter 2.

3.1 RELAXING ASSUMPTIONS 1-3

3.1.1 Relaxing Assumption 1: Cost of Adoption is Positive

Let C_A be the cost of adopting *Treatment*. It is reasonable to assume that the adoption of a new health care intervention will incur some costs, such as those associated with conveying public health messages, training and learning by doing. Recall that the current information regarding incremental net benefit is characterized by a normal prior *pdf* with mean b_0 and variance v_0, where $b_0 > 0$ and $v_0 > 0$. The prior mean incremental net benefit

(b_0) is positive, and if $C_A = 0$, then adopting *Treatment*, rather than retaining *Standard*, maximizes the expected net benefit for future patients. On the other hand, if $C_A > 0$, adopting *Treatment* maximizes expected net benefit if, and only if, the mean total incremental net benefit realized by future patients exceeds the cost of adoption, *i.e.*, if, and only if, $N(0)b_0 > C_A \Leftrightarrow b_0 - C_A/N(0) > 0$, where $N(0) = hk$ is the pre-trial patient horizon. Likewise, at the end of a trial of size *n* per arm, *Treatment* should be adopted if, and only if, $b_1 - C_A/N(n) > 0$, where $N(n)$ is the post-trial patient horizon. In effect, a positive cost of adoption reduces the mean incremental net benefit by $C_A/N(0) = C_A/kh$ with adoption prior to the trial and by $C_A/N(n)$ if adopting after the trial. Therefore, under the assumption that $b_0 - C_A/kh > 0$, the expected value of sample information becomes

$$\text{EVSI}(n) = N(n)\left\{\mathcal{D}\left(b_0 - C_A/kh, v_0\right) - \text{E}_{\hat{b}}\mathcal{D}\left(b_1 - C_A/N(n), v_1\right)\right\},$$

where $\mathcal{D}(\cdot,\cdot)$ and $\text{E}_{\hat{b}}\mathcal{D}(\cdot,\cdot)$ are defined in Chapter 2. For large patient horizons or for small costs of adoption, relaxing the assumption that the cost of adoption is zero may only have a small effect on the expected value of sample information and, consequently, on the optimal sample size.

A positive cost of adoption also reduces the opportunity cost for patients receiving the *Standard* while the trial is performed to $b_0 - C_A/hk$.

3.1.2 Relaxing Assumption 2: Not All Patients Are Recruited into the Trial

In almost all trials only a small fraction of the eligible patients from the jurisdiction of interest are recruited. As a result the trial will take longer and (i) the post-trial patient horizon will be reduced and (ii) more patients will incur and opportunity cost. From Chapter 2, the post-trial patient horizon $N(n) = k(h-t)$, where *k* is the annual incidence, *h* the time horizon for the intervention (in years) and *t* is the duration of the trial (in years). If *a* is the annual accrual rate, then $t = 2n/a$, so that $N(n;k,h,a) = k(h-2n/a)$. If Assumption 2 holds, and all patients are recruited into the trial, then *a* = *k* and the post-trial patient horizon is $kh-2n$, as given in Chapter 2. However, if not all patients are recruited into the trial, *i.e.* *a* < *k*, then $N(n) = k(h-2n/a) < kh-2n$ and the post-trial patient horizon and, therefore, the expected value of sample information, is reduced.

All patients receiving *Standard* while the trial is conducted, denoted as $\tilde{n}(n)$, incur an expected opportunity cost of $b_0 - C_A/hk$. $\tilde{n}(n)$ is the total number of incident patients during the time period when the trial is performed *minus* the number of patients who receive *Treatment* in the trial, *i.e.* $\tilde{n}(n) = kt - n = 2nk/a - n$. If Assumption 2 holds and all patients are recruited into the trial, then *a* = *k*, and $\tilde{n}(n) = n$, as given in Chapter 2. However, if not all patients are recruited into the trial, *i.e.* *a* < *k*, then $\tilde{n}(n) = 2nk/a - n > n$, and the expected opportunity cost and, therefore, the expected total cost, is increased.

Since relaxing Assumption 2 decreases expected value of sample information and increases the expected total cost, it is more likely in any particular example that there is no sample size for which the expected value of sample information is greater than the

expected total cost. Therefore, by relaxing Assumption 2 it is more likely that the current information is sufficient for decision making.

3.1.3 Relaxing Assumption 3: Results are Not Available Immediately After the Last Patient is Randomized

In all trials, there is a delay from when the last patient is randomized until when the results are available. There is a period of patient follow-up during which patient health outcomes and cost data are collected. In addition, time is required to collect the data, perform the analyses and present the results. As a result, the trial will take longer and (i) the post-trial patient horizon will be reduced and (ii) more patients will incur an opportunity cost. If τ is the duration of time from when the last patient is randomized and the evidence is updated, referred to as the follow-up period, then the trial duration is $t = 2n/a + \tau$. Therefore, if $\tau > 0$, the post-trial patient horizon becomes $N(n)$ $= k(h-t) = k\{h-(2n/a+\tau)\} < k\{h-(2n/a)\}$, reducing the expected value of information. Similarly, if $\tau > 0$, the number of patients incurring an opportunity cost becomes $\tilde{n}(n) = kt - n = k(2n/a+\tau) - n \ > k(2n/a) - n$, increasing the expected total cost.

Since relaxing Assumption 3 decreases expected value of sample information and increases the expected total cost, it is more likely in any particular example that there is no sample size for which the expected value of sample information is greater than the expected total cost. Therefore, relaxing Assumption 3 increases the chance that the current information is sufficient for decision making.

3.1.4 The CADET-Hp Trial

Recalling from Chapter 1, Section 1.3.1, the CADET-Hp Trial is a randomized controlled trial performed in Canada. The results are published in Chiba *et al*. (2002) and Willan (2004). Patients with uninvestigated dyspepsia were randomized between

T: Omeprazole 20 mg, metronidazole 500 mg and clarithromycin 250 mg, and

S: Omeprazole 20 mg, placebo metronidazole and placebo clarithromycin.

A total of 188 patients were randomized, 142 (= n_T) to *Treatment* and 146 (= n_S) to *Standard*. The binary measure of effectiveness was treatment success and defined as the presence of no or minimal dyspepsia symptoms at one year. Total costs were determined from the societal perspective and are given in Canadian dollars. Under Assumptions 1-3 (*i.e.* $C_A = 0$, $a = k$, $\tau = 0$), and with an incidence (k) of 80,000 per year, a time horizon (h) of 20 years, a fixed cost (C_f) of $800,000, and a variable cost (C_v) of $2000, the optimal sample size per arm (n*) is 465, and corresponds to an expected net gain (ENG) of $1,349,325.

Under Assumptions 2 and 3 (*i.e.* $a = k$, $\tau = 0$), plots of expected net gain versus sample size per arm are given in Figure 3.1 for the following values for the cost of adoption: 0, 1 mil., 5 mil. and 10 mil. Although the expected net gain increases considerably with the cost of adoption, the optimal sample size changes very little. The optimal sample size, the optimum ENG and the per cent reduction in ENG for a trial with 465 patients per arm (*i.e.* the optimal sample size for $C_A = 0$) is given in Table 3.1 for the cost of adoption values considered in Figure 3.1. Although optimal sample size increases a little and the optimum expected net gain increases considerably with the cost of adoption, the

reduction in expected net gain for a trial with 465 is less than 0.51%, even when the cost of adoption is 10 mil. Therefore, for this example at least, the optimal sample size is very robust to the specification of the cost of adoption, and determining optimal sample size on even a very uncertain cost of adoption does not lead to a significant reduction in the expected net gain. Nonetheless, a more precise value for the cost of adoption may be required to apply the optimum decision rule to adopt *Treatment* if, and only if, the mean incremental net benefit exceeds the cost of adoption divided by the patient horizon.

For the CADET-Hp Trial the patient follow-up is at least a year since the measure of effectiveness is defined as the presence of no or minimal dyspepsia symptoms at one year. Allowing six months for data collection and analysis, a reasonable value for τ is 1.5 years. Assuming that 800 patients are recruited into the trial per year (*i.e.* $a = 0.01k$), $\tau = 1.5$ and $C_A = 5{,}000{,}000$, plots of expected value of sample information, the expected total cost and expected opportunity cost, as functions of sample size, are given in Figure 3.2. Since the expected value of sample information is less than the expected total cost for all sample sizes, then, under the assumptions that $C_A = 5{,}000{,}000$, $a = 0.01k$ and $\tau = 1.5$, there is sufficient information for decision making, and since $b_0 > C_A/(kh)$, *i.e.* $87.29 > 5000000/(80000*20) = 3.125$, the optimum decision is to adopt *Treatment*.

From Figure 3.2 it is easy to see that the major proportion of total cost is opportunity cost, more than 10,000,000 of which is incurred during the follow-up period, see vertical intercept for the opportunity cost line. The opportunity cost incurred during the follow-up period cannot be overcome by increasing the accrual rate, as illustrated in the Figure 3.3,

where the expected value of sample information, the expected total cost and expected opportunity cost, as a function of sample size, are plotted under the assumptions that C_A = 5,000,000, $a = k$ and $\tau = 1.5$. Again, the expected value of sample information is less than the expected total cost for all sample sizes. Plots of the expected value of sample information as a function of sample size for two sets of assumptions (C_A = 5,000,000, $a = 0.01k$, $\tau = 1.5$) and (C_A = 5,000,000, $a = k$, $\tau = 0$) are given in Figure 3.4, illustrating that the relaxation of Assumptions 2 and 3 has much less effect on the expected value of sample information than on the expected total cost.

3.1.5 The Prostate Trial

Recall from Chapter 2, Section 2.3.2, that the Prostate Trial is a trial of symptomatic, hormone resistant prostate cancer, where patients were randomized between prednisone alone (*Standard*) and prednisone plus mitoxantrone (*Treatment*). Cost data given in Canadian dollars, including hospital admissions, outpatient visits, investigations, therapies and palliative care, was available for 114 patients, 61 randomized to *Treatment* and 53 randomized to *Standard*. The measure of effectiveness was quality-adjusted survival, given in quality-adjusted life-weeks. Under Assumptions 1-3 (*i.e.* $C_A = 0$, $a = k$, $\tau = 0$), and with an incidence (k) of 2500 per year, a time horizon (h) of 20 years, a fixed cost (C_f) of \$1,00,000, and a variable cost (C_v) of \$2000, the optimal sample size per arm (n^*) is 197, and corresponds to an expected net gain (ENG) of \$570,651.

Under Assumptions 2 and 3 (*i.e.* $a = k$, $\tau = 0$), plots of expected net gain versus sample size per arm are given in Figure 3.5 for the following values for the cost of adoption: 0, 1

mil., 5 mil. and 10 mil. The optimal sample size, the optimum ENG and the per cent reduction in ENG for a trial with 197 patients per arm (*i.e.* the optimal sample size for $C_A = 0$) is given in Table 3.2 for the cost of adoption values considered in Figure 3.5. Although optimal sample size increases a little and the optimum expected net gain increases considerably with the cost of adoption, the reduction in expected net gain for a trial with 197 is less than 0.86%, even when the cost of adoption is 10 mil. As with the CADET-Hp example, the optimal sample size is seen to be very robust to the specification of the cost of adoption.

Since median survival is about one year, a reasonable follow-up period to minimize censoring might be 18 months. Allowing six months for data collection and analysis, a reasonable value for τ is 2 years. Assuming that 250 patients are recruited into the trial per year (*i.e.* $a = 0.1k$), $\tau = 1.5$ and $C_A = 5{,}000{,}000$, plots of the expected value of sample information, the expected total cost and expected opportunity cost, as functions of sample size, are given in Figure 3.6. Since the expected value of sample information is less than the expected total cost for all sample sizes, then under the assumptions that $C_A = 5{,}000{,}000$, $a = 0.1k$ and $\tau = 2$, there is sufficient information for decision making, and since $b_0 > C_A/(kh)$, *i.e.* $5551 > 5000000/(2500*20) = 100$, the optimum decision is to adopt *Treatment*.

From Figure 3.6 it is easy to see that the major proportion of total cost is opportunity cost, more than 28,000,000 of which is incurred during the follow-up period, see vertical intercept for the opportunity cost line. The opportunity cost incurred during the follow-up

period cannot be overcome by increasing the accrual rate, as illustrated in the Figure 3.7, where the expected value of sample information, the expected total cost and expected opportunity cost, as a function of sample size, are plotted under the assumptions that C_A = 5,000,000, $a = k$ and $\tau = 2$. Again, the expected value of sample information is less than the expected total cost for all sample sizes. Plots of EVSI as a function of sample size for two sets of assumptions (C_A = 5,000,000, $a = 0.1k$, $\tau = 2$) and (C_A = 5,000,000, $a = k$, $\tau = 0$) are given in Figure 3.8, again illustrating that the relaxation of Assumptions 2 and 3 has much less effect on the expected value of sample information than on the expected total cost.

3.1.6 The Early ECV Trial

Recall from Chapter 2, Section 2.3.3, that the Early ECV Trial was a pilot study in which 232 pregnant women presenting in the breech position were randomized between early (*Treatment*) versus late (*Standard*) 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%). We assume that the threshold value to achieve a non-caesarean delivery in these patients is $1000. (All costs are given in Canadian dollars.) This amount reflects both 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. For a time horizon (h) of 20 years, an incidence of (k)

50,000, a fixed cost (C_f) of 500,000 and the cost per patient (C_v) of 1600, the optimal sample size (n^*) is 345 per arm, corresponding to an ENG of 742,655.

Under Assumptions 2 and 3 (*i.e.* $a = k$, $\tau = 0$), plots of expected net gain versus sample size per arm are given in Figure 3.9 for the following values for the cost of adoption: 0, 1 mil., 5 mil. and 10 mil. The optimal sample size, the optimum ENG and the per cent reduction in ENG for a trial with 345 patients per arm (*i.e.* the optimal sample size for $C_A = 0$) is given in Table 3.3 for each value for the cost of adoption considered in Figure 3.9. Although optimal sample size increases a little and the optimum expected net gain increases considerably with the cost of adoption, the reduction in expected net gain for a trial with 345 is less than 1.22%, even when the cost of adoption is 10 mil. As with the CADET-Hp and Prostate examples, the optimal sample size is seen to be very robust to the specification of the cost of adoption.

Since the measure of effectiveness (non-caesarian delivery) is known soon after randomization, a reasonable follow-up period is six months. Assuming that 1000 patients are recruited into the trial per year (*i.e.* $a = 0.02k$), $\tau = 0.5$ and $C_A = 5{,}000{,}000$, plots of the expected value of sample information, the expected total cost and expected opportunity cost, as functions of sample size, are given in Figure 3.10. Since the expected value of sample information is less than the expected total cost for all sample sizes, then under the assumptions that $C_A = 5{,}000{,}000$, $a = 0.02k$ and $\tau = 0.5$, there is sufficient information for decision making, and since $b_0 > C_A/(kh)$, *i.e.*

$69.40 > 5000000/(50000*20) = 5$, the optimum decision is to adopt *Treatment*.

From Figure 3.10 it is easy to see that the major proportion of total cost is opportunity cost, more than 1,800,000 of which is incurred during the follow-up period, see vertical intercept for the opportunity cost line. The opportunity cost incurred during the follow-up period cannot be overcome by increasing the accrual rate, as illustrated in the Figure 3.11, where the expected value of sample information, the expected total cost and expected opportunity cost, as a function of sample size, are plotted under the assumptions that C_A = 5,000,000, $a = k$ and $\tau = 0.5$. Again, the expected value of sample information is less than the expected total cost for all sample sizes. Plots of the expected value of sample information as a function of sample size for two sets of assumptions (C_A = 5,000,000, $a = 0.02k$, $\tau = 0.5$) and (C_A = 5,000,000, $a = k$, $\tau = 0$) are given in Figure 3.12, again illustrating that the relaxation of Assumptions 2 and 3 has much less effect on the expected value of sample information than on the expected total cost.

3.2 RELAXING ASSUMPTION 4

3.2.1 Imperfect Implementation

The three examples given in the previous section all have one thing in common. With realistic assumptions regarding the cost of adoption, patient accrual rate and the follow-up period, an analysis based on expected value of information methods leads to the conclusion that in each example there is sufficient evidence based on the current information to adopt *Treatment*. In contrast, a frequentist analysis would lead to the opposite conclusion, since in each example the z-statistic (*i.e.* $b_0 / \sqrt{v_0}$) does not reach the traditional level of significance of 5%, although one should not expect the two

approaches to lead to the same conclusions in every example. Relaxing Assumption 4 profoundly affects the value of information solution, making in more likely that current information is sufficiently for decision making. Assumption 4 implies perfect implementation, in that if the incremental net benefit after allowing for the cost of adoption is positive, *i.e.* $b_0 - C_A/kh = 0$, and no further evidence is sought or expected, then all future patients will receive *Treatment*. Relaxing this assumption and assuming that the extent of implementation depends on the strength (not just the direction) of the evidence can dramatically increase expected value of sample information and decrease the opportunity cost, thereby making in more likely that more evidence is required.

Let p_0 be the probability that a future patient receives *Treatment*, given evidence characterized by (b_0, v_0) and assuming no new information is sought or expected. Further let p_1 be the post-trial probability that a future patient would receive *Treatment*, given evidence characterized by (b_1, v_1), again assuming no further information is sought or expected. Assumption 4 can be relaxed by allowing $p_i < 1$. Given the evidence characterized by (b_0, v_0), the expected opportunity loss per patient of adopting *Treatment* is given in Chapter 2 as:

$$\text{EOLpp}_{T0} = \int_{-\infty}^{\infty} \text{OLpp}_T(b)\, f(b; b_0, v_0)\, \text{d}b = \int_{-\infty}^{0} -b\, f(b; b_0, v_0)\, \text{d}b = \mathcal{D}(b_0, v_0),$$

where, recalling from Chapter 2, $\text{OLpp}_T(b)$ is the opportunity loss function per person of adopting *Treatment* if b_0 is positive, and $f(b; b_0, v_0)$ is the *pdf* for a normal random variable with mean b_0 and variance v_0.

Recalling that the opportunity loss of an action is the maximum net benefit minus the net benefit of the action taken, the per-patient opportunity loss function associated with retaining *Standard* is given by:

$$\mathrm{OLpp}_S(b) = \begin{Bmatrix} \mathrm{Max}(\mathrm{NB}_T, \mathrm{NB}_S) - \mathrm{NB}_S = \mathrm{NB}_S - \mathrm{NB}_S = 0 & : b \le 0 \\ \mathrm{Max}(\mathrm{NB}_T, \mathrm{NB}_S) - \mathrm{NB}_S = \mathrm{NB}_T - \mathrm{NB}_S = b & : b > 0 \end{Bmatrix}.$$

Therefore, given the evidence characterized by (b_0, v_0), the expected opportunity loss per patient of retaining *Standard* is given by:

$$\begin{aligned} \mathrm{EOLpp}_{S0} &= \int_{-\infty}^{\infty} \mathrm{OLpp}_S(b)\, f(b; b_0, v_0)\, \mathrm{d}b \\ &= \int_{0}^{\infty} b\, f(b; b_0, v_0)\, \mathrm{d}b \\ &= \int_{0}^{\infty} b\, f(b; b_0, v_0)\, \mathrm{d}b + \int_{-\infty}^{0} b\, f(b; b_0, v_0)\, \mathrm{d}b - \int_{-\infty}^{0} b\, f(b; b_0, v_0)\, \mathrm{d}b \\ &= \int_{-\infty}^{\infty} b\, f(b; b_0, v_0)\, \mathrm{d}b + \int_{-\infty}^{0} -b\, f(b; b_0, v_0)\, \mathrm{d}b \\ &= b_0 + \mathcal{D}(b_0, v_0) \end{aligned}$$

Therefore, the expected opportunity loss per patient with the current information characterized by (b_0, v_0) is given by:

$$\mathrm{EOLpp}_0 = p_0 \mathcal{D}(b_0, v_0) + (1 - p_0)\{b_0 + \mathcal{D}(b_0, v_0)\} = \mathcal{D}(b_0, v_0) + (1 - p_0) b_0 .$$

For perfect implementation (*i.e.* $p_0 = 1$) $\mathrm{EOLpp}_0 = \mathcal{D}(b_0, v_0)$, as given in Chapter 2. However as p_0, the probability that a future patient receives *Treatment*, decreases, the expected opportunity loss per patient increases, thereby increasing the value of new information. Table 3.4 contains the expected opportunity loss per patient for various values for p_0 for the three examples discussed in Sections 2.3 and 3.1. As illustrated in

this table even small departures from perfect implementation (*i.e.* $p_0 = 0.75$) result in large (4.54 to 11.3 fold) increases in the expected opportunity loss. This in turn will result in large increases in the expected value of perfect and sample information where implementation has a positive relationship with level of evidence. This relationship can also be altered by implementation programs and incentives for maximising net benefit in practice.

The post-trial expected opportunity loss for adopting *Treatment* based on the evidence characterized (b_1,v_1) is $\mathcal{D}(b_1, v_1)$. The post-trial expected opportunity loss for retaining the *Standard* is given by:

$$
\begin{aligned}
\mathrm{EOLpp}_{S1} &= \int_{-\infty}^{\infty} \mathrm{OLpp}_S(b)\, f(b; b_1, v_1)\, \mathrm{d}b \\
&= I(b_1 \le 0) \int_0^{\infty} b\, f(b; b_1, v_1)\, \mathrm{d}b + I(b_1 > 0) \int_0^{\infty} b\, f(b; b_1, v_1)\, \mathrm{d}b \\
&= I(b_1 \le 0) \int_0^{\infty} b\, f(b; b_1, v_1)\, \mathrm{d}b + \int_{-\infty}^{0} b\, f(b; b_1, v_1)\, \mathrm{d}b - \int_{-\infty}^{0} b\, f(b; b_1, v_1)\, \mathrm{d}b + I(b_1 > 0)\{b_1 + \mathcal{D}(b_1, v_1)\} \\
&= I(b_1 \le 0) \int_{-\infty}^{\infty} b\, f(b; b_1, v_1)\, \mathrm{d}b + \int_{-\infty}^{0} -b\, f(b; b_1, v_1)\, \mathrm{d}b + I(b_1 > 0)\{b_1 + \mathcal{D}(b_1, v_1)\} \\
&= I(b_1 \le 0)\{-b_1 + \mathcal{D}(b_1, v_1)\} + I(b_1 > 0)\{b_1 + \mathcal{D}(b_1, v_1)\} \\
&= I(b_1 \le 0)(-b_1) + I(b_1 > 0)(b_1) + \mathcal{D}(b_1, v_1) \\
&= |b_1| + \mathcal{D}(b_1, v_1).
\end{aligned}
$$

Therefore, the expected opportunity loss per patient based on the evidence characterized by (b_1, v_1) is given by:

$$\mathrm{EOLpp}_1 = p_1 \mathcal{D}(b_1, v_1) + (1 - p_1)\{|b_1| + \mathcal{D}(b_1, v_1)\} = \mathcal{D}(b_1, v_1) + (1 - p_1)|b_1|,$$

and the expected value of sample information of a trial of *n* patients per arm is given by

$$\text{EVSI}(n) = k\left\{h-(2n/a+\tau)\right\}\left\{\mathcal{D}\left(b_0,v_0\right)+(1-p_0)b_0-\left[\text{E}_{\hat{b}}\mathcal{D}\left(b_1,v_1\right)+\text{E}_{\hat{b}}(1-p_1)\left|b_1\right|\right]\right\}.$$

Relaxing Assumption 4 increases the expected value of sample information by $k\left\{h-(2n/a+\tau)\right\}\left\{(1-p_0)b_0-\text{E}_{\hat{b}}(1-p_1)\left|b_1\right|\right\}$, which is positive under the assumption that implementation increases with the strength of the evidence.

To relax Assumption 4, a functional relationship between the strength of evidence and the probability that a future patient receives *Treatment* must be hypothesized. The function must between 0 and 1 and be a non-decreasing in the strength of evidence. Assuming that the strength of evidence can be best characterized by the z-statistic, let $p_i = g(z_i)$ where $z_i = b_i/\sqrt{v_i}$, i = 0, 1, and consider the "sliding-step" function given by:

$$g(z) = \left\{\begin{matrix}\min\left(1,\max\left(0,(z-\gamma)/(\beta-\gamma)\right)\right):0\le\gamma<\beta\\ I\left(z>\beta\right):0\le\gamma=\beta\end{matrix}\right\}.$$

The "sliding-step" function is zero for $z<\gamma$; one for $z>\beta$; and, linear for $\gamma\le z\le\beta$, if $\gamma < \beta$, see Figure 3.13. If $\gamma = \beta$, then $g(z)$ is zero if $z < \beta$ and one if $z \ge \beta$. Assumption 4 implies $\gamma=\beta=0$. The "sliding-step" function has been used previously to relate the strength of evidence to the probability of regulatory approval and to the probability of the adoption of a new intervention, see Kikuchi, Pezeshk and Gittins (2008), Willan and Pinto (2005) and Willan (2008). Although the choices of γ and β are somewhat arbitrary, it is illustrated in the examples that the solutions are quite robust to the values chosen.

Relaxing Assumption 4 also has an impact on expected total cost. Under Assumption 4 and assuming $b_0 > C_A/(hk)$, all future patients would receive *Treatment* if the trial is not

performed. Therefore, if the trial is performed, the number of patients who are denied *Treatment*, and thereby incur an opportunity cost, is equal to $\tilde{n}(n) = (2n/a + \tau)k - n$. That is, the number of patients who incur an opportunity cost equal all patients incident during the trial minus the *n* patients who receive *Treatment* in the trial. With Assumption 4 relaxed, *i.e.* letting $p_0 < 1$, the number of patients who incur an opportunity cost becomes $\tilde{n}(n) = p_0(2n/a + \tau)k - n < (2n/a + \tau)k - n$. Therefore, relaxing Assumption 4 reduces the number of patients that incur an opportunity cost, and thereby reduces the expected total cost.

3.2.2 The CADET-Hp Trial

As the base case we set $\gamma = \Phi^{-1}(0.75) = 0.674$ and $\beta = \Phi^{-1}(0.99) = 2.33$, where $\Phi^{-1}(\cdot)$ is the inverse of the *cdf* for a normal random variable with mean 0 and variance 1. These values for γ and β can be interpreted as follows: if the null hypothesis that $b \le 0$ cannot be rejected at the 0.25 level of significance, then no future patients would receive *Treatment*, while on the other hand, if $b \le 0$ can be rejected at the 0.01 level of significance, then all future patients would receive *Treatment*. Applying the "sliding step" function, the probability that a future patient receives *Treatment* if a new trial is not performed, is $p_0 = g(z_0) = g\left(87.29/\sqrt{5358.2}\right) = g(1.192) = 0.3133$, and therefore, relaxing Assumption 4 increases the $EOLpp_0$ from $\mathcal{D}(b_0, v_0) = 4.548$ to $\mathcal{D}(b_0, v_0) + (1 - p_0)b_0 = 4.548 + (1 - 0.3133)87.29 = 64.49$, leading to a dramatic, 14-fold, increase in the potential value of additional information. For the parameter values that were used to generate Figure 3.2, which are given in Table 3.5, the plots of the

expected value of sample information and expected total cost, as functions of sample size, are given in Figure 3.14. The optimal sample size is 501 per arm, yielding an expected value of sample information of $69,664,117 and an expected net gain of $61,125,828. The financial and opportunity costs are $2,804,000 and $5,734,289 respectively.

The expected value of sample information and expected opportunity cost for entering 501 patients per arm under Assumption 4 are $3,991,419 and $18,489,868, respectively. Thus, at the optimal sample size of 501, relaxing Assumption 4 leads to a 17.5-fold increase in the expected value of sample information and 3.2-fold decrease in the expected opportunity cost. The dramatic increase in the expected value of sample information relates to the fact that without additional information from a new trial only 31.33% of future patients will receive *Treatment*, even though prior to the trial the expected incremental net benefit is positive. Relaxing Assumption 4 implies that if another trial is not performed 68.67% of future patients will receive *Standard*, compared to none under Assumption 4. The expected opportunity loss for these patients is $64.49, compared $4.59 under Assumption 4. The information from a new trial is expected to reduce expected opportunity loss by reducing the uncertainty, but by relaxing Assumption 4 the information from a new trial also reduces expected opportunity loss by increasing the expected proportion of patients receiving *Treatment*.

Although the general shape of the sliding step function (*i.e.* non-decreasing in the z-statistic between 0 and 1) is reasonable, the robustness of the choices of γ and β need to

be examined. A sensitivity analysis regarding the values of γ and β is provided in Table 3.6. For each combination for the values of $\gamma = \Phi^{-1}(0.5), \Phi^{-1}(0.75)$ and $\Phi^{-1}(0.95)$ and $\beta = \Phi^{-1}(0.95), \Phi^{-1}(0.99)$ and $\Phi^{-1}(0.999)$, the optimal sample size and corresponding ENG are provided. In addition, the expected net gain from entering 501 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 is reported. Although the optimal sample size varies considerably with γ and β, the per cent reduction in ENG from entering 501 patients per arm is quite small, reaching a maximum of 15.1% for $\gamma = \Phi^{-1}(0.5)$ and $\beta = \Phi^{-1}(0.95)$, and is less than 5% for all the remaining cases considered. This illustrates a good degree of robustness with regard to the choices of γ and β. The only case for which a sample size of 501 results in a sizable (15.1%) deviation from optimum expected net gain is the case where $\gamma = \Phi^{-1}(0.5)$ and $\beta = \Phi^{-1}(0.95)$. This is a fairly unrealistic case since in assumes that 50 per cent of patients would receive *Treatment* if the z-statistic is 0.825 (*i.e.* the z-statistic associated with a level of significance of 0.205), and that all patients would if it exceeds 1.65.

3.2.3 The Prostate Trial

Again using as the base case of $\gamma = \Phi^{-1}(0.75) = 0.674$ and $\beta = \Phi^{-1}(0.99) = 2.33$, the probability that a future patient receives *Treatment* if a new trial is not performed, is $p_0 = g(z_0) = g\left(5551/\sqrt{14597242}\right) = g(1.453) = 0.4713$, and therefore, relaxing Assumption 4 increases the EOLpp$_0$ from $\mathcal{D}(b_0, v_0) = 132.0$ to $\mathcal{D}(b_0, v_0) + (1 - p_0)b_0$

$= 132.0 + (1 - 0.4713)5551 = 3067$, leading to a dramatic, 23-fold, increase in the potential value of additional information. For the parameter values that were used to generate Figure 3.6, which is given in Table 3.5, the plots of the expected value of sample information and expected total cost, as functions of sample size, are given in Figure 3.15. The optimal sample size is 154 per arm, yielding an expected value of sample information of $104,875,120 and an expected net gain of $83,412,431. The financial and opportunity costs are $1,616,000 and $19,846,689 respectively.

The expected value of sample information and expected opportunity cost for entering 154 patients per arm under Assumption 4 are $2,672,699 and $43,998,367, respectively. Thus, at the optimal sample size of 154, relaxing Assumption 4 leads to a 39.2-fold increase in the expected value of sample information and 2.22-fold decrease in the expected opportunity cost.

A sensitivity analysis regarding the values of γ and β is provided in Table 3.7. For each combination for the values of $\gamma = \Phi^{-1}(0.5), \Phi^{-1}(0.75)$ and $\Phi^{-1}(0.95)$ and $\beta = \Phi^{-1}(0.95), \Phi^{-1}(0.99)$ and $\Phi^{-1}(0.999)$, the optimal sample size and corresponding ENG are provided. In addition, the expected net gain from entering 154 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 is reported. Although the optimal sample size varies considerably with γ and β, with the exception of two cases, the per cent reduction in ENG from entering 154 patients per arm is quite small,

reaching a maximum of 4.60% for $\gamma = \Phi^{-1}(0.95)$ and $\beta = \Phi^{-1}(0.999)$, and is less than 2.4% for the remaining cases considered. The two cases for which there are marked reduction in the expected net gain from entering 154 patients per arm are $\gamma = \Phi^{-1}(0.5), \beta = \Phi^{-1}(0.95)$ and $\gamma = \Phi^{-1}(0.75), \beta = \Phi^{-1}(0.95)$. For the case $\gamma = \Phi^{-1}(0.5), \beta = \Phi^{-1}(0.95)$, the optimal sample size is 0, meaning that the current information is sufficient for decision making, and entering 154 patients leads to an expected net loss of over 17 million dollars, mostly relating to opportunity cost. The second case where $\gamma = \Phi^{-1}(0.75), \beta = \Phi^{-1}(0.95)$, the optimal sample size is 95, and entering 154 patients per arm leads to a 56.5% reduction in the expected net gain, again mostly due to opportunity cost. These are fairly unrealistic cases since the first assumes that 50 per cent of patients would receive *Treatment* if the z-statistic is 0.825 (*i.e.* the z-statistic associated with a level of significance of 0.205), and that all patients would if it exceeds 1.65. The second assumes that 50 per cent of patients would receive *Treatment* if the z-statistic is 1.162 (*i.e.* the z-statistic associated with a level of significance of 0.123), and that all patients would if it exceeds 1.65.

3.2.3 The Early ECV Trial

Again using as the base case of $\gamma = \Phi^{-1}(0.75) = 0.674$ and $\beta = \Phi^{-1}(0.99) = 2.33$, the probability that a future patient receives *Treatment* if a new trial is not performed is $p_0 = g(z_0) = g\left(69.40/\sqrt{3725}\right) = g(1.137) = 0.2800$, and therefore, relaxing Assumption 4 increases the EOLpp$_0$ from $\mathcal{D}(b_0, v_0) = 4.573$ to $\mathcal{D}(b_0, v_0) + (1 - p_0)b_0$

$= 4.573 + (1 - 0.2800)69.40 = 54.54$, leading to a dramatic, 12-fold, increase in the potential value of additional information. For the parameter values that were used to generate Figure 3.10, which are given in Table 3.5, the plots of the expected value of sample information and expected total cost, as functions of sample size, are given in Figure 3.16. The optimal sample size is 509 per arm, yielding an expected value of sample information of $38,080,062 and an expected net gain of $34,623,685. The financial and opportunity costs are $2,128,800 and $1,327,577 respectively.

The expected value of sample information and expected opportunity cost for entering 509 patients per arm under Assumption 4 are $3,031,078 and $4,855,180, respectively. Thus, at the optimal sample size of 509, relaxing Assumption 4 leads to a 12.6-fold increase in the expected value of sample information and 3.66-fold decrease in the expected opportunity cost.

A sensitivity analysis regarding the values of γ and β is provided in Table 3.8. For each combination for the values of $\gamma = \Phi^{-1}(0.5), \Phi^{-1}(0.75)$ and $\Phi^{-1}(0.95)$ and $\beta = \Phi^{-1}(0.95), \Phi^{-1}(0.99)$ and $\Phi^{-1}(0.999)$, the optimal sample size and corresponding ENG are provided. In addition, the expected net gain from entering 509 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 are reported. Although the optimal sample size varies considerably with γ and β, the per cent reduction in ENG from entering 509 patients per arm is quite small, reaching a maximum

of 8.01% for $\gamma = \Phi^{-1}(0.5)$ and $\beta = \Phi^{-1}(0.95)$, and is less than 4% for all the remaining cases considered. This illustrates a good degree of robustness with regard to the choices of γ and β. The only case for which a sample size of 509 results in a sizable (8.01%) deviation from optimum expected net gain is the case where $\gamma = \Phi^{-1}(0.5)$ and $\beta = \Phi^{-1}(0.95)$. This is a fairly unrealistic case since in assumes that 50 per cent of patients would receive *Treatment* if the z-statistic is 0.825 (*i.e.* the z-statistic associated with a level of significance of 0.205), and that all patients would if it exceeds 1.65.

3.3 RELAXING ASSUMPTION 5: THE DISCOUNT RATE IS POSITIVE

Since the expected value of sample information and expected total cost associated with a trial are realized in the future, discounting should be considered. Assuming a discount rate of $r > 0$, the expression for expected net gain becomes:

$$\begin{aligned}
\mathrm{ENG}(n) = &\left\{(t^U - t)(1+r)^{-t^L} + \sum_{i=t^U}^{h-1}(1+r)^{-i}\right\} k(\mathrm{EOLpp}_0 - \mathrm{EOLpp}_1) \\
&- \left\{C_f + \left[(t_a - t_a^L)(1+r)^{-t_a^L} + \sum_{i=0}^{t_a^L-1}(1+r)^{-i}\right] aC_v\right\} \\
&- \left\{(t - t^L)(1+r)^{-t^L} + \sum_{i=0}^{t^L-1}(1+r)^{-i}\right\} p_0 k\left\{b_0 - C_A/(hk)\right\} \\
&+ \left\{(t_a - t_a^L)(1+r)^{-t_a^L} + \sum_{i=0}^{t_a^L-1}(1+r)^{-i}\right\}(a/2)\left\{b_0 - C_A/(hk)\right\},
\end{aligned}$$

where $t = 2n/a + \tau$ is the trial duration; t^L is the integer part of *t*; $t^U = t^L + 1; t_a = 2n/a$ is the duration of accrual; and, t_a^L is the integer part of t_a.

For various discount rates and all three examples Table 3.9 contains optimal sample size, expected value of sample information, expected total cost, expected net gain, and per cent reduction in ENG from entering the optimal number of patients assuming a discount rate of 0. The values of the other parameters (*i.e.*λ, *k*, *h*, *a*, τ, C_f, C_v, C_a, γ and β) are given in Table 3.5. Discounting affects the expected value of sample information much more the expected total cost. This is expected because the value of information is realized much further into the future than costs are. Cost are incurred from time 0 until time *t*, while the value of information is realized from time *t* until time *h*. Discount rate has a sizeable affect on the solution, and in each example a discount rate of 5% almost halves the expected net gain and reduces the optimal sample size by about 25%. Nonetheless, in all examples the per cent reduction in the expected net gain from entering the optimal sample size assuming a discount rate of 0 is less than 1% for discount rates of 5% and even for a discount rate of 10% the reduction in expected net gain is less than 5%.

3.4 RELAXING ASSUMPTION 6

3.4.1 Research has prospective value across jurisdictions

3.5 DISCUSSION

Table 3.1 The effect of the cost of adoption on optimal sample size and optimum ENG for the CADET-Hp Trial

Cost of Adoption	Optimal Sample Size	Optimum ENG	Reduction in ENG with a Trial of 465 Patients per Arm
0	465	1,349,325	0
1 Million	469	1,436,586	0.00798%
5 Million	487	1,803,771	0.164%
10 Million	507	2,304,967	0.506%

Table 3.2 The effect of the cost of adoption on optimal sample size and optimum ENG for the Prostate Trial

Cost of Adoption	Optimal Sample Size	Optimum ENG	Reduction in ENG with a Trial of 197 Patients per Arm
0	197	570,651	0
1 Million	199	624,006	0.00222%
5 Million	206	845,418	0.301%
10 Million	214	1,140,631	0.854%

Table 3.3 The effect of the cost of adoption on optimal sample size and optimum ENG for the Early ECV Trial

Cost of Adoption	Optimal Sample Size	Optimum ENG	Reduction in ENG with a Trial of 345 Patients per Arm
0	345	742,655	0
1 Million	351	840,500	0.0273%
5 Million	375	1,270,443	0.467%
10 Million	403	1,899,974	1.21%

Table 3.4 Expected opportunity loss per patient for various values for probability that a future patient receives the new intervention (p_0) for all three examples*

p_0	CADET-Hp $(b_0, \mathcal{D}_0) = (87.29, 4.548)$	Prostate $(b_0, \mathcal{D}_0) = (5551, 132.0)$	Early ECV $(b_0, \mathcal{D}_0) = (69.40, 4.573)$
1	4.548	132.0	4.573
0.75	25.23	1487	20.78
0.5	45.92	2842	36.99
0.25	66.60	4196	53.19
0	87.29	5551	69.40

*$\mathcal{D}_0 = \mathcal{D}(b_0, v_0)$

Table 3.5 Parameter values used for the examples

Parameter	CADET-Hp	Prostate	Early ECV
Annual Incidence (k)	80,000	2500	50,000
Time Horizon (h)	20	20	20
Annual Accrual Rate (a)	800	250	1000
Duration of Follow-up (τ)	1.5	2	0.5
Fixed Cost (C_f)	800,000	1,000,000	500,000
Variable Cost (C_a)	2000	2000	1600
γ	$\Phi^{-1}(0.75) = 0.674$	$\Phi^{-1}(0.75) = 0.674$	$\Phi^{-1}(0.75) = 0.674$
β	$\Phi^{-1}(0.99) = 2.33$	$\Phi^{-1}(0.99) = 2.33$	$\Phi^{-1}(0.99) = 2.33$

Table 3.6 Optimal sample size (n^*) and optimum expected net gain (ENG(n^*)), the expected net gain (ENG(501)) and the per cent reduction $(100*(\text{ENG}(n^*)-\text{ENG}(501))/\text{ENG}(n^*))$ from optimum of entering 501 patients per arm (base case), as a function of γ and β, for the CADET-Hp Trial

n^* ENG(n^*) ENG(501) Per cent reduction	$\beta = \Phi^{-1}(0.95)$ = 1.64	$\beta = \Phi^{-1}(0.99)$ = 2.33	$\beta = \Phi^{-1}(0.999)$ = 3.09
$\gamma = \Phi^{-1}(0.5) = 0$	255 14,800,258 12,558,280 15.1%	418 37,369,819 37,115,476 0.581%	595 47,793,593 47,519,518 0.573%
$\gamma = \Phi^{-1}(0.75) = 0.674$	340 37,331,923 36,362,507 2.60%	501 61,125,828 (base case)	676 67,988,853 66,843,696 1.68%
$\gamma = \Phi^{-1}(0.95) = 1.64$	519 102,635,623 102,620,526 0.0147%	664 97,431,465 96,385,028 1.07%	831 91,421,720 87,307,738 4.50%

Table 3.7 Optimal sample size (n^*) and optimum expected net gain ENG(n^*), the expected net gain ENG(154) and the per cent reduction $(100*(\text{ENG}(n^*)-\text{ENG}(154))/\text{ENG}(n^*))$ from optimum of entering 154 patients per arm (base case), as a function of γ and β, for the Prostate Trial

n^* ENG(n^*) ENG(154) Per cent reduction	$\beta = \Phi^{-1}(0.95)$ = 1.64	$\beta = \Phi^{-1}(0.99)$ = 2.33	$\beta = \Phi^{-1}(0.999)$ = 3.09
$\gamma = \Phi^{-1}(0.5) = 0$	0 0 -17,605,893 (undefined)	128 46,521,169 46,105,214 0.894%	192 76,869,299 75,952,128 1.19%
$\gamma = \Phi^{-1}(0.75) = 0.674$	95 3,731,501 1,624,637 56.5%	154 83,412,431 (base case)	218 112,442,677 109,795,230 2.35%
$\gamma = \Phi^{-1}(0.95) = 1.64$	159 211,073,211 211,062,733 0.00496%	209 201,903,562 199,868,863 1.01%	270 191,206,864 182,406,971 4.60

Table 3.8 Optimal sample size (n^*) and optimum expected net gain (ENG(n^*)), the expected net gain (ENG(509)) and the per cent reduction $(100*(\text{ENG}(n^*)-\text{ENG}(509))/\text{ENG}(n^*))$ from optimum of entering 509 patients per arm (base case), as a function of γ and β, for the Early ECV Trial.

n^* ENG(n^*) ENG(509) Per cent reduction	$\beta = \Phi^{-1}(0.95)$ = 1.64	$\beta = \Phi^{-1}(0.99)$ = 2.33	$\beta = \Phi^{-1}(0.999)$ = 3.09
$\gamma = \Phi^{-1}(0.5) = 0$	271 12,305,290 11,319,335 8.01%	427 22,609,394 22,491,368 0.522%	596 27,363,907 27,230,249 0.488%
$\gamma = \Phi^{-1}(0.75) = 0.674$	356 24,621,457 24,206,712 1.68%	509 34,623,685 (base case)	678 37,345,577 36,849,317 1.33%
$\gamma = \Phi^{-1}(0.95) = 1.64$	529 52,307,159 52,300,337 0.130%	668 49,914,513 49,456,171 0.918%	827 47,135,328 45,337,008 3.82%

Table 3.9 Optimal sample size (*n**), expected value of sample information (EVSI), expected total cost (ETC) and expected net gain (ENG) by discount rate

CADET-Hp Trial					
Discount Rate	*n**	EVSI	ETC	ENG	Reduction in ENG*
0	501	69,664,117	8,538,289	61,125,828	0
2	476	56,278,691	8,206,873	48,071,818	0.113%
5	404	41,695,417	7,452,356	34,243,060	0.839%
10	340	27,124,899	6,749,381	20,375,518	3.98%
Prostate Trial					
Discount Rate	*n**	EVSI	ETC	ENG	Reduction in ENG*
0	154	104,875,120	21,462,689	83,412,431	0
2	142	84,066,286	20,444,176	63,622,110	0.120%
5	127	61,916,191	19,210,490	42,705,701	0.853%
10	105	39,520,587	17,517,590	22,002,997	4.70%
Early ECV Trial					
Discount Rate	*n**	EVSI	ETC	ENG	Reduction in ENG*
0	509	38,080,062	3,456,377	34,623,685	0
2	463	31,068,400	3,222,723	27,845,677	0.126%
5	409	23,570,612	2,951,038	20,619,574	0.817%
10	342	15,925,207	2,619,944	13,305,263	3.40%

* Per cent reduction in ENG from entering the optimal number of patients assuming a discount rate of 0

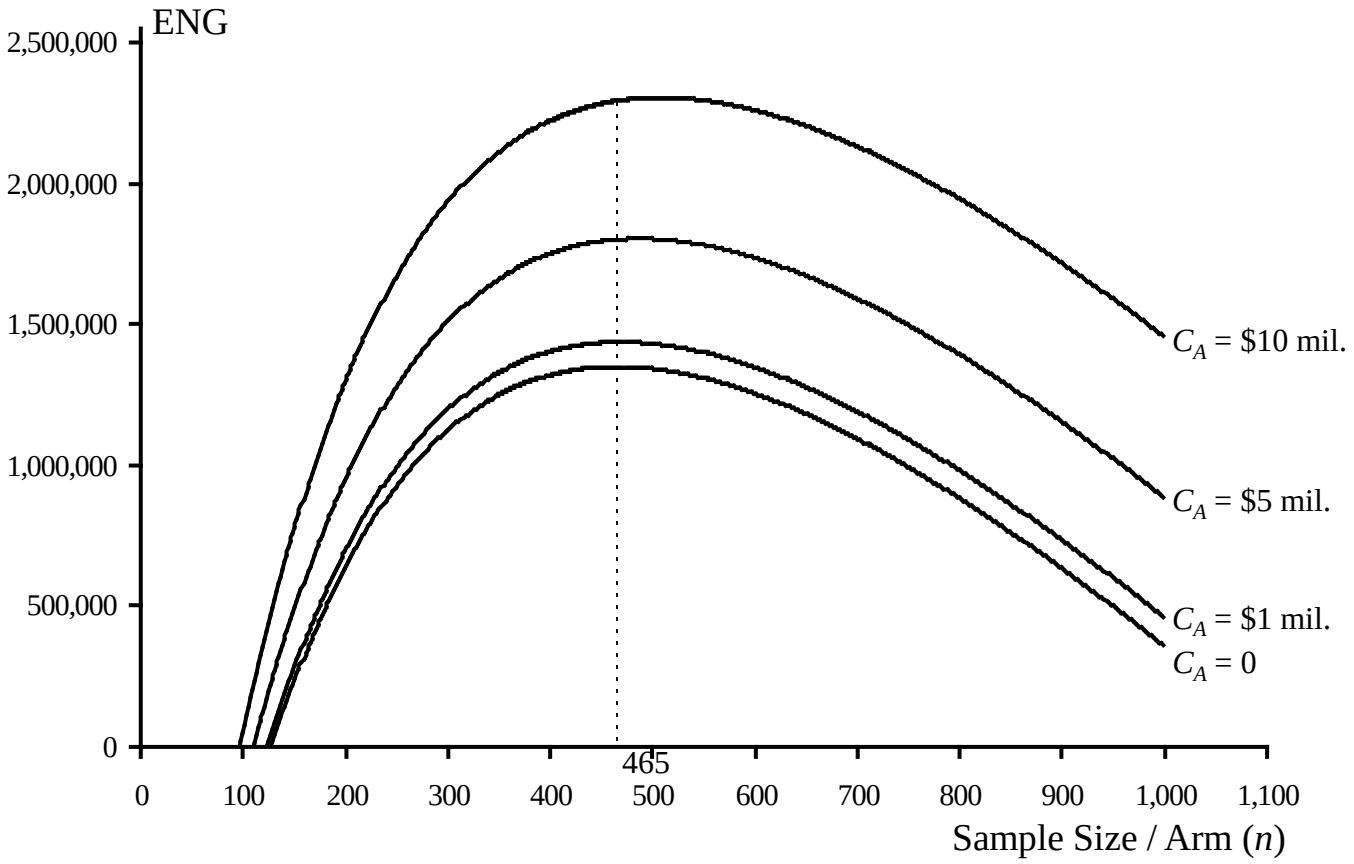

Figure 3.1 Expected net gain (ENG), as a functions of sample size (n) for various values of the cost of adoption (C_A) for the CADET-Hp Trial

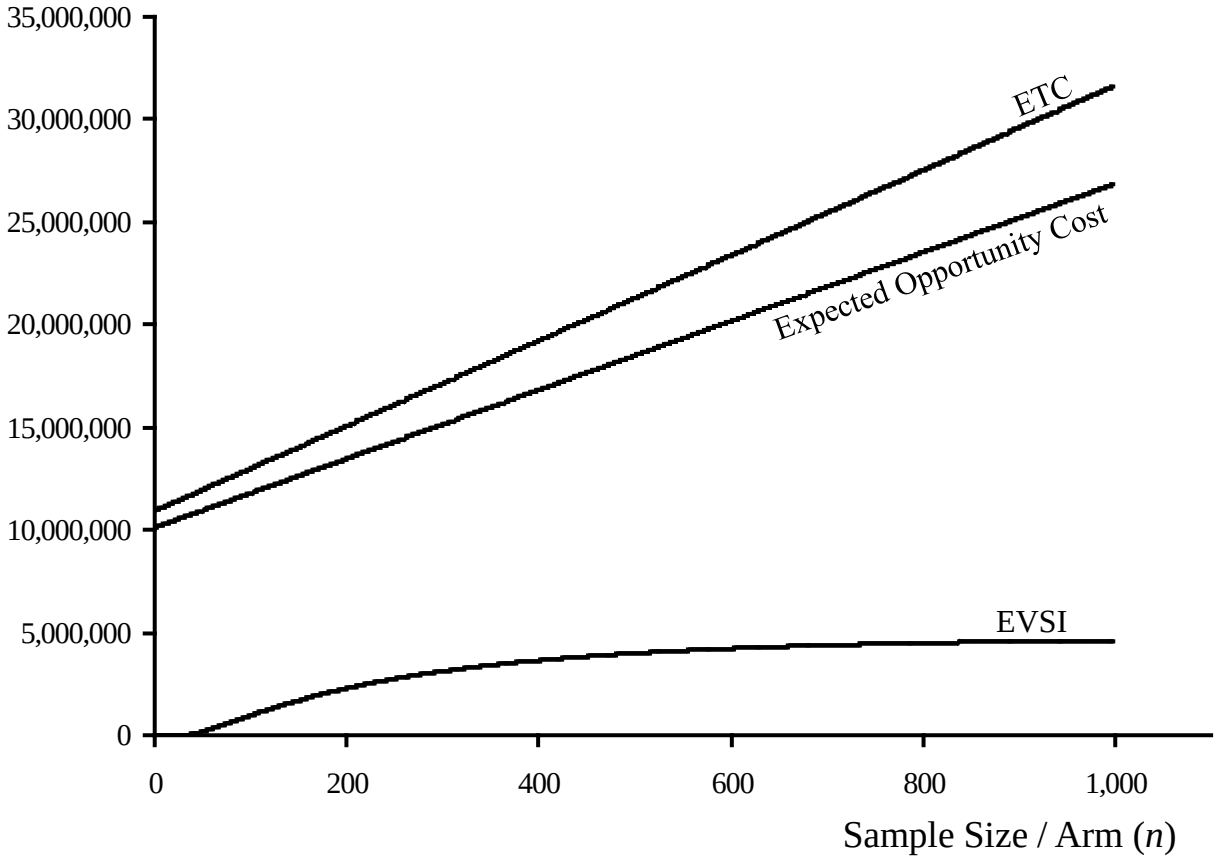

Figure 3.2 Expected value of sample information (EVSI), expected total cost (ETC) and expected opportunity cost as functions of sample size (n) for the CADET-Hp Trial, assuming the cost of adoption (C_A) is 5,000,000, accrual rate (a) is 800 per year (*i.e.* $a = 0.01k$) and duration of follow-up (τ) is 1.5 years

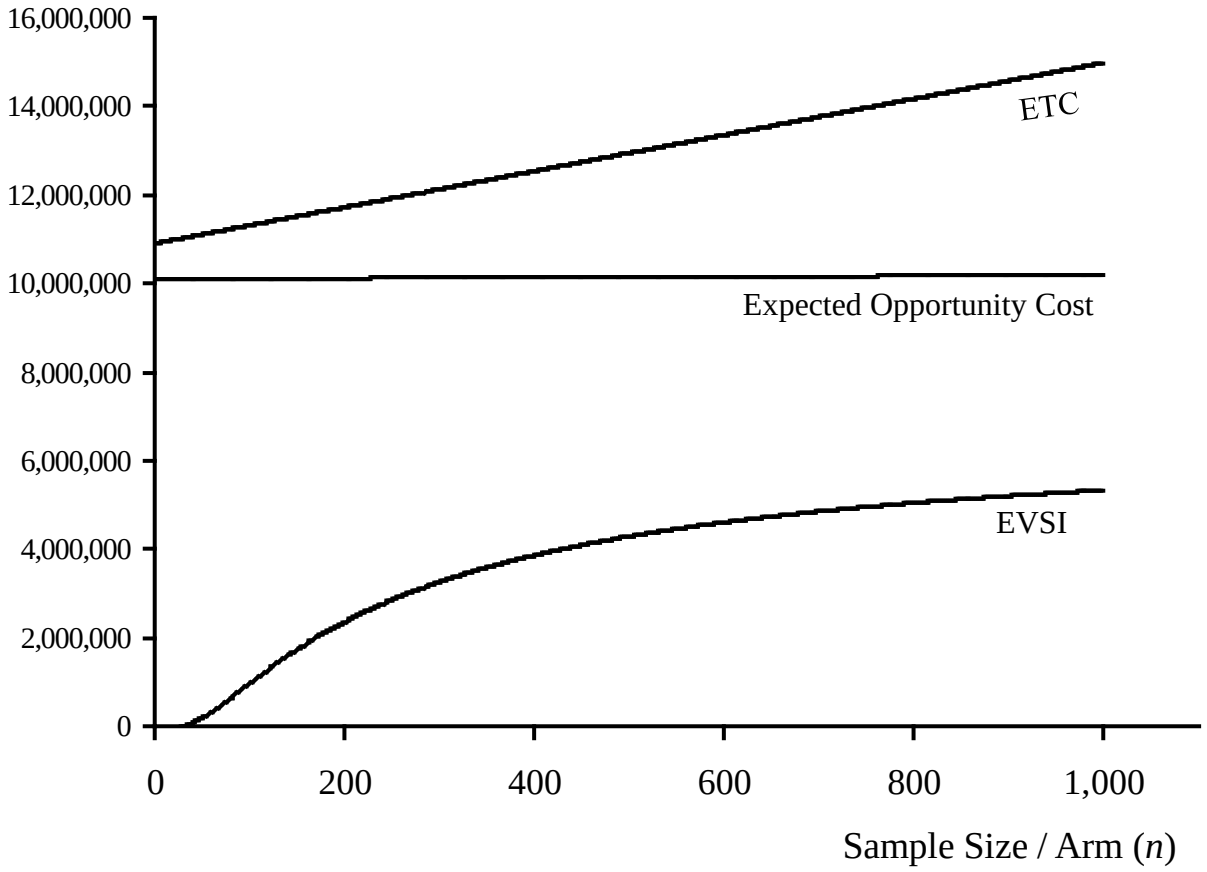

Figure 3.3 Expected value of sample information (EVSI), expected total cost (ETC) and expected opportunity cost as functions of sample size (n) for the CADET-Hp Trial, assuming the cost of adoption (C_A) is 5,000,000, accrual rate (a) is 80,000 per year (*i.e.* $a = k$) and duration of follow-up (τ) is 1.5 years

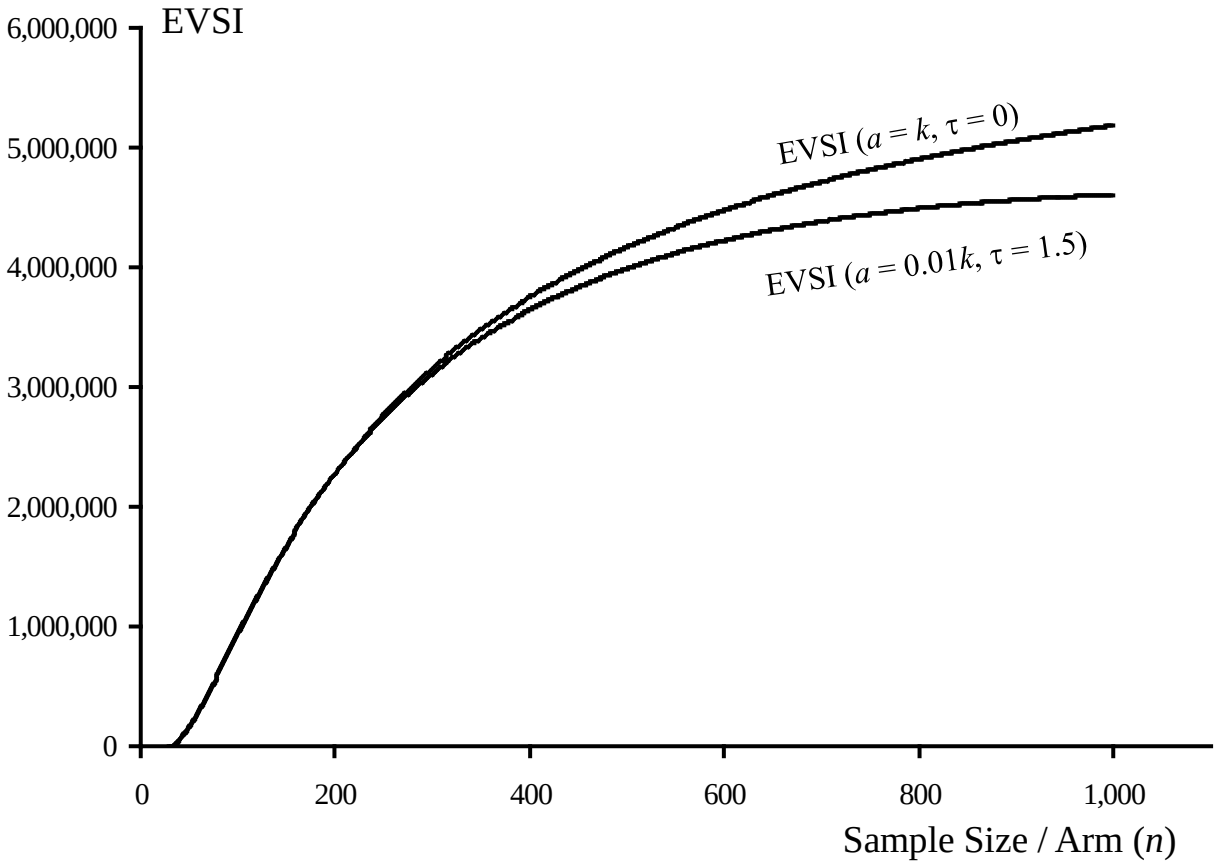

Figure 3.4 Expected value of sample information (EVSI), as a function of sample size (n) for the CADET-Hp Trial with the cost of adoption (C_A) equal to 5,000,000 and two sets of values for the accrual rate (a) and follow-up (τ)

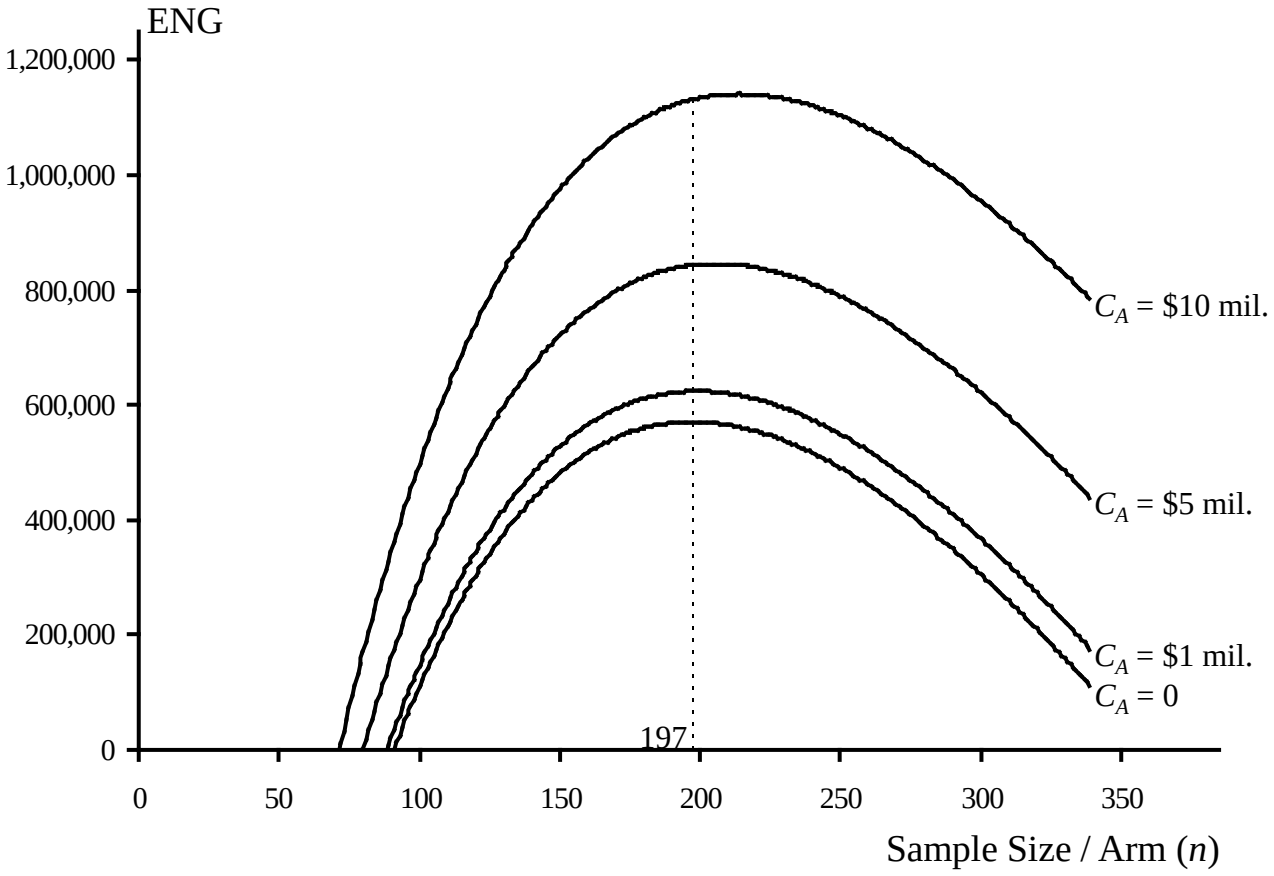

Figure 3.5 Expected net gain (ENG), as a functions of sample size (n) for various values of the cost of adoption (C_A) for the Prostate Trial

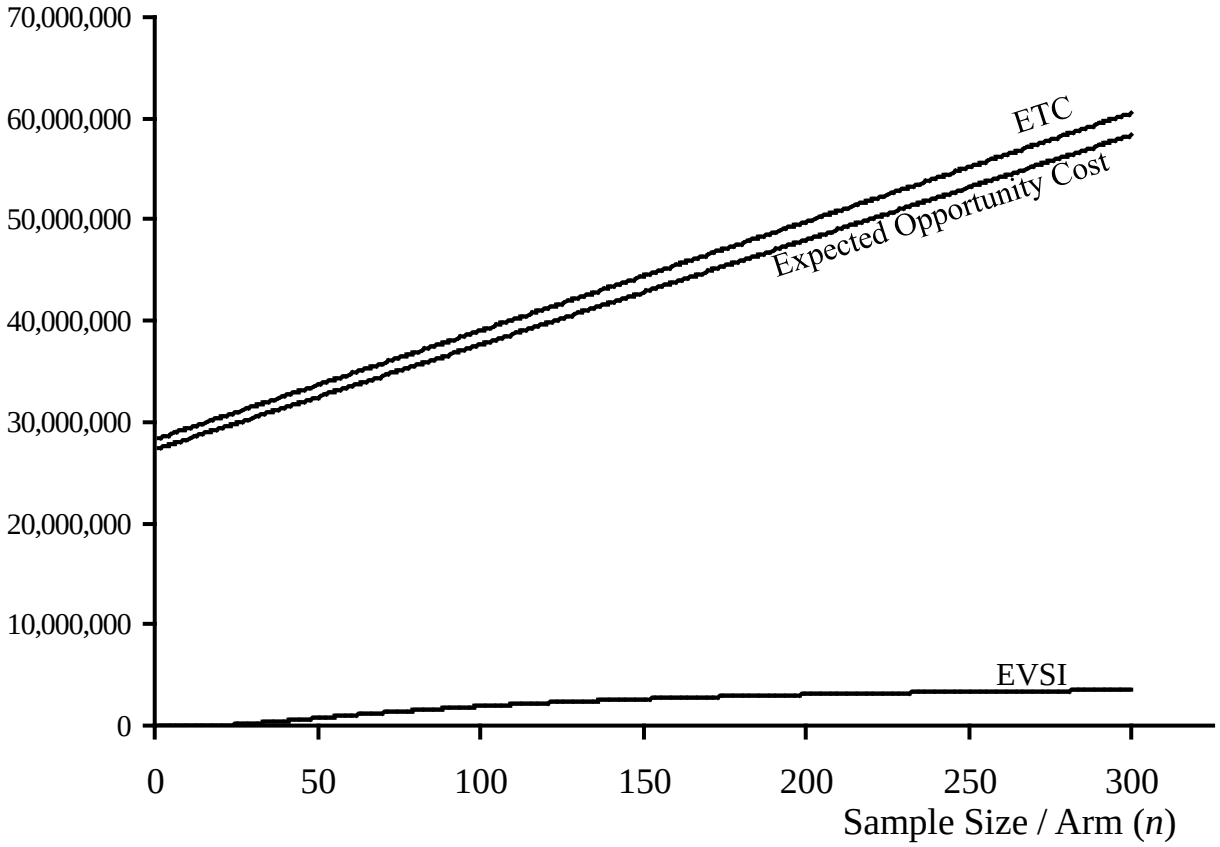

Figure 3.6 Expected value of sample information (EVSI), expected total cost (ETC) and expected opportunity cost as functions of sample size (n) for the Prostate Trial, assuming the cost of adoption (C_A) is 5,000,000, accrual rate (a) is 250 per year (*i.e.* $a = 0.1k$) and duration of follow-up (τ) is 2 years

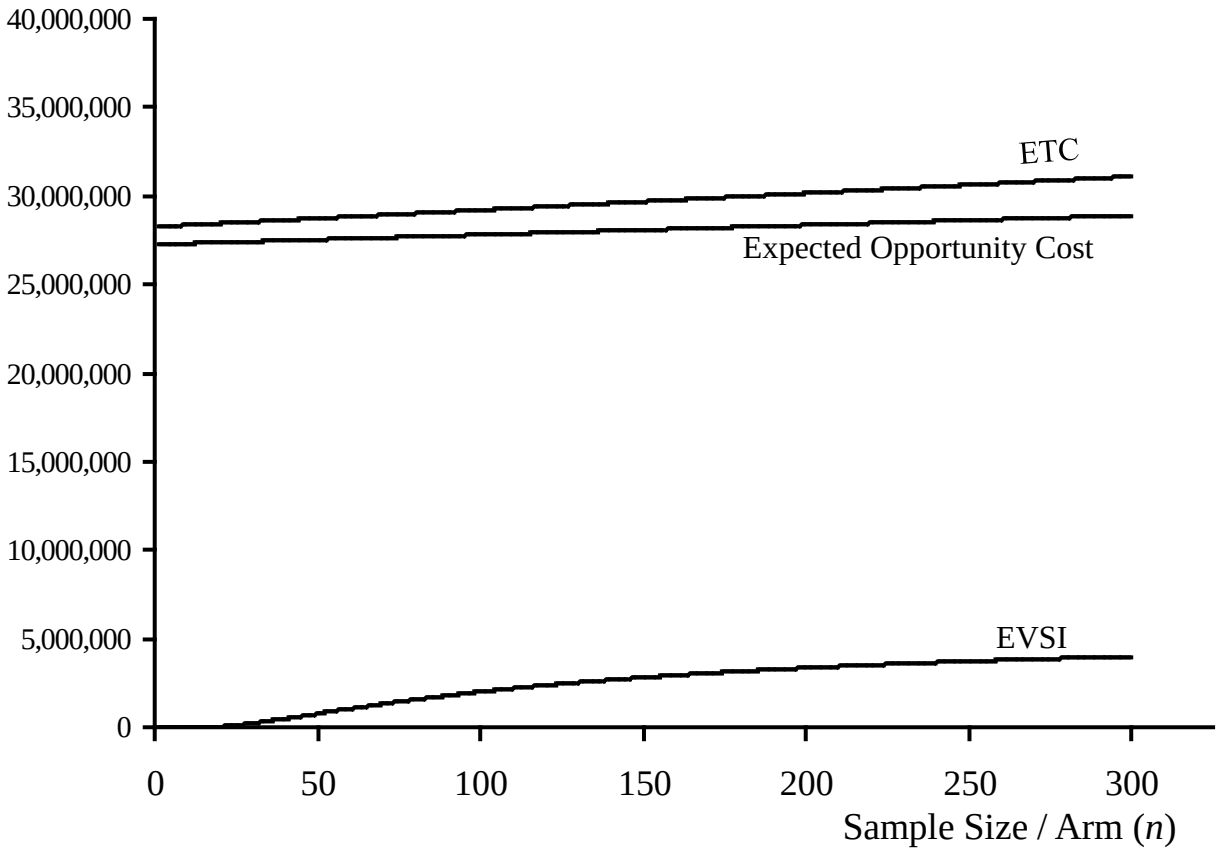

Figure 3.7 Expected value of sample information (EVSI), expected total cost (ETC) and expected opportunity cost as functions of sample size (n) for the Prostate Trial, assuming the cost of adoption (C_A) is 5,000,000, accrual rate (a) is 2500 per year (*i.e.* $a = k$) and duration of follow-up (τ) is 2 years

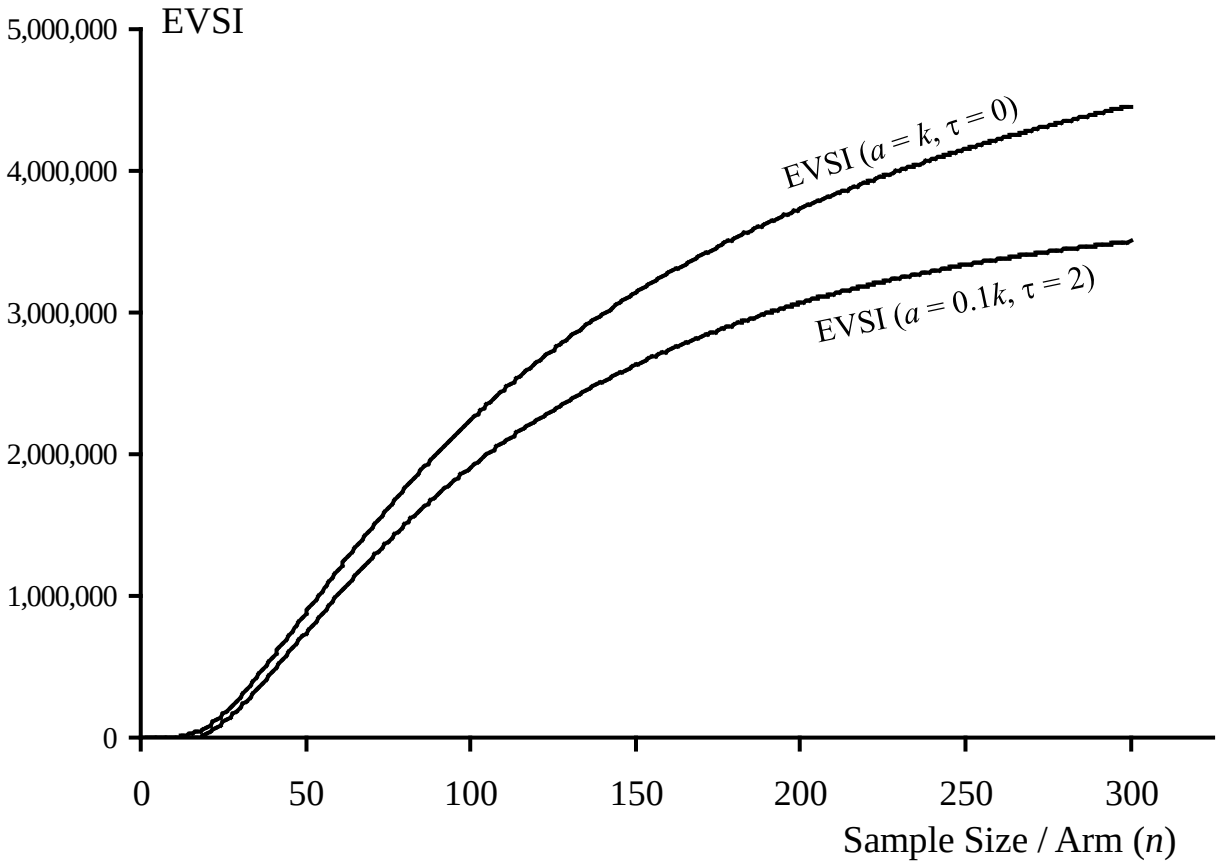

Figure 3.8 Expected value of sample information (EVSI), as a function of sample size (n) for the Prostate Trial with the cost of adoption (C_A) equal to 5,000,000 and two sets of values for the accrual rate (a) and follow-up (τ)

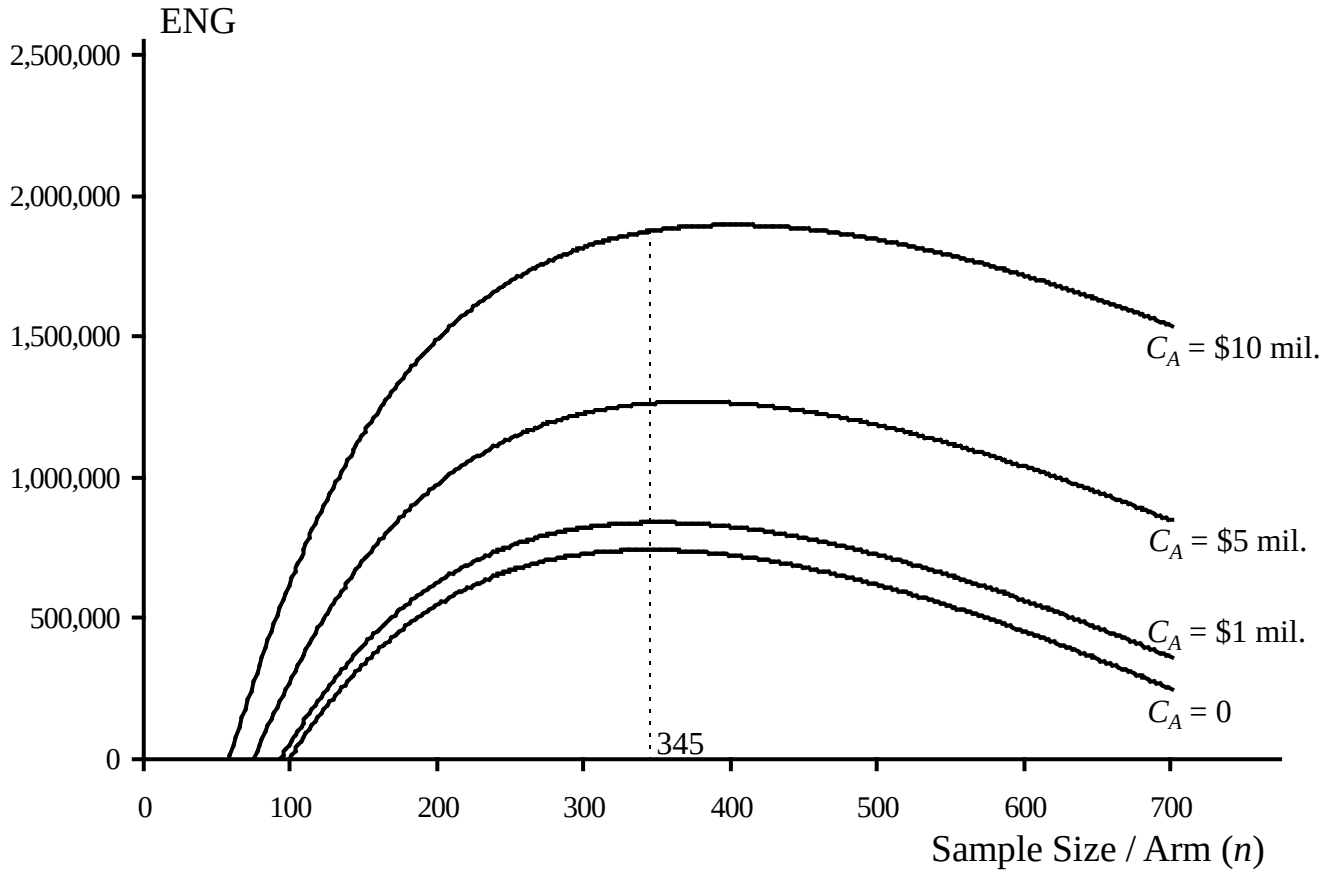

Figure 3.9 Expected net gain (ENG), as a functions of sample size (n) for various values of the cost of adoption (C_A) for the Early ECV Trial

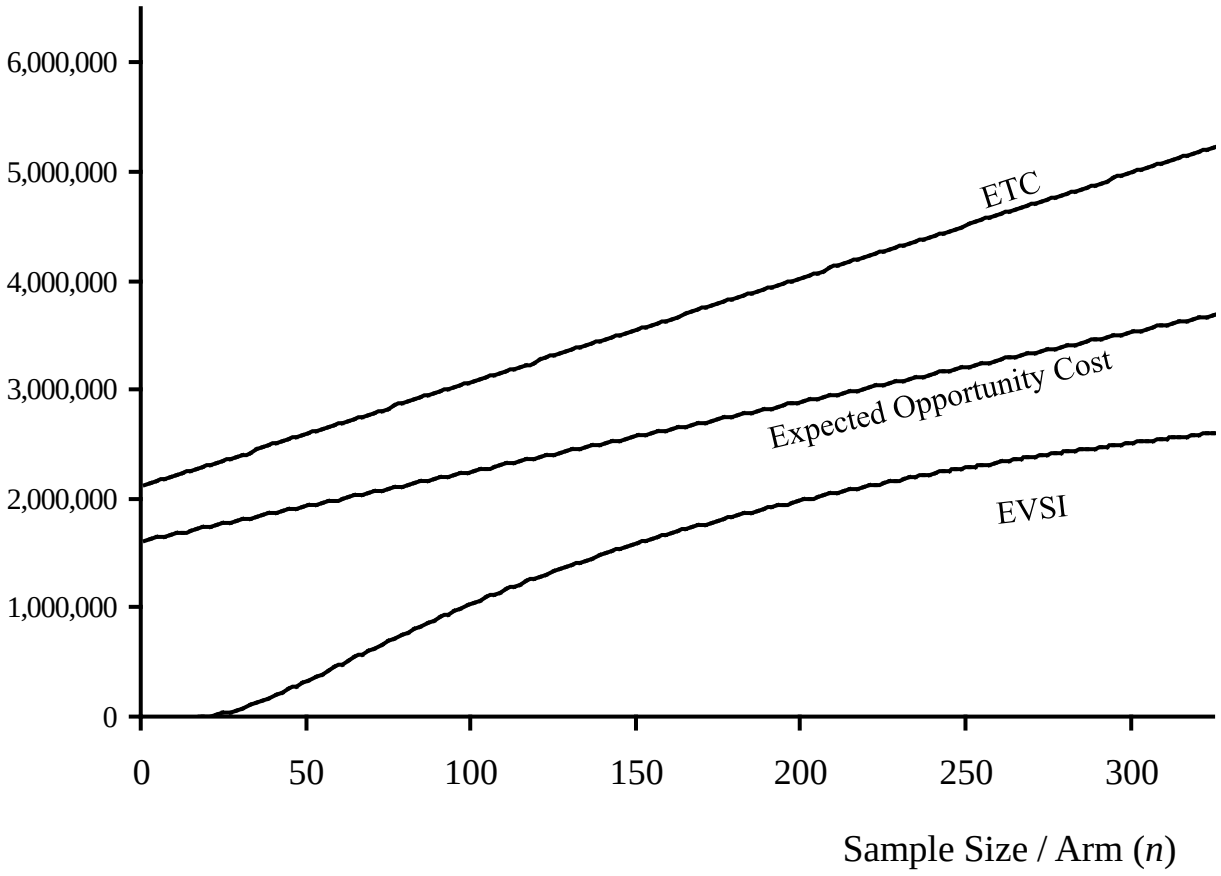

Figure 3.10 Expected value of sample information (EVSI), expected total cost (ETC) and expected opportunity cost as functions of sample size (n) for the Early ECV Trial, assuming the cost of adoption (C_A) is 5,000,000, accrual rate (a) is 1000 per year (*i.e.* $a = 0.02k$) and duration of follow-up (τ) is 0.5 years

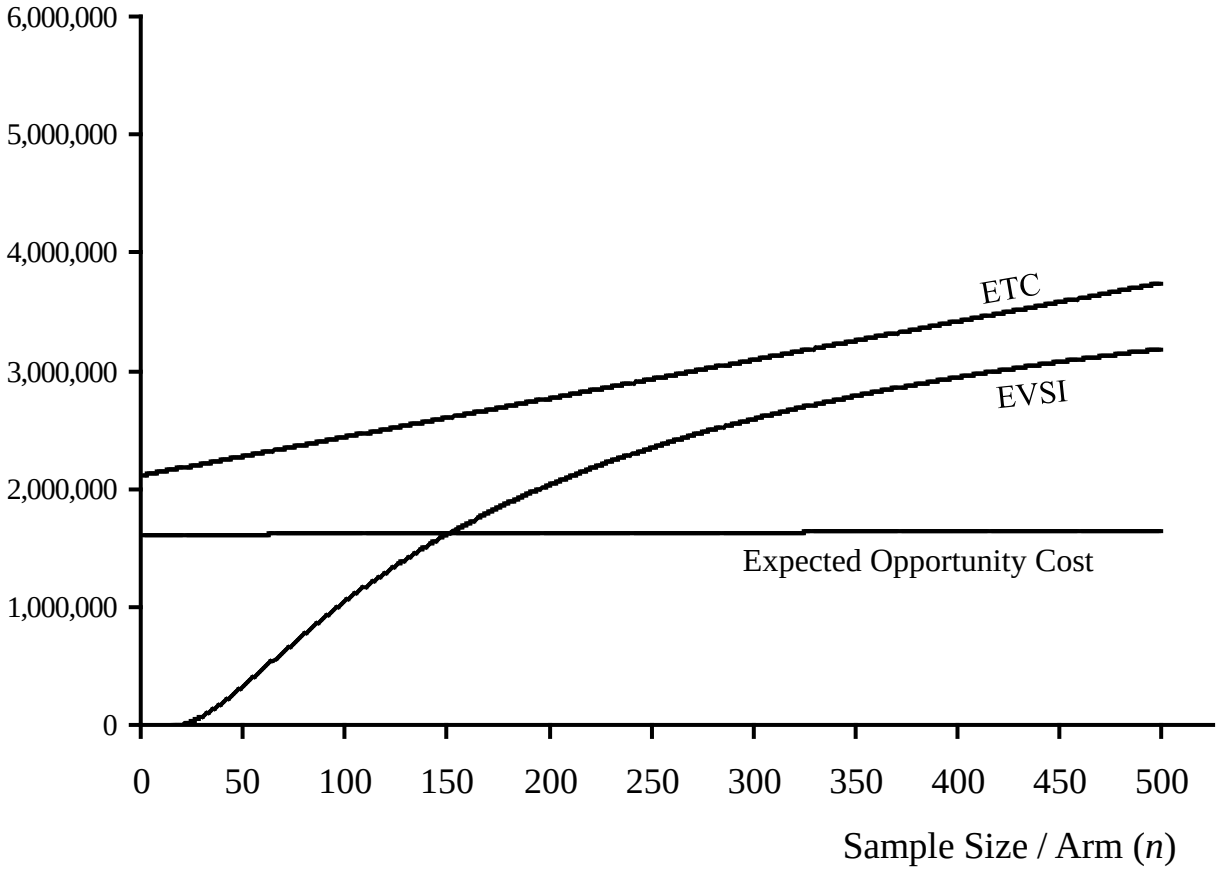

Figure 3.11 Expected value of sample information (EVSI), expected total cost (ETC) and expected opportunity cost as functions of sample size (n) for the Early ECV Trial, assuming the cost of adoption (C_A) is 5,000,000, accrual rate (a) is 2500 per year (*i.e.* $a = k$) and duration of follow-up (τ) is 0.5 years

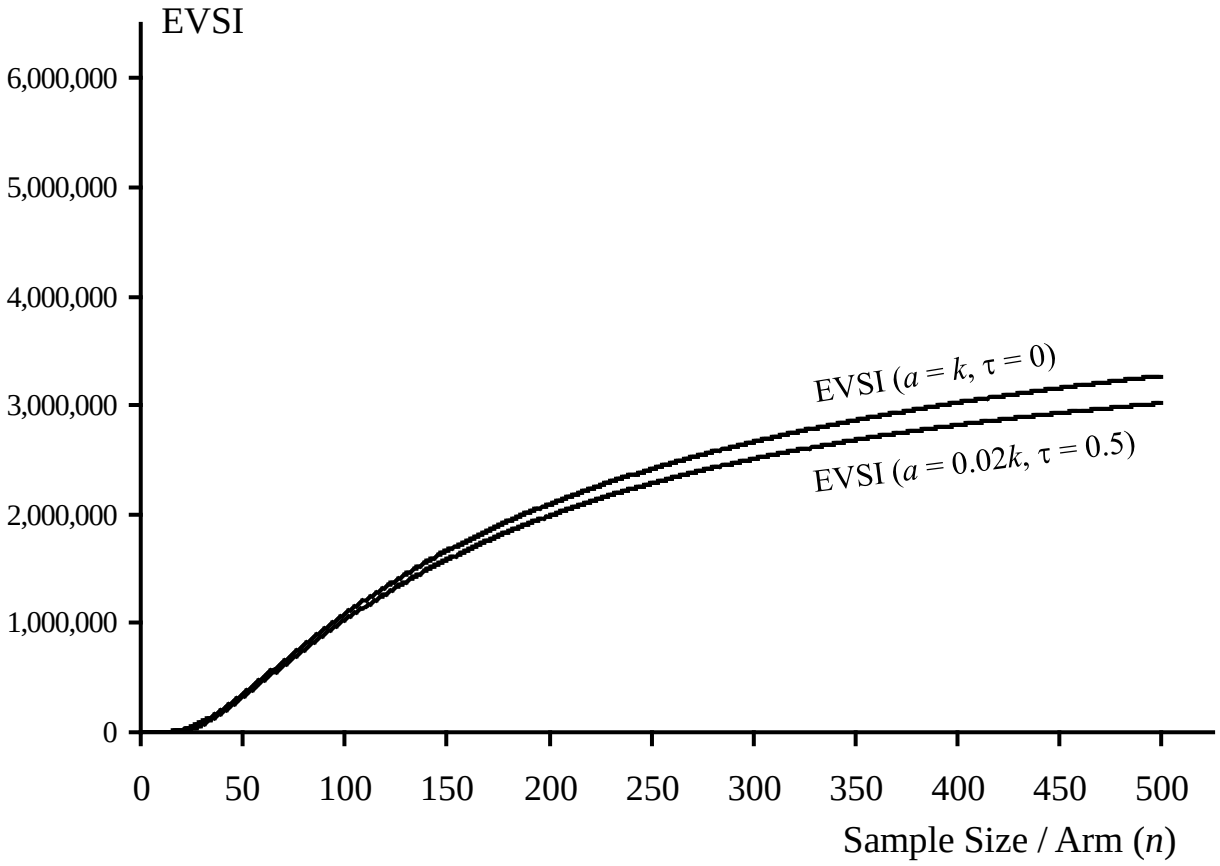

Figure 3.12 Expected value of sample information (EVSI), as a function of sample size (n) for the Early ECV Trial with the cost of adoption (C_A) equal to 5,000,000 and two sets of values for the accrual rate (a) and follow-up (τ)

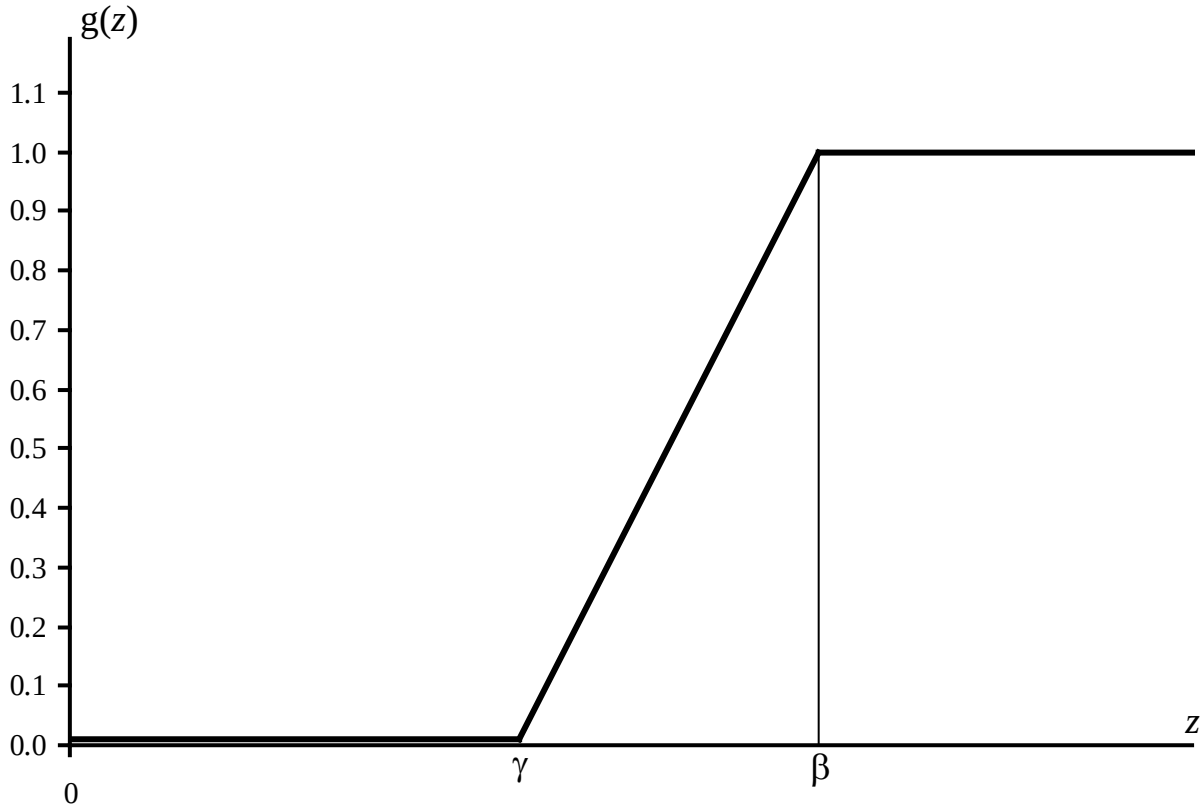

Figure 3.13 The probability that a future patient receives the new intervention as a function of the *z*-statistic

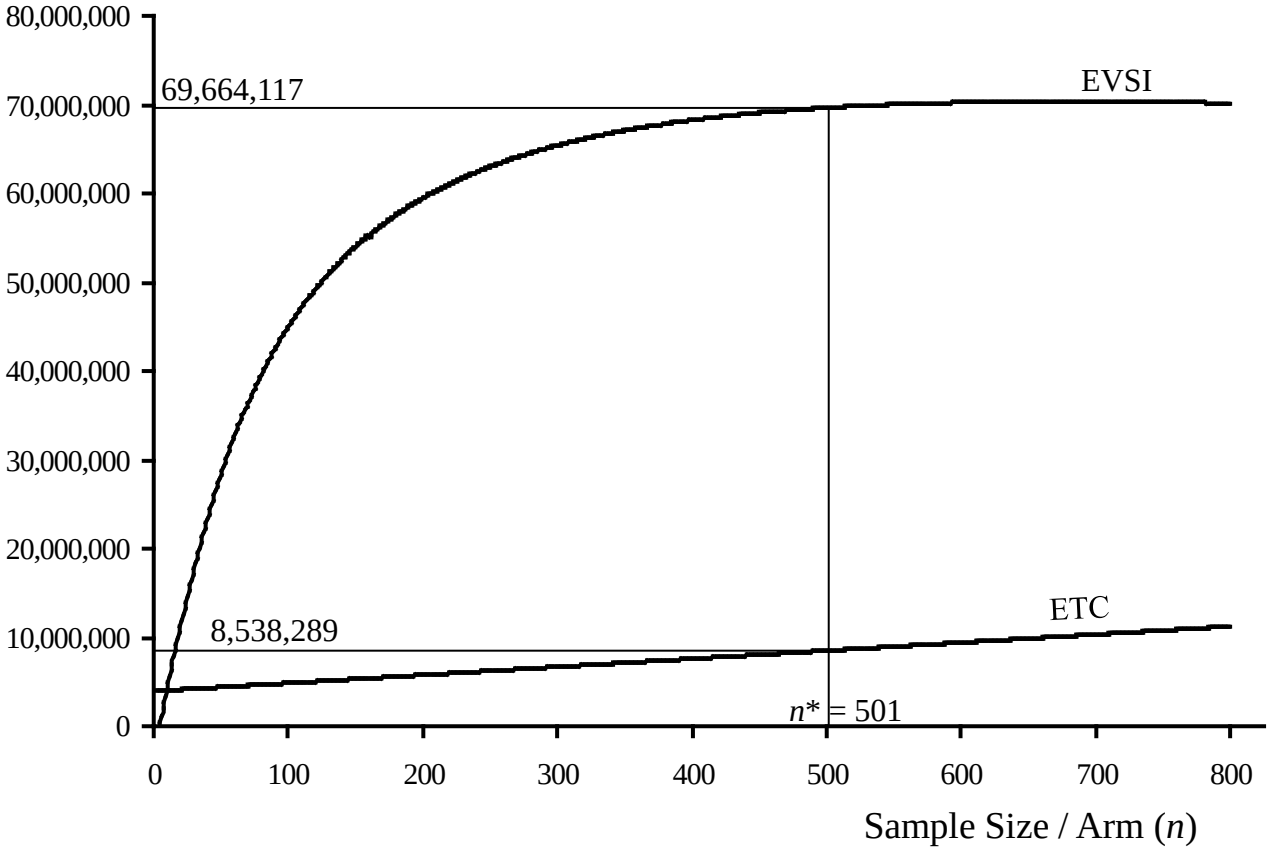

Figure 3.14 Expected value of sample information (EVSI) and expected total cost (ETC) as functions of sample size (n) for the CADET-Hp Trial, relaxing Assumption 4, with $\gamma = \Phi^{-1}(0.75) = 0.674$ and $\beta = \Phi^{-1}(0.99) = 2.33$, and assuming the cost of adoption (C_A) is 5,000,000, accrual rate (a) is 800 per year (*i.e.* $a = 0.01k$) and duration of follow-up (τ) is 1.5 years

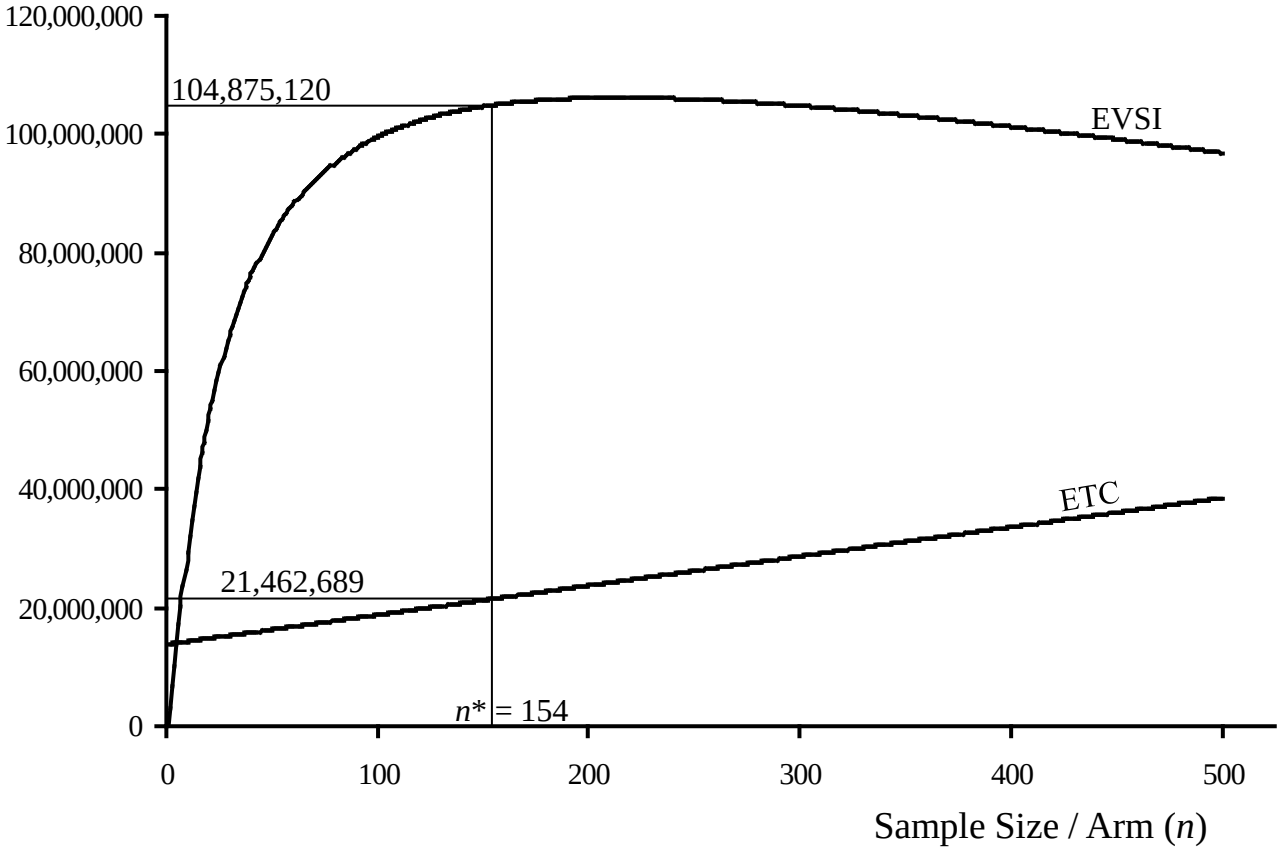

Figure 3.15 Expected value of sample information (EVSI) and expected total cost (ETC) as functions of sample size (n) for the Prostate Trial, relaxing Assumption 4, with $\gamma = \Phi^{-1}(0.75) = 0.674$ and $\beta = \Phi^{-1}(0.99) = 2.33$, and assuming the cost of adoption (C_A) is 5,000,000, accrual rate (a) is 250 per year (*i.e.* $a = 0.1k$) and duration of follow-up (τ) is 2 years

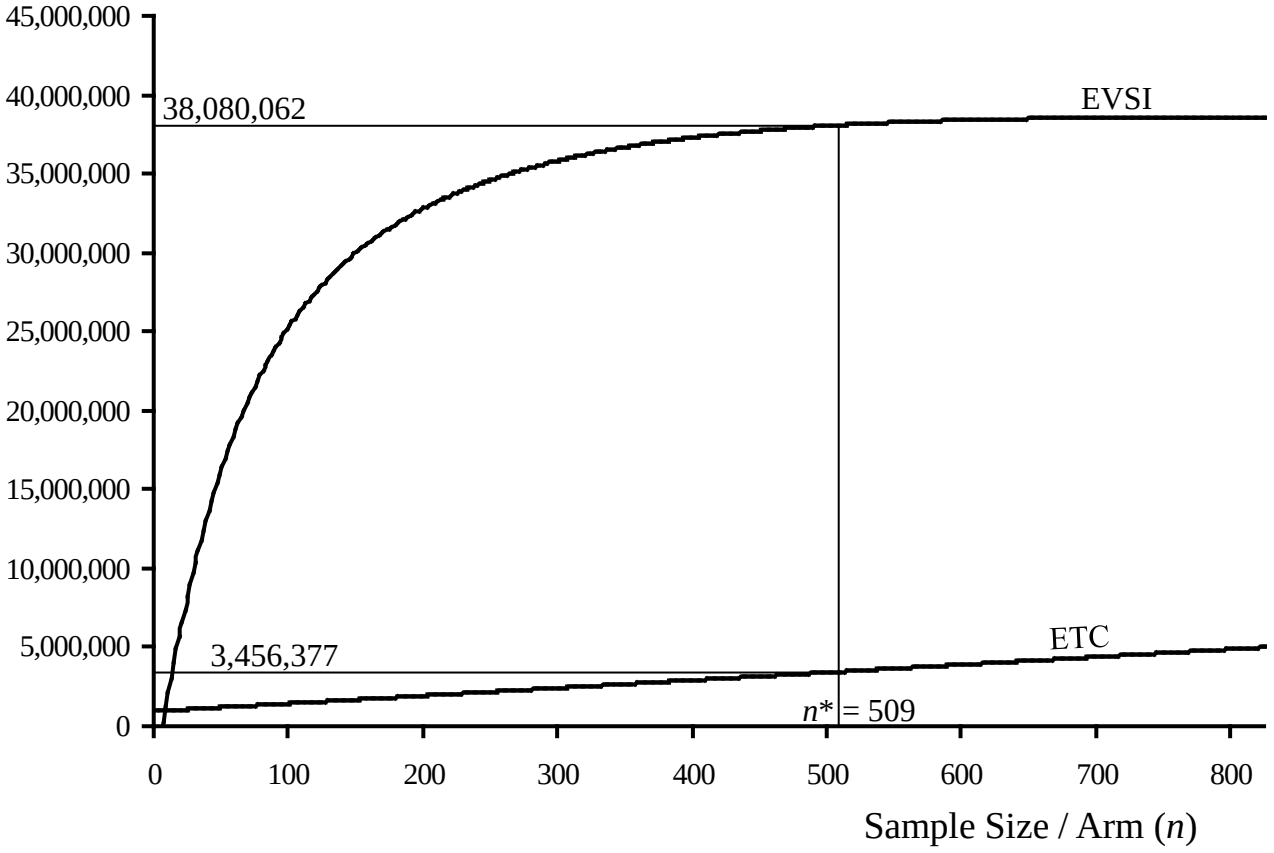

Figure 3.16 Expected value of sample information (EVSI) and expected total cost (ETC) as functions of sample size (n) for the Early ECV Trial, relaxing Assumption 4, with $\gamma = \Phi^{-1}(0.75) = 0.674$ and $\beta = \Phi^{-1}(0.99) = 2.33$, and assuming the cost of adoption (C_A) is 5,000,000, accrual rate (a) is 1000 per year (*i.e.* $a = 0.02k$) and duration of follow-up (τ) is 0.5 years