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On a simple quickest detection rule for health-care technology assessment

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On a simple quickest detection rule for health-care technology assessment

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Abstract. In this paper we propose a solution to the Bayesian problem of a decision maker who chooses, while observing trial evidence, an optimal stopping time at which either to invest in a newly developed health care technology or abandon research.

We show how optimal stopping boundaries can be computed as a function of the observed cumulative net benefit derived from the new health care technology. At the optimal stopping time, the decision taken is optimal and the decision maker either invest or abandon the technology with consequent health benefits to patients. The model takes into account the cost of decision errors and explicitly models these in the payoff to the heath care system. The implications in terms of opportunity costs of decisions taken at sub-optimal time is discussed and put in the value of information framework. In a case study it is shown that the proposed method, when compared with traditional ones, gives substantial economic gains both in terms of QALYs and reduced trial costs.

Keywords: Optimal stopping, HTA, Bayes, Value of Information
JEL codes:

1. introduction

Health technology assessment (HTA) decisions are based on evidence of relative costs and effectiveness of alternative interventions. Decision makers, when evidence suggests that the incremental net benefit of the new intervention is positive, are faced with the decision of whether to adopt the new intervention over the existing one or, given the uncertainty surrounding the evidence, wait for more information. When uncertainty about the net benefit of alternative treatments is present, there is a positive probability that the decision taken is wrong. Claxton (1999) argued that there are two conceptually separate but simultaneous decisions that must be made within a health care system: i) should a technology be adopted or reimbursed on the basis of existing evidence (and uncertainty surrounding outcomes and resources used) and ii) is further evidence required to support this adoption or reimbursement decision, and if existing evidence is deemed insufficient and further research is needed, what is the appropriate design for it ?

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In this paper we introduce a sequential value of information (S-VoI) Bayesian model for the evaluation of health care technologies. In our sequential approach the decision maker takes the reimbursement decision at a time when postponing the decision further in order to collect more evidence looses its value and, at the decision time, selects a strategy that gives maximal health benefit to patients, relative to the costs. Traditional sample size calculations for randomised clinical trials are based on arbitrary rules of inference such as probability of type I and type II errors. The values typically chosen for these error probabilities do not reflect the *cost* of making such error (William and Pinto, 2005).

In response, the value of information approach developed by Raiffa and Schlaifer (1961) and applied to HTA by Claxton and Posnett (1996) and Claxton (1999), proposes to assess whether more research is needed by weighing the value of new evidence with the cost of undertaking new research. In this framework, an *upper* estimate to the benefit of the healthcare technology is computed either analytically or by simulation and if the value of the upper estimate is greater than cost of new research additional evidence is required in order to take a decision.

It has been argued that in the absence of sunk cost or irreversibilities the decision to adopt a technology can be based on expected cost effectiveness. However, when reversing erroneous decisions is costly consideration of uncertainty become more important (Griffin et al., 2011).

The explicit inclusion of a sunk investment cost is important as in the absence of such costs decision makers could switch between technologies as new evidence becomes available. The implication of uncertainty and cost associated with the investment is that the decision makers need to be sufficiently confident that the selected policy is sustainable, as reversing the decision involves an economic cost. The presence of uncertainty and the degree of irreversibility mean that there is economic value in employing a modelling approach that has flexibility in the timing of a decision (Palmer and Smith, 2000). Palmer and Smith (2000) apply the Dixit and Pindyck (1994) real option approach to the adjustment (under a certain degree of irreversibility and uncertainty) of the incremental cost-effectiveness ratio for a drug. The conclusion is that for innovations with high uncertainty, large reversal cost and low opportunity costs of delay should be reimbursed at a lower rate than treatments with opposite characteristics.

The investment option approach has been implemented as a watchful waiting regime for diseases with slow progression (Driffield and Smith, 2007). In this case the patient management strategy involves postponing curative treatment. The patient undergoes a period of close observation and periodic tests that monitor the progression of the disease.

Forster and Pertile (2012) illustrated through a combined real-option and decision-theoretic approach to HTA that view adoption, treatment and research decision as a single economic project that existing models found in the HTA literature consider only some of the dimensions relevant to optimal decisions, thus leading to

potential efficiency losses in resources allocation. When adoption treatment and research decisions are viewed as a single economic project, the optimal rule must account for a number of dimensions such as i) the expected costs and benefits of additional research ii) the size of the treatment population over the stages of the project iii) flexibility and irreversibility of actions iv) the dynamic nature of the decision process.

More recently Pertile et al. (Forthcoming) discussed the use of real option as a way to view adoption, treatment and research decisions as a single economic project and argue that the dynamic approach to HTA can provide efficiency gains in resource allocation. However, presently the real option approach has not been implemented in any systematic way (Meltzer and Smith, 2012).

In this paper we introduce a sequential value of information (S-VoI) Bayesian model for the evaluation of health care technologies that allows to find an optimal stopping time at which the decision maker (i) knows that the value of further evidence is zero (i.e. zero value of waiting) and (ii) selects a strategy (either invest or abandon research) that gives maximal health benefit to patients. The S-VoI framework involves observing a trial and at each observation update a Bayesian posterior probability about the effectiveness of the healthcare technology. With only prior information the value of (further) information is a the maximum and it gradually reduces to zero as the trial continues.

In contrast to traditional approaches found in the literature the proposed framework introduces a dynamic sequential Bayesian approach to decision making under uncertainty when the objective of the DM is to maximise health benefit. The proposed model has a number of advantages over existing methodology (i) by finding an optimal stopping time the decision is taken at the point where there in no value for further waiting (ii) error probabilities can be computed and the decision maker can assess the cost of error (iii) sample size is reduced to the minimum necessary in order to make a decision with minimal error. As a consequence the proposed method maximises expected gains both in terms of health to the population and minimised trial costs. Traditional decision tools such as the expected value of perfect information (EVPI) are based on ex-ante calculation and therefore consider only the deterministic time dimension. The proposed methodology improves decision making by enlarging the strategy space to stopping times.

In the paper clinical evidence is modelled as a noisy process: we start with a discrete binomial tree and, by allowing the number of observation within a time interval to increase, on the limit the random variable's distribution is obtained reflecting the uncertainty surrounding each clinical outcome. The methodology presented in the paper is based upon the work of Shiryaev (1978) and Peskir and Shiryaev (2006). However, there are some crucial difference between our approach and Peskir and Shiryaev's work: (i) we maximise health benefits (i.e. monetary payoffs) rather than minimising a risk function which has Type I and Type II error probabilities as arguments (ii) we observe an arithmetic Brownian motion

and define the likelihood ratio process as the Radon-Nikodyn derivative and while Peskir and Shiryaev (2006) solve the risk function via the posterior probability process, in our approach, given that the likelihood ratio process follows a geometric Brownian motion, it is possible to formulate the solution of the optimal stopping problem in terms of the likelihood ratio (iii) we depart from the traditional rules of statistical inference by incorporating a rate of discounting for the expected payoffs; in this way the optimal stopping problem fully incorporates the economic nature of decision making in HTA.

The paper is organised as follows: section two gives some background, section three deals with the probabilistic environment required for sequential hypothesis testing, section four specifies the decision problem while section five presents the solution to the optimal stopping problem. Section six discusses results implications for the value of information and the irrelevance of inference and section seven presents a case study comparing the model decision with a traditional decision making approach for robot-assisted laparoscopic prostaectomy.

2. Clinical trials

The decision maker wishes to test whether a newly produced health technology has effectiveness greater than the minimum required for reimbursement. The decision maker wishes to test if the newly developed health-care technology exceeds the health care system threshold value λ and sets up a a set of tests aimed at uncovering whether the new technology provides the increased effectiveness.

Within such scenario we observe a sequence of outcomes from a clinical trial. The trial evolves through time and at regular points we observe an outcome representing information about the effectiveness of the healthcare technology.

The outcome of a clinical trial is measured in terms of the cumulative benefit to the population and is denoted by X_i for each step i. We model the uncertainty of the trial's outcome by allowing X_i to go either up by a factor u or down by a factor d.

Trials evidence is noisy, which implies that trend in the sequence of observed outcomes cannot be clearly observed. The two factors are given by

$$\begin{aligned} u &= \theta\mu dt + \sigma\sqrt{dt} \\ d &= \theta\mu dt - \sigma\sqrt{dt} \end{aligned} \tag{1}$$

where $\theta \in [0, 1]$ and dt is obtained by splitting an interval $[0, t]$ into n parts (i.e. $dt = t/n$) and μ is the value of the effectiveness threshold for the health care system.

Following the above we model the evolution of the health benefit as binomial tree. The random variable X_i can take values $X_{i-1} + u$ or $X_{i-1} + d$ with equal probability $p = 0.5$. The factor $\sigma\sqrt{dt}$ determines the size of the noise. The total

accumulated evidence after n steps is equal to $X_n = \sum_{i=1}^{n} X_i$. The sequence $X_0, X_1, X_2, \ldots$ describes a stochastic process, where X_0 is the initial value.

Denote $X_t = \lim_{n\to\infty} X_n(t)$ where the limit is understood to be in distribution and $n \to \infty$ implies $dt \downarrow 0$. According to the CLT, the distribution of X_t exists and is given by

$$X_t \sim N(\theta\mu t, \sigma^2 t)$$

implying that in the continuous time limit the process X_t follows the arithmetic Brownian motion

$$X_t = \theta\mu t + \sigma W_t, \tag{2}$$

where $(W_t)_{t\geq 0}$ is a standard Brownian motion. The decision maker problem is to find an optimal time at which to make an investment/abandonment decision about the new technology. If the trial's outcome supports the hypothesis H_1 that the effectiveness of the new technology is greater than the health care system minimum requirement there is investment, else, under the alternative H_0 research is abandoned and there is no adoption. The problem is then to sequentially test for $H_0 : \theta = 0$ vs $H_1 : \theta = 1$.

3. Sequential hypothesis testing

The sequential testing problem of two hypotheses is discussed in Shiryaev (1978) and Peskir and Shiryaev (2006). As in their setup we assume that what follows takes place on a probability space $(\Omega, \mathcal{F}, Q_p)$ and that we are given mutually independent random variables $\theta = \theta(\omega)$ and a standard Wiener process $W = (W_t)_{t\geq 0}$ under the probability measure Q_p.

The probability measure Q_p has the following structure

$$Q_p = pQ_1 + (1-p)Q_0 \tag{3}$$

for $p \in [0, 1]$.

Since we take a Bayesian viewpoint θ is considered a random variable taking the value of 1 or 0, and Q_p is such that $Q_p\{\theta = 1\} = p$ and $Q_p\{\theta = 0\} = 1 - p$. As outlined above, we observe a process $X = (X_t)_{t\geq 0}$ taking the form

$$X_t = \theta\mu t + \sigma W_t, \tag{4}$$

where $\mu > 0$ and $\sigma^2 > 0$ are given and fixed. The conditional distribution of X_t is

$$X_t \mid \ \theta \sim N(\mu\theta t, \sigma^2 t)$$

and thus p and $1-p$ play the role of a priori probability for the statistical hypotheses

$$H_1 : \ \theta = 1 \quad \text{and} \quad H_0 : \ \theta = 0 \tag{5}$$

respectively.

The process X_t generates the filtration $\mathcal{F}_t^X = \sigma(X_s : 0 \leq s \leq t)$, which is augmented with the Q_p-null sets. The likelihood ratio process Λ_t is defined as the Radon-Nikodym derivative

$$\Lambda_t = \frac{d(Q_1 \mid \mathcal{F}_t^X)}{d(Q_0 \mid \mathcal{F}_t^X)} \tag{6}$$

Proposition 3.1. *The likelihood ratio process admits the following representation:*

$$\Lambda_t = \exp\left(\frac{\mu}{\sigma^2}\left(X_t - \frac{\mu}{2}t\right)\right), \quad t \geq 0 \tag{7}$$

Proof. See Appendix □

Note that under hypotheses H_1 and H_0 the corresponding probability measures are Q_1 and Q_0 respectively. These measures are mutually singular since it holds that

$$\Lambda_t \ \longrightarrow \ \begin{cases} 0, & \text{a.s. under } Q_0 \\ \infty, & \text{a.s. under } Q_1 \end{cases} \qquad \text{as } t \to \infty$$

In other words, if we can observe $(X_t)_{t\geq 0}$ we can take these distributions apart from the limiting value of the likelihood ratio and decide between the two hypotheses.

The likelihood ratio process can be expressed as a stochastic differential equation (SDE).

Proposition 3.2. *The likelihood ratio process $(\Lambda_t)_{t\geq 0}$ solves the stochastic differential equation*

$$d\Lambda_t = \frac{\mu}{\sigma}\Lambda_t dW_t \tag{8}$$

Thus the likelihood ratio Λ follows a geometric Brownian motion on the state space $E = [0, \infty)$. In addition the process $(\Lambda_t)_{t\geq 0}$ is a martingale.

Proof. See Appendix □

Peskir and Shiryaev (2006) express the *posterior probability process* $\pi_t = Q_p(\theta = 1 \mid \mathcal{F}_t^X)$ as a function of the likelihood ratio process using Bayes rule:

$$\pi_t(\Lambda) = \left(\frac{p}{1-p}\Lambda_t\right) \Big/ \left(1 + \frac{p}{1-p}\Lambda_t\right). \tag{9}$$

Therefore, we can also write the likelihood ratio process as a function of the prior and the posterior probability process

$$\Lambda_t = \frac{\pi_t}{1-\pi_t}\frac{1-p}{p}. \tag{10}$$

In the remainer we will work with $(\Lambda_t)_{t\geq 0}$ or $(\pi_t)_{t\geq 0}$ interchangeably.

4. Decision problem

The observed process $(X_t)_{t\geq 0}$ represents the outcome of the randomised clinical trial (RCT) in terms of cumulative health benefit and expresses the extent of effectiveness of the health care technology. The decision maker seeks to test if the new technology is more effective than the minimum required by the heath care system. The value μ represents the health benefit derived from adopting this new technology. If the new technology is more effective than the threshold λ specified by the health care system the decision maker will invest into this new technology.

The decision maker values payoffs in terms of Quality of Adjusted Life Years (QALY). This is a standard measure[3] for health benefit in health care technology assessments and allows to attach a monetary value to the benefits derived from adopting the technology, conditional on the technology being effective.

We seek to establish an optimal stopping time τ at which the decision takes an investment or abandonment decision about the health care technology. In the model adoption/abandonment decisions are based upon the present net monetary value of QALY gained/lost.

When undertaking the investment the decision maker incurs a sunk cost I. In the investment equation (11) below P_1 represents the monetary benefit from adopting the new health care technology conditional on $\theta = 1$ and P_0 represents the monetary loss of adopting the technology conditional on $\theta = 0$. Thus, $-P_0$ is the opportunity cost of adopting the new technology when this is in fact not better than the standard care, in effect making a type I error.

[3]This is the standard in the UK. Other measures that are specific to the heath care technology can also be used. We use QALY to keep the analysis tractable in terms of monetary benefits/costs.

The table below summarises the various payoffs under investment and abandonment

	$\theta = 1$	$\theta = 0$
Investment	$P_1 > 0$	$P_0 > 0$
Abandonment	$-P_1$	0

The net present value of the investment, denoted by, F_I, is

$$\begin{aligned} F_I(\Lambda) &= \pi(\Lambda)P_1 - (1-\pi(\Lambda))P_0 - I \\ &= \left[\left(\frac{p}{1-p}\Lambda\right) \Big/ \left(1 + \frac{p}{1-p}\Lambda\right)\right] P_1 \\ &\quad - \left[\left(1 - \left(\frac{p}{1-p}\Lambda\right) \Big/ \left(1 + \frac{p}{1-p}\Lambda\right)\right)\right] P_0 - I, \end{aligned} \tag{11}$$

If research is abandoned there is no investment. In equation (12) below $-P_1$ describes the monetary loss incurred when research is abandoned conditional on $\theta = 1$, in effect making a type II error. It is assumed that forgone benefits and costs are the same. Therefore the expected payoff of abandoning, denoted by F_A is negative as it identifies the expected QALY loss due to keeping standard care when in fact the new health care technology is more effective. So,

$$F_A(\Lambda) = -\pi(\Lambda)P_1 = -\left[\left(\frac{p}{1-p}\Lambda\right) \Big/ \left(1 + \frac{p}{1-p}\Lambda\right)\right] P_1 \tag{12}$$

Figure (1) show F_I and F_A as function of the likelihood ratio. It can be noted that both payoffs are non-linear in Λ (even though they are affine in the posterior probability, π). Additionally the function F_A is concave and the function F_I is convex.

Assuming that all payoffs and trial costs are discounted at a rate $r > 0$ the decision maker needs to find a stopping time τ^* that solves the following optimal stopping problem

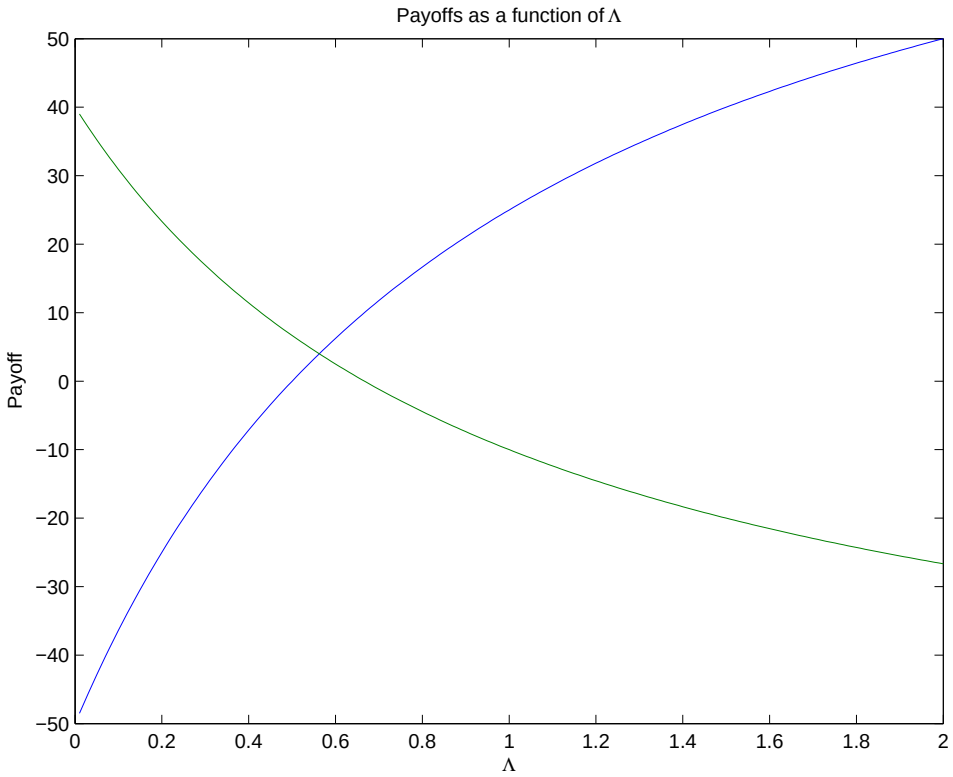


FIGURE 1. Payoffs of investment and abandonment as a function of the likelihood ratio, Λ

$$
\begin{aligned}
F^*(\Lambda) &= \sup_\tau \mathbb{E}_\Lambda \left[-c \int_0^\tau e^{-rt} dt + e^{-r\tau} \left(\max \left[F_I(\Lambda_\tau), F_A(\Lambda_\tau) \right] \right) \right] \\
&= -\frac{c}{r} + \sup_\tau \mathbb{E}_\Lambda \left[e^{-r\tau} \left[\max \left(F_I(\Lambda_\tau), F_A(\Lambda_\tau) \right) \right] + e^{-r\tau} \frac{c}{r} \right] \\
&= -\frac{c}{r} + \sup_\tau \begin{cases} \mathbb{E}_\Lambda[e^{-r\tau}(F_I(\Lambda_\tau) + \frac{c}{r})] & \text{if } \Lambda_\tau \geq \bar{\Lambda} \\ \mathbb{E}_\Lambda[e^{-r\tau}(F_A(\Lambda_\tau) + \frac{c}{r})] & \text{if } \Lambda_\tau < \bar{\Lambda} \end{cases}
\end{aligned}
$$

(13)

where $\bar{\Lambda}$ is the unique point for which $F_I(\bar{\Lambda}) = F_A(\bar{\Lambda})$. The term c represents the cost stream connected to running the trial. This includes sampling costs and the forgone health benefits associated with allocating resources to the trial rather than treating patients. These costs are incurred up to the time at which a decision of investment or abandonment is made.

The solution to (13) can intuitively be though of taking the following form. The state space will be split in 3 regions. The first one is a region around $\bar{\Lambda}$ where continuation of the trial is optimal, hence called *continuation region*, denoted by

$$C = \{\Lambda \in \mathbb{R}_+ | F^*(\Lambda) > \max(F_A(\Lambda), F_I(\Lambda))\}.$$

When Λ gets large enough we enter the *investment region*, where adoption of the health-care technology is optimal. This region is denoted by

$$D_I = \{\Lambda \in \mathbb{R}_+ | F^*(\Lambda) = F_I(\Lambda)\}.$$

Conversely, when Λ gets low enough, we enter the *abandonment region*, where abandoning the clinical trial is optimal. This region is denoted by

$$D_A = \{\Lambda \in \mathbb{R}_+ | F^*(\Lambda) = F_A(\Lambda)\}.$$

5. Problem Solution

The likelihood ratio process $(\Lambda_t)_{t\geq 0}$ follows a geometric Brownian motion for which it is possible to find a solution to the optimal stopping problem (13). At the heart of the approach lie functions of the form

$$\varphi(\Lambda) = A\Lambda^{\beta_1} + B\Lambda^{\beta_2}, \tag{14}$$

which solve the differential equation

$$\mathcal{A}_\Lambda \varphi = r\varphi. \tag{15}$$

Here $\mathcal{A}$ denotes the *generator* (or *characteristic operator*) of the process $(\Lambda_t)_{t\geq 0}$,

$$\mathcal{A}_\Lambda f = \frac{1}{2}\frac{\mu^2}{\sigma^2}\frac{\partial^2 f}{\partial \Lambda^2}, \tag{16}$$

A and B are arbitrary constants (to be determined as part of the solution) and $\beta_1 > 1$ and $\beta_2 < 0$ are the roots of the quadratic equation

$$\mathcal{Q}(\beta) = \frac{1}{2}\frac{\mu^2}{\sigma^2}\beta(\beta - 1) - r = 0. \tag{17}$$

The following proposition gives sufficient conditions for the existence of a solution to the optimal stopping problem (13). For each pair (Λ_A, Λ_I), $\Lambda_A < \bar{\Lambda} < \Lambda_I$, define the functions

$$\hat{\varphi}(\Lambda) = A\left(\Lambda^{\beta_1} - \Lambda_A^{\beta_1-\beta_2}\Lambda^{\beta_2}\right), \quad \text{and} \quad \check{\varphi}(\Lambda) = B\left(\Lambda^{\beta_2} - \Lambda_I^{\beta_2-\beta_1}\Lambda^{\beta_1}\right).$$

Then define the function φ by

$$\varphi(\Lambda) = \frac{\hat{\varphi}(\Lambda)}{\hat{\varphi}(\Lambda_I)}F_I(\Lambda_I) + \frac{\check{\varphi}(\Lambda)}{\check{\varphi}(\Lambda_A)}F_A(\Lambda_A).$$

It follows from Thijssen (2013, Proposition 6) that

$$\begin{aligned}\varphi(\Lambda) =&\mathbb{E}_\Lambda\left[e^{-r\hat{\tau}(\Lambda_I)}\middle|\hat{\tau}(\Lambda_I) < \check{\tau}(\Lambda_A)\right]Q_\Lambda(\hat{\tau}(\Lambda_I) < \check{\tau}(\Lambda_A))F_I(\Lambda_I)\\ &+\mathbb{E}_\Lambda\left[e^{-r\check{\tau}(\Lambda_A)}\middle|\hat{\tau}(\Lambda_I) > \check{\tau}(\Lambda_A)\right]Q_\Lambda(\hat{\tau}(\Lambda_I) > \check{\tau}(\Lambda_A))F_I(\Lambda_I),\end{aligned}$$

where

$$\hat{\tau}(\Lambda_I) = \inf\{t \geq 0 | \Lambda_t \geq \Lambda_I\},$$

is the first hitting time of Λ_I from below and

$$\check{\tau}(\Lambda_A) = \inf\{t \geq 0 | \Lambda_t \leq \Lambda_A\},$$

is the first hitting time of Λ_A from above.

So, if one defines the function

$$F(\Lambda) = \begin{cases} F_I(\Lambda) & \text{if } \Lambda \geq \bar{\Lambda} \\ F_A(\Lambda) & \text{if } \Lambda < \bar{\Lambda}, \end{cases}$$

and the stopping time $\tau^* = \hat{\tau}(\Lambda_I) \wedge \check{\tau}(\Lambda_A)$, then φ is simply the unconditional expectation of the present value of abandonment or investment, whichever threshold is reached first:

$$\varphi(\Lambda) = \mathbb{E}_\Lambda\left[e^{-r\tau^*}F(\Lambda_{\tau^*})\right].$$

Proposition 5.1. *Suppose that the system of equations*

$$-\frac{\hat{\varphi}'(\Lambda_I,\Lambda_A)}{\hat{\varphi}(\Lambda_I;\Lambda_A)}F_I(\Lambda_I) + F_I'(\Lambda_I) + \frac{\hat{\varphi}'(\Lambda_I,\Lambda_I)}{\hat{\varphi}(\Lambda_A;\Lambda_I)}F_A(\Lambda_A) \tag{18}$$

$$-\frac{\check{\varphi}'(\Lambda_A,\Lambda_I)}{\hat{\varphi}(\Lambda_A;\Lambda_I)}F_A(\Lambda_A) + F_A'(\Lambda_A) + \frac{\check{\varphi}'(\Lambda_A,\Lambda_A)}{\hat{\varphi}(\Lambda_I;\Lambda_A)}F_A(\Lambda_A) \tag{19}$$

has a solution (Λ_A, Λ_I), with $\Lambda_A < \bar{\Lambda} < \Lambda_I$. Suppose, in addition, that

(1) φ is strictly convex, and

(2) φ is more convex than F_A on $(0, \bar{\Lambda})$, i.e. $F_A''/F_A' > \varphi''/\varphi'$ on $(0, \bar{\Lambda})$.

Then the optimal stopping problem (13) *has the solution*

$$F^*(\Lambda) = \begin{cases} F_A(\Lambda) & \text{if } \Lambda \leq \Lambda_A \\ \frac{\hat{\varphi}(\Lambda)}{\hat{\varphi}(\Lambda_I)}F_I(\Lambda_I) + \frac{\check{\varphi}(\Lambda)}{\check{\varphi}(\Lambda_A)}F_A(\Lambda_A) & \text{if } \Lambda \in (\Lambda_A, \Lambda_I) \\ F_I(\Lambda) & \text{if } \Lambda \geq \Lambda_I, \end{cases} \tag{20}$$

and the optimal stopping time is $\tau^* = \hat{\tau}(\Lambda_I) \wedge \check{\tau}(\Lambda_A)$.

Proof. Note that

$$\mathcal{A}_\Lambda\hat{\varphi} - r\hat{\varphi} = \mathcal{A}_\Lambda\check{\varphi} - r\check{\varphi} = 0,$$

and that

$$\hat{\varphi}(\Lambda_A) = \check{\varphi}(\Lambda_I) = 0.$$

Also, since F_I is concave it is less convex than φ on $[\bar{\Lambda}, \infty)$. Therefore, the result follows immediately from Thijssen (2013, Proposition 7).

□

Figure 2 shows the solution for a case with cost of sampling equal to $c = 10$, a prior set to $p = 0.5$, discount rate of $r = 0.15$, payoff of investment $P_1 = 130$, Investment cost of $I = 60$ and losses from adoption when in fact the technology is not more effective than standard care of $P_0 = 60$. The process X_t has standard deviation $\sigma = 0.2$ and mean $\mu = 0.25$. For this base-case scenario it turns out that the conditions of Proposition 5.1 are satisfied for $p \in [0, 0.72]$. For higher values of p, F_A is more convex than φ, which implies that the value function F^* is no longer superharmonic. Since superharmonicity of the value function is a necessary condition for optimal stopping, no solution exists for high values of p. Essentially, for such values it is always optimal to adopt the technology immediately.

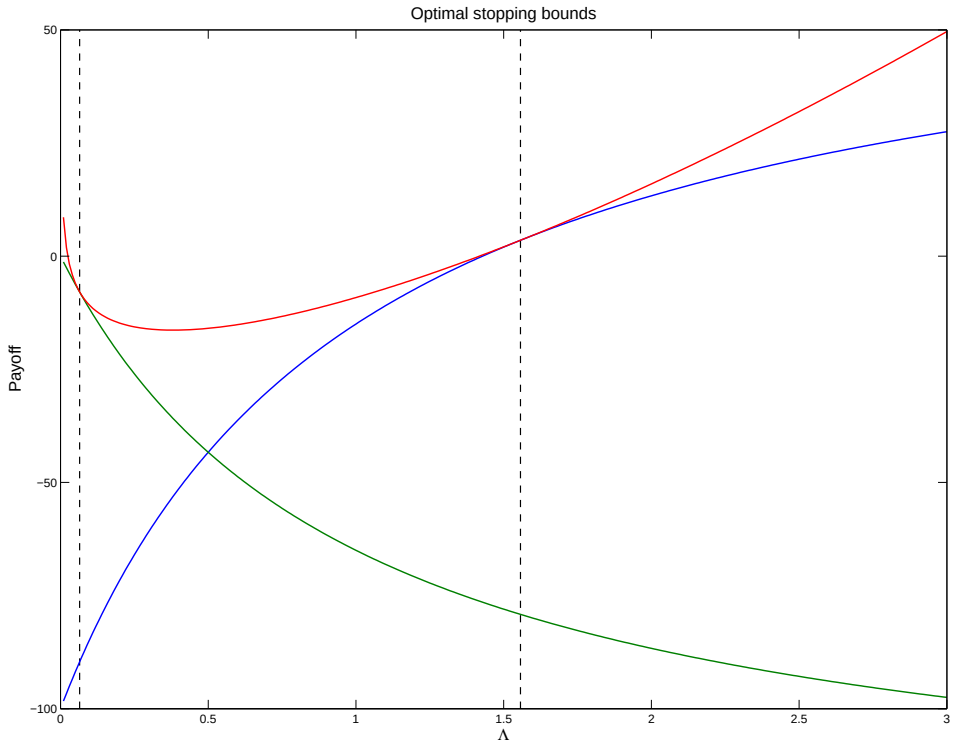


FIGURE 2. Value function F^* and bounds Λ_I, Λ_A for the case with $c = 10$, $p = .5$, $r = .15$, $P_1 = 130$, $P_0 = 60$, $I = 50$, $\mu = .25$, and $\sigma = .2$.

Figure 3 shows some simulated sample paths for the likelihood ratio process and some hypothetical bounds. Different values for μ and σ in the likelihood ratio process lead to different hitting times.

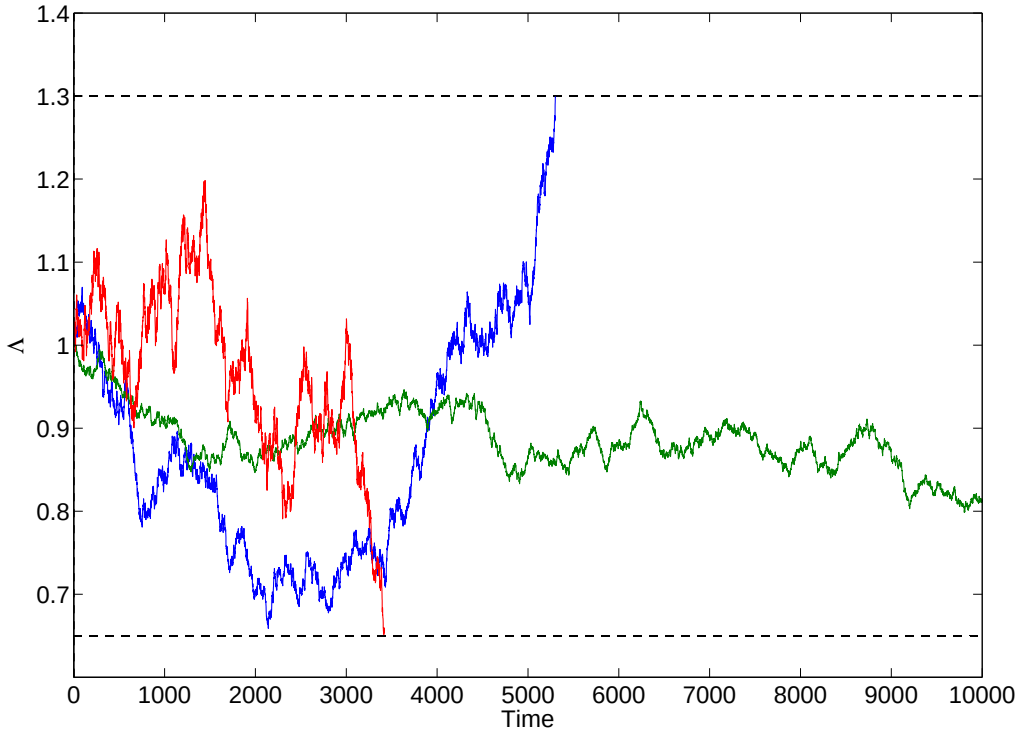


FIGURE 3. Some sample paths of the likelihood ratio process. Parameters are similar as for Figure 2.

6. Analysis of the model

It has been argued (see Claxton (1999)) that classical statistical inference (and its Bayesian counterpart) is arbitrary and irrelevant to clinical decision making. He suggests to use the expected value of perfect information (EVPI) as a way to deal with uncertainty in health-care technology (HCT) assessment. The EVPI is given by the probability that a decision based on mean net benefit is incorrect (i.e. not cost effective) and the size of the opportunity loss of this wrong decision. It should be noted however, that the EVPI represents the *maximum* value of additional information (clinical research) and it is used to decide whether to fund more

research. In particular, if the estimated costs of additional research (e.g. another trial) are higher than the EVPI, proposed research should not be undertaken and a decision for adoption by the health care system can be made on existing evidence.

This approach involves checking if sufficient information has been gathered and belongs to a framework where there is irreversibility of investment and where the decision maker is confronted with a 'invest now or never' type of decision (Pratt et al., 1995). Where reversing policy is costly and the decision maker has the possibility of deferring decision a sequential approach arises naturally.

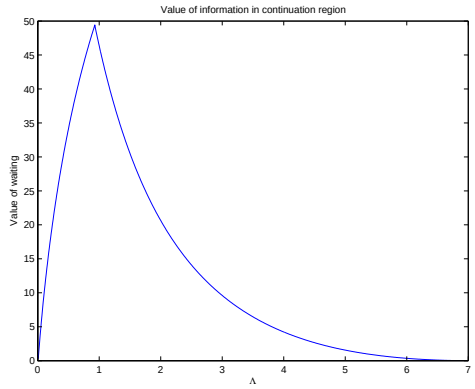
6.1. **Option value and waiting for more information.** In between the thresholds the solution (20) gives the value of the investment / abandonment option *at any point* in the trial. When this value is compared to the investment/abandonment payoff, equation (20) reflects the value of waiting for more evidence (i.e. the value of information or the opportunity cost of investment with current evidence).

Figure 4b shows the function $\varphi(\Lambda)$ for different values of σ. It can be noted that the value of the investment option (i.e. the option of investing now or investing later with more evidence) increases with σ. As uncertainty increases, there is more to be gained in waiting, and Figure 4b shows that it is possible to quantify the waiting value for different levels of uncertainty. Figure 2 shows the investment option value against the investment payoff $F_I(\Lambda)$ and $F_A(\Lambda)$. As the value of waiting for more evidence decreases, at the investment point Λ_I, the value of the investment option $\varphi(\Lambda)$ and the payoff $F_I(\Lambda)$ coincide and the value of waiting goes to zero. Similarly, on the other side, when the value of waiting for more evidence decreases, at the abandonment point Λ_A, the value of the abandonment option $\varphi(\Lambda)$ and the payoff $F_A(\Lambda)$ coincide and the value of waiting goes to zero.

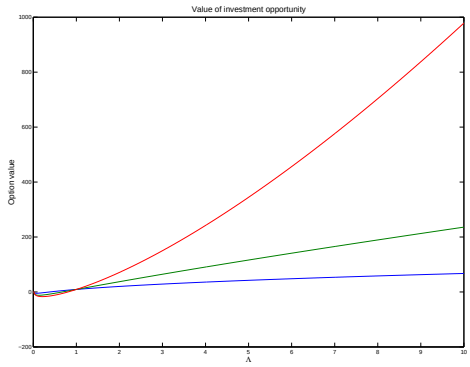
Figure 4a shows the value of waiting (i.e. value of information) at different values for Λ. The value of information is at the highest around the initial point $\Lambda = 1$ as at this point the evidence in favour of H_0 and H_1 are equal as there is only prior information available. As Λ increases there is less and less value in waiting and this reaches zero at the optimal adoption/abandonment time τ^*. Outside of the threshold region waiting has no value and the decision maker should act immediately .

6.2. **Posterior probability.** In the health technology assessment literature one of the relevant decision tools is the probability of a drug being cost-effective (i.e. net benefit to be greater than the cost-effectiveness threshold).

While the standard approach is to compute the probability via simulation methods, in our proposed model the posterior probability $\pi(\Lambda)$ of making a gain of P_1 and the probability $(1 - \pi)$ of making loss P_0, can be obtained by looking at the posterior value at the decision bound. In this way it is possible to assess the probability for the heath-care technology to provide a gain P_1 or a loss P_0, in turn



(A) Value of information at different Λ



(B) $\varphi(\Lambda)$ for different values of σ

FIGURE 4. Value of information

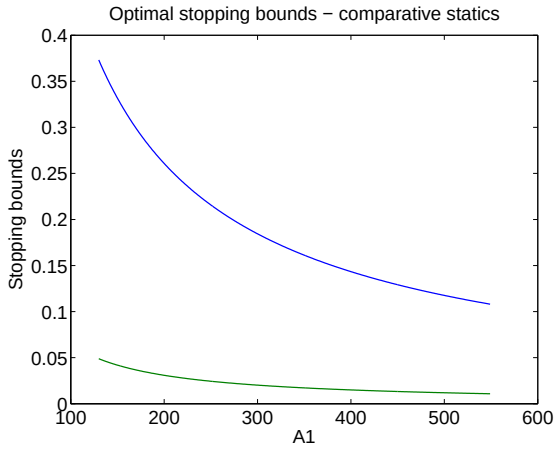
allowing to determine the probability for the heath-care technology to be cost effective.

6.3. **Comparative statics.** It is possible to explore the impact of varying parameters on the decision bounds. In this section we explore the comparative statics of the payoffs P_1, P_0, parameters μ, σ, cost c and the discount rate r. The prior has been set to a neutral value of $1/2$ for all cases.

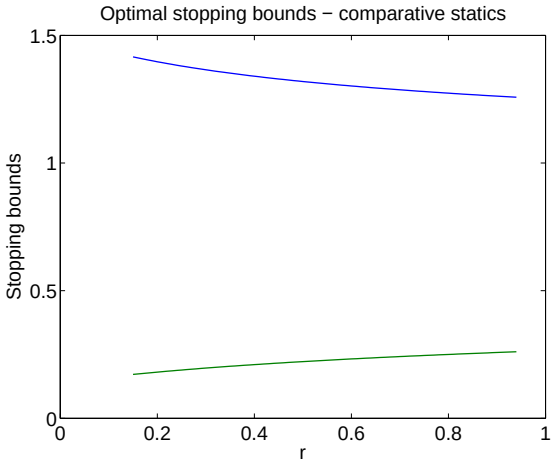
Figure (5a) show the variation in bounds due to changing the payoff P_1. The payoff P_1 enters both the adoption and the abandonment payoff consequently affecting both upper and lower bounds. As the benefit from adoption increases the loss from not adopting a beneficial technology increases accordingly. It should be noted that as the payoff P_1 increases the upper bound eventually goes below the starting value for the likelihood ratio and the posterior process. As one would expect, holding P_0 and the required initial investment costs constant while increasing substantially the payoff P_1, due to the large gain to the healthcare system, above a certain threshold value it becomes optimal to invest immediately.

Figure (5b) show the bounds variation due to changing the loss P_0. This loss enters the adoption payoff and thus affects only the upper bound. When the loss P_0 increases the adoption payoff decreases forcing the upper bound upwards to reflect the penalty brought in by a larger decision error. A large negative payoff to the healthcare system makes adoption more difficult, as one would expect.

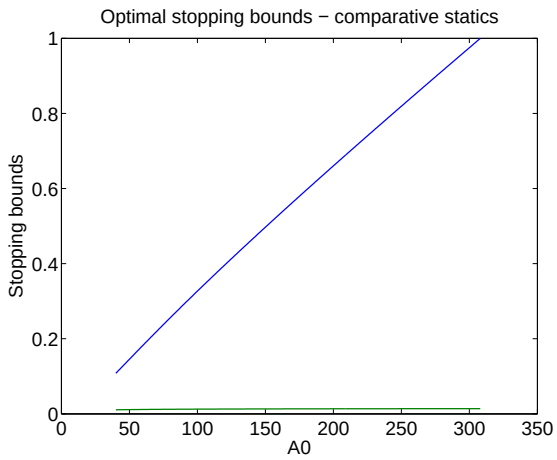
Figure (5c) show the bounds variation due to changing the drift μ. It should be noted that increasing μ and holding σ constant implies that the volatility of the likelihood process given by μ/σ increases. As the volatility of the likelihood process increases the probability of hitting the bounds increase and thus the bounds widen allowing for the larger fluctuations. With a healthcare technology that has high



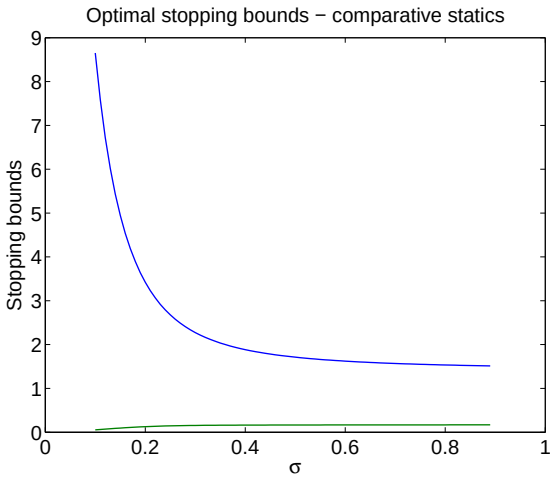
(A) Comparative statics for P_1



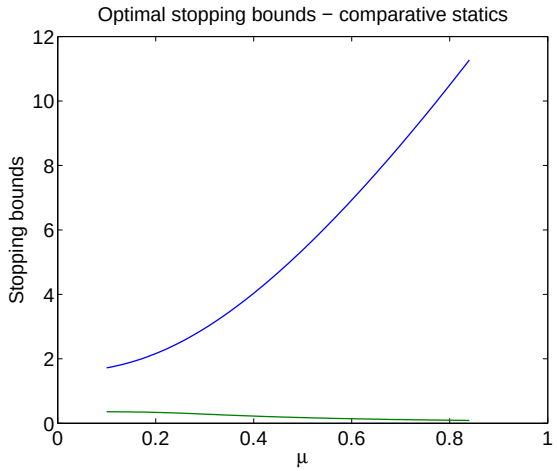
(D) Comparative statics for r



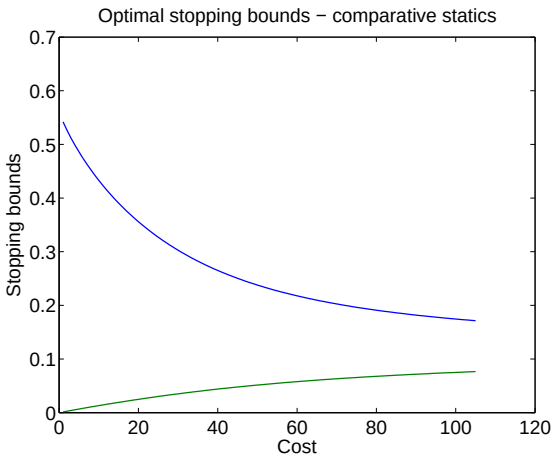
(B) Comparative statics for P_0



(E) Comparative statics for σ

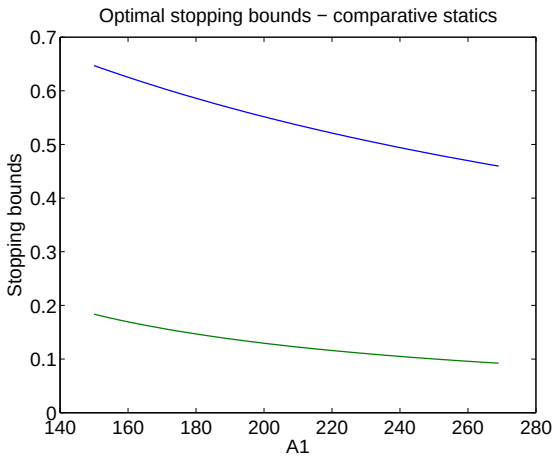


(C) Comparative statics for μ

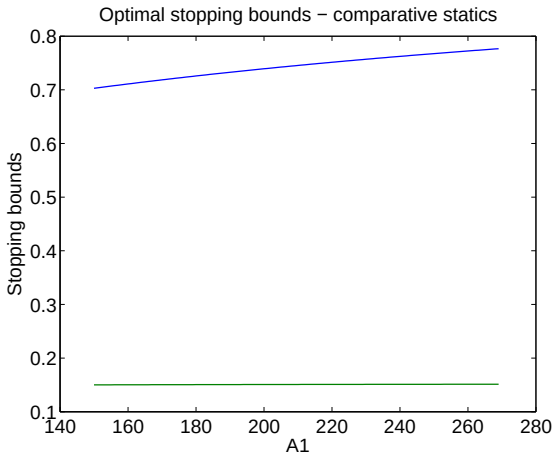


(F) Comparative statics for C

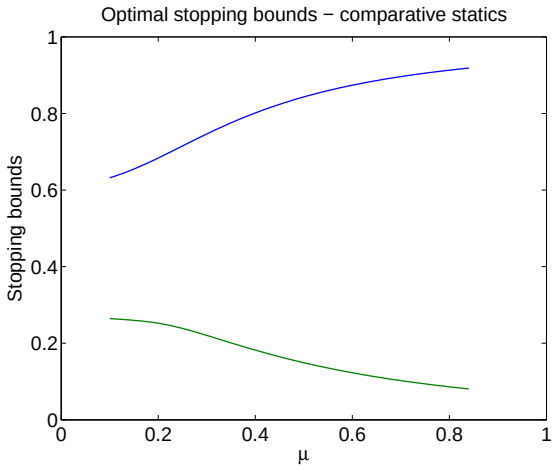
FIGURE 5. Bounds variation for parameter change in terms of the likelihood ratio.



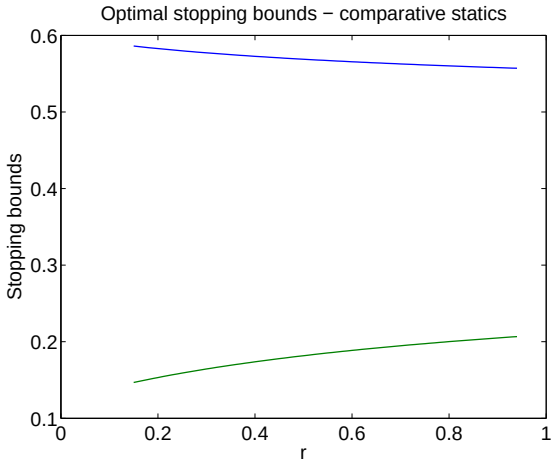
(A) Comparative statics for P_1



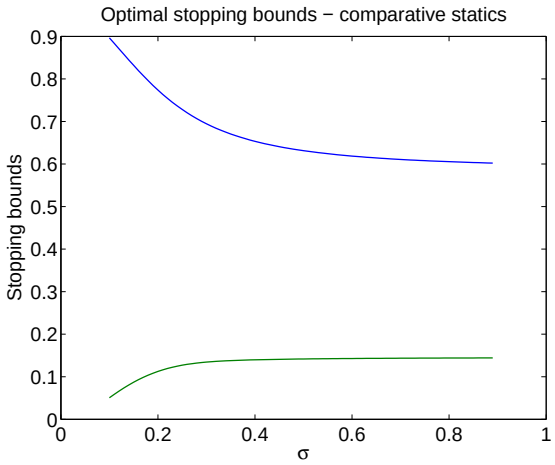
(B) Comparative statics for P_0



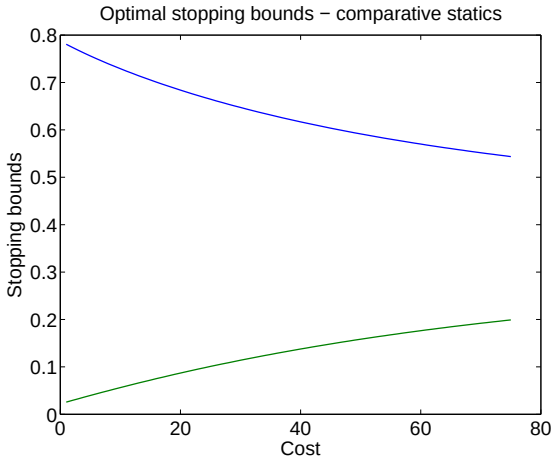
(C) Comparative statics for μ



(D) Comparative statics for r



(E) Comparative statics for σ



(F) Comparative statics for C

FIGURE 6. Bounds variation for parameter change in terms of the posterior (π) .

benefits for the health care system the likelihood ratio becomes more volatile and the larger bounds allow for the wider fluctuation of the likelihood ratio process.

Figure (5e) show the bounds variation due to changing the volatility σ. As for μ, σ also determines the likelihood process volatility. In this case increasing σ leads to a reduction in the likelihood process' volatility. The likelihood ratio will oscillate less, thus having a lower chance of hitting that is reflected by the narrower bounds. As with the mean effectiveness, σ affects the volatility of the likelihood process. A healthcare technology that has high uncertainty about its effectiveness will cause the likelihood ratio to decrease its volatility with consequently narrower bounds.

Figure (5d) show the bounds variation due to changing the discount rate r. The discount rate r enters the payoff functions and a high r decreases the present value of both the benefit and loss. Keeping all other parameters constant, increasing the discount rate r has the effect of correspondingly decreasing both upper and lower bounds. The discount rate affects project's present value and a high discount rate will decrease payoff values affecting decision bounds.

Figure (5f) show the bounds variation due to changing the sampling costs C. Increasing the cost of sampling leads to narrower decision bounds. When the cost of conducting the trial are high the decision bounds become narrower forcing an earlier decision.

7. Some Probabilities

7.1. **Probability of adoption/abandonment.** We compute the probability of hitting the adoption or investment bound. The expected discount factor, under the posterior probability $Q_{\pi(\Lambda)}$ (below simply noted as Q_Λ) is given by

$$\begin{aligned} \mathbb{E}_\Lambda[e^{-r\tau^*}] &= \mathbb{E}_\Lambda[e^{-r\check{\tau}(\Lambda_A)} \mid \tau^* = \check{\tau}(\Lambda_A)]Q_\Lambda(\tau^* = \tau(\Lambda_A)) \\ &+ \mathbb{E}_\Lambda[e^{-r\hat{\tau}(\Lambda_I)} \mid \tau^* = \hat{\tau}(\Lambda_I)]Q_\Lambda(\tau^* = \tau(\Lambda_I)). \\ &= \frac{\hat{\varphi}(\Lambda)}{\hat{\varphi}(\Lambda_I)} + \frac{\check{\varphi}(\Lambda)}{\check{\varphi}(\Lambda_I)} \end{aligned} \tag{21}$$

Using the fact that

$$Q_\Lambda(\tau^* = \check{\tau}(\Lambda_A)) = 1 - Q_\Lambda(\tau^* = \hat{\tau}(\Lambda_I))$$

and writing the discount factors in (21) as

$$\mathbb{E}_\Lambda[e^{-r\check{\tau}(\Lambda_A)} \mid \tau^* = \check{\tau}(\Lambda_A)] = \left(\frac{\Lambda}{\Lambda_A}\right)^{\beta_2}$$

and

$$\mathbb{E}_\Lambda[e^{-r\hat{\tau}(\Lambda_I)} \mid \tau^* = \hat{\tau}(\Lambda_I)] = \left(\frac{\Lambda}{\Lambda_I}\right)^{\beta_1}$$

we obtain

$$Q_\Lambda(\tau^* = \check{\tau}(\Lambda_A)) = \frac{\mathbb{E}_\Lambda[e^{-r\tau^*}] - \left(\frac{\Lambda}{\Lambda_I}\right)^{\beta_1}}{\left[\left(\frac{\Lambda}{\Lambda_A}\right)^{\beta_2} - \left(\frac{\Lambda}{\Lambda_I}\right)^{\beta_1}\right]}. \tag{22}$$

7.2. **Error Probabilities.** We can compute the *ex ante* probabilities that we make an erroneous decision. These probabilities can be thought of as the Bayesian sequential equivalents of the probabilities of Type I and Type II errors. One has to be careful, however, in interpreting these probabilities as such, because the approach to inference here is decidedly non-frequentist.

For abandonment and adoption bounds Λ_A and Λ_I, respectively, define the probabilities

$$\alpha = Q_0\left(\tau^* = \hat{\tau}(\Lambda_I)\right), \quad \text{and} \quad \beta = Q_1\left(\tau^* = \check{\tau}(\Lambda_A)\right).$$

From Poor and Hadjiliadis (2009) it now follows that

$$\alpha = \frac{1 - \Lambda_A}{\Lambda_I - \Lambda_A} \quad \text{and} \quad \beta = \Lambda_A \frac{\Lambda_I - \Lambda_A}{\Lambda_I - \Lambda_A} \tag{23}$$

8. Case study: standard vs robot-assisted laparoscopic prostaectomy

In this section we apply the model developed above to the HTA of robot-assisted and standard laparoscopic prostaectomy from the perspective of the UK national health service using data from a published study (Close et al., 2013). The application of the model developed above to this case study if for illustration purposes only and aims at showing the value that our approach can have for HTA.

Standard laparoscopic prostaectomy and robot-assisted laparoscopic prostaectomy are favoured over the open technique as these cause less bleeding and allow for a quicker return to activities. Robot assisted laparoscopic prostaectomy is increasingly used compared to standard laparoscopic technique. However, the high costs has led authorities to question the value of robotic-assisted procedure to patients and the health care system.

Many of the existing cost studies on prostaectomy techniques do not include cost effectiveness analysis that takes into account the value of relative gains that men achieve if a particular technique has better outcomes.

Close et al. (2013)conduct a cost-utility analysis for two indipendent cohort of 5000 men undertaking respectively robotic or laparoscopic prostaectomy over 10 years. They report that the use of robotic prostaectomy was on average £1412

TABLE 1. Cost-effectivness of standard vs robot-assisted laparoscopi prostaectomy

Parameter	**Description**	**Source**	**Value**
$E_1 - E_0$	Incremental QALY gain	Close *et al*	0.08 QALY
$C_1 - C_0$	Incremental cost	Close *et al*	£1412
σ	Std. deviation	Close *et al*	£1071
μ	Incremental QALY gain	Set as $NIMB > 0$	£1413
p	Prior	Assumed	0.5
r	Discount rate	Close *et al*	3.5%
c	Cost of sampling	Assumed	£10
I	Close *et al*	0	
n	Number of patients	Close *et al*	10000

more costly than laparoscopic prostaectomy and that it was also more effective with mean gain of QALY of 0.08 (95% CI,0.01-0.15) over 10 years for a case load of 200 patients per year. As we take the point of view of the UK health service, we seek to establish if robot prostaectomy is cost-effective at the UK NICE threshold of $\lambda = £30,000$ at such threshold value the mean gain is of £2400.

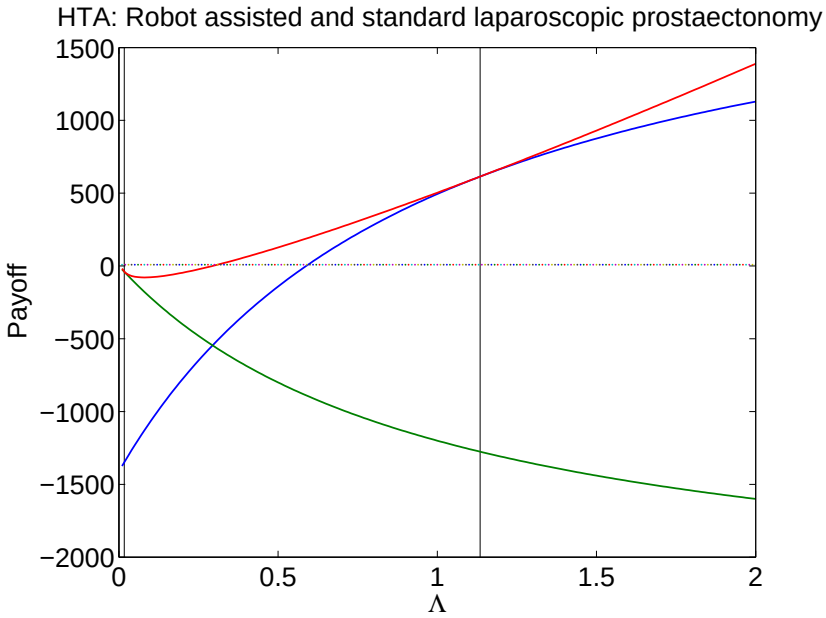
Confidence intervals give a standard deviation σ of £1071 indicating considerable uncertainty. We set the minimum required μ for adoption by the national health service to £1413, just greater than the incremental cost of the robot assisted surgery. In other words we set μ such that the net incremental mean benefit[4] is positive, ensuring a positive gain to the heath service if the technology is adopted. The adoption excess benefit P_1 is set for each patient at £2400 and the cost of wrongly adopting the technology P_0 is set equal to the incremental cost at £1412. The prior is set to a neutral value of $p = 0.5$, the discount rate is set to $r = 0.035$ and initial investment I is assumed to be zero. Having no information on the cost of following patients and reporting the outcome of the procedure, we assume sampling costs for each observation c to be £50. Parameters are summarised in Table 1.

Figure 7a shows the optimal stopping bounds obtained with such values. The upper bound is $\Lambda_I = 1.30$ and the lower bound $\Lambda_A = 0.0035$. Correspondingly these bounds in terms of the posterior are $\pi_I = 0.56$ and $\pi_A = 0.003$.

The value of the likelihood ratio at the point estimate is $\Lambda = 8.24$ and $\pi = 0.89$, much higher than the required adoption bounds. These value suggest that there is enough evidence to make a investment decision.

8.1. **Probability of adoption/abandonment.** Using formulas in section (7) it is possible to compute the probability of abandonment and the probability of

[4] $NIMB = (E_1 - E_0)\lambda - (C_1 - C_0)$



(A) Optimal stopping bounds for Close et al. (2013)

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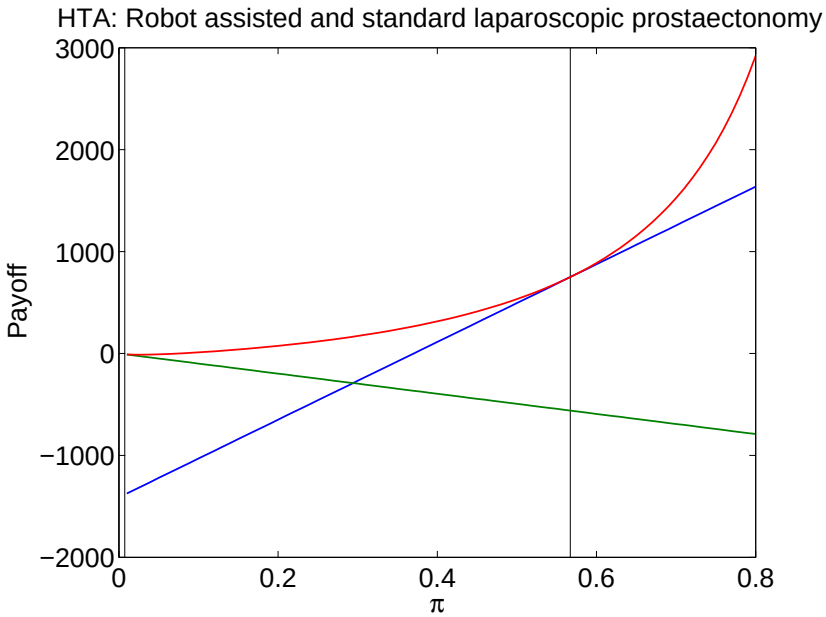

(B) Optimal stopping bounds (π) for Close et al. (2013).

investment. The probability of abandonment $P_A(\tau^* = \check{\tau}(\Lambda_A)) = 0.69$ and the probability of investment $P_I(\tau^* = \hat{\tau}(\Lambda_I)) = 0.31$.

The probability of committing a type I error $\alpha = 0.77$ while the probability of committing a type II error is $\beta = 0.0035$. These results seem to go against

standard practice of keeping Type I error probabilities low. The reason for a high α and low β in this model is as follows. A Type I error implies that one adopts the technology if it's not effective. This may be costly due to the additional cost of the technology, but does not harm patients and, therefore, has no costs in terms of health benefits. A Type II error, however, implies not treating with a superior technology. This error carries with it large opportunity costs: the health benefits that *would have been* realised if the technology had been accepted. The model, therefore, does what one would expect: it keeps β low. As a consequence α will be large.

9. Conclusion

The Bayesian Sequential Value of Information presented in this paper brings together statistical and economic modelling, allowing for flexible decisions that account for irreversibility costs. The model provides rules that allow the decision maker to take the decision that maximise health benefits and reduce losses on the health care system.

Our novel approach to healthcare technology assessment makes use of Bayes rule in order to compute the posterior probability for the effectiveness of the healthcare technology at each point during the randomised control trial. Decision bounds are a function of uncertainty and prior information and follow from the parameters of the model. Decisions are taken at the moment in which the net benefit of the healthcare technology hits a pre-specified threshold value. At this optimal stopping time there is not more gain to be made by further waiting.

Appendix

A. Proof of Lemma 3.1

The Wiener process X_t under P_1 and under P_0 takes the form

$$dX_t = \sigma dW_t \quad P_p = P_0$$

and

$$dX_t = \theta\mu dt + \sigma dW_t \quad P_p = P_1$$

Girsanov's Theorem allows for the change of measure P_1 to P_0.

Define $u(t,\omega) = \frac{-\mu}{\sigma}$ and

$$\begin{aligned}
\Lambda_t(t,\omega) &= exp\left(\frac{\mu}{\sigma}\int_0^t dW_s - \frac{\mu^2}{2\sigma^2}\int_0^t ds\right) \\
&= exp\left(\frac{\mu}{\sigma}\int_0^t \sigma dW_s - \frac{\mu}{2\sigma^2}t\right) \\
&= exp\left(\frac{\mu}{\sigma^2}\left[\int_0^t \sigma dW_s - \frac{\mu}{2}t\right]\right) \\
&= exp\left(\frac{\mu}{\sigma^2}\left(X_t - \frac{\mu}{2}t\right)\right)
\end{aligned}$$

Also, the $(\Lambda_t)_{t\geq 0}$ process is a martingale.

$$\begin{aligned}
\mathbb{E}_{P_0}[\Lambda_t \mid \mathcal{F}_s] &= \mathbb{E}_{P_0}[e^{\frac{\mu}{\sigma^2}(X_t - \frac{\mu}{2}t)} \mid \mathcal{F}_s] \\
&= \mathbb{E}_{P_0}[e^{\frac{\mu}{\sigma^2}[(X_t - X_s) - \frac{\mu}{2}(t-s)]} e^{\frac{\mu}{\sigma^2}(X_s - \frac{\mu}{2}s)} \mid \mathcal{F}_s] \\
&= \Lambda_s \mathbb{E}_{P_0}[e^{\frac{\mu}{\sigma^2}[(X_t - X_s) - \frac{\mu}{2}(t-s)]} \mid \mathcal{F}_s] \\
&= \Lambda_s e^{-\frac{\mu^2}{2\sigma^2}(t-s)} \mathbb{E}_{P_0}[e^{\frac{\mu}{\sigma^2}(X_t - X_s)}] \\
&= \Lambda_s e^{-\frac{\mu^2}{2\sigma^2}(t-s)} e^{\frac{\mu^2}{2\sigma^2}(t-s)} \\
&= \Lambda_s \qquad \text{(A.1)}
\end{aligned}$$

■

B. Proof of Lemma 3.2

Apply Ito's lemma to $\Lambda_t = \exp\left(\frac{\mu}{\sigma}\left(X_t - \frac{\mu}{2}t\right)\right)$ gives

$$\begin{aligned} d\Lambda_t &= \frac{\partial \Lambda}{\partial t}dt + \frac{\partial \Lambda}{\partial x}dx + \frac{1}{2}\frac{\partial^2 \Lambda}{\partial x^2}dx^2 \\ &= -\frac{1}{2}\frac{\mu^2}{\sigma^2}\Lambda_t + \frac{\mu}{\sigma^2}\Lambda_t \sigma dW_t + \frac{1}{2}\frac{\mu^2}{\sigma^4}\Lambda_t \sigma_t^2 dt \\ &= \frac{\mu}{\sigma}\Lambda dW_t \end{aligned}$$

■

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