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Value of information and pricing new healthcare interventions

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Abstract

Previous application of value-of-information methods to optimal clinical trial design have predominantly taken a societal decision-making perspective, implicitly assuming that healthcare costs are covered through public expenditure and trial research is funded by government or donation-based philanthropic agencies. In this paper, we consider the interaction between interrelated perspectives of a societal decision maker (e.g. the National Institute for Health and Clinical Excellence [NICE] in the UK) charged with the responsibility for approving new health interventions for reimbursement and the company that holds the patent for a new intervention. We establish optimal decision making from societal and company perspectives, allowing for trade-offs between the value and cost of research and the price of the new intervention. Given the current level of evidence, there exists a maximum (threshold) price acceptable to the decision maker. Submission for approval with prices above this threshold will be refused.

Given the current level of evidence and the decision maker's threshold price, there exists a minimum (threshold) price acceptable to the company. If the decision maker's threshold price exceeds the company's, then current evidence is sufficient since any price between the thresholds is acceptable to both. On the other hand, if the decision maker's threshold price is lower than the company's, then no price is acceptable to both and the company's optimal strategy is to commission additional research. The methods are illustrated using a recent example from the literature.

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Value of Information and Pricing New Health Care Interventions

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Abstract

Previous application of value of information methods to optimal clinical trial design have predominantly taken a societal decision making perspective, implicitly assuming that health care costs are covered through public expenditure and trial research is funded by government or donation-based philanthropic agencies. In this paper, we consider the interaction between interrelated perspectives of a societal decision maker (*e.g.* NICE in the UK) charged with the responsibility for approving new health interventions for reimbursement and the company that holds the patent for a new intervention. We establish optimal decision making from societal and company perspectives, allowing for tradeoffs between the value and cost of research and the price of the new intervention.

Given the current level of evidence, there exists a maximum (threshold) price acceptable to the decision maker. Submission for approval with prices above this threshold will be refused. Given the current level of evidence and the decision maker's threshold price, there exists a minimum (threshold) price acceptable to the company. If the decision maker's threshold price exceeds the company's then current evidence is sufficient since any price between the thresholds is acceptable to both. On the other hand, if the decision maker's threshold price is lower than the company's then no price is acceptable to both and the company's optimal strategy is to commission additional research. The methods are illustrated using a recent example from the literature.

1. Introduction

Recently, there has been much interest in using value of information methods to determine optimal sample size for randomized clinical trials[1-28]. Value of information methods are proposed as an alternative to traditional frequentist approaches based on tests of hypotheses and arbitrarily determined quantities, such as the type I and II error probabilities and the smallest clinically important difference. Using value of information methods, the sample size that maximizes the expected net gain can be determined, where the expected net gain is the difference between the expected value of the (sample) information provided by a trial and the expected total cost. If the maximum expected net gain is negative, decision making can be made based on current information, adopting the new intervention if, and only if, the expected incremental net benefit is positive. On the other hand, if the maximum expected net gain is positive then a trial is worthwhile, with the optimal sample size being that which maximizes the expected net gain.

Taking a societal perspective, where health care costs are covered through public expenditure and trial research is funded by government or donation-based philanthropic agencies, Willan and Pinto[20] provide a solution under restrictive assumptions. Subsequent papers[6-9,23,24] provide solutions with the assumptions relaxed.

Industry perspectives can also been taken. Gittins and Pezeshk[11,12], Kikuchi, Pezeshk and Gittins[16], Pezeshk and Gittins[17] and Pezeshk[18] use a decision theoretic approach to determine optimal sample size under the assumptions that the number of patients receiving the new intervention is a function of the observed size of the treatment effect and the associated statistical significance. Willan[22] provides a solution for optimal sample size from an industrial

perspective, in which the value of the information from a new trial relates to the expected increase in the probability of regulatory approval and market share.

The purpose of this paper is to establish a value of information framework for exploring the interaction between the interrelated perspectives of a societal decision maker (*e.g.* NICE in the UK) and a company that submits evidence in support of a new intervention for the purposes of supporting the approval of the new intervention for reimbursement. As discussed by Eckermann and Willan[6,8] and Griffin *et al*.[29], approving a new intervention based solely on the criterion that the current estimated of incremental net benefit is positive ignores the uncertainty associated with the estimate.

From a societal perspective it will be optimal to undertake further research if the expected value of information from such research exceeds the expected opportunity cost. Current evidence is sufficient (*i.e.*, adopting now is optimal) only if for any potential research design the expected cost of research exceeds its expected value. Expected value of research falls as positive INB becomes more certain, or as the price of the new intervention is reduced. The expected opportunity cost of research increases as expected INB increases or as price reduces. Consequently, given the option for the decision maker to request additional research, our framework can be used to establish a stricter criterion for current evidence of incremental net benefit and price at which adopting is optimal, allowing for the uncertainty associated with current evidence.

Assuming that the decision maker and the company are acting optimally and are risk neutral, the framework can also be used to establish the maximum (threshold) price acceptable to the decision maker and a minimum (threshold) price acceptable to the company.

If the decision maker's threshold price exceeds the company's then the current evidence is sufficient for decision making since any price between the two thresholds is acceptable to both. On the other hand, if the company's threshold price exceeds the decision maker's then no price is acceptable to both and, as we subsequently demonstrate, the company's optimal strategy is to collect additional evidence prior to submitting for approval.

Consider the perspective of a societal decision maker who is charged with the responsibility of deciding whether or not to add a new intervention to the formulary for reimbursement at a given price. The decision maker can accept the new intervention, reject it outright or request additional research. To the decision maker, the value of additional research is the expected reduction in opportunity loss from making decisions in the face of uncertain incremental net benefit. However, assuming it is infeasible to accept the new intervention while research is undertaken, there is also an expected opportunity cost to the decision maker of delaying the decision, since denying the new intervention to patients until the evidence is updated forgoes expected incremental net benefit of the new intervention. We show that as the price of the new intervention increases, the value of additional research increases, while the opportunity cost decreases. Consequently, there exists a threshold price for the societal decision maker, above which the expected value of sample information from additional evidence exceeds its expected cost, *i.e.* the expected net gain from additional evidence is positive.

The other perspective to consider is that of the company requesting that the intervention be added to the formulary for reimbursement. The company incurs a financial cost of conducting further research and an opportunity cost from revenue foregone while the research is conducted. The value of additional research, from a company perspective, relates to expected increase in the decision maker's threshold price associated with a reduction in uncertainty and, as we subsequently show, decreases as the price increases. We also show that as the price increases, the cost in foregone revenue increases. Hence, as the price of the intervention increases over the range for which expected net benefit is positive, the expected net gain of additional evidence from the company's perspective decreases due to both increasing cost and falling value. Therefore, for the company, there exists a threshold price below which the value of new evidence exceeds its cost, *i.e.* the expected net gain is positive, making additional research worthwhile.

If the company's maximum (with respect to research design) expected net gain is positive with the price set at the decision maker's threshold (or, equivalently, if the company's threshold price exceeds that of the decision maker) then a further research is optimal from the company's perspective. That is, where there is positive expected net gain of further research for the company with the price set low enough to be acceptable to the decision maker, no common price exists at which both parties would prefer to add the intervention to the formulary. Conversely, if the company's maximum expected net gain is negative with the price set to the decision maker's threshold price then it will be optimal to submit a proposal for approval at the decision maker's threshold price rather than commission further research.

Methods for establishing the societal decision maker's and the company's threshold prices, given current evidence and expected actions and allowing for their interaction, are provided in Section 2 and illustrated in Section 3 with an example taken from a recent publication. Extensions to the model to account for partial revenue per patient, discounting and cost of adopting the new intervention are established in Section 4. Section 5 discusses implications of the findings for pricing and reimbursement in processes of health technology assessment within a jurisdiction. Further research on optimal solutions across jurisdictions and the importance of appropriate threshold value for health outcomes in the determination of incremental net benefit are also discussed.

2. Methods

2.1. Incremental net benefit and expected value of information

Consider the cost-effectiveness assessment of a new health care intervention, referred to as *Treatment* (*T*), versus the appropriate comparator, referred to as *Standard* (*S*). Let e_{ji}, $j = T, S$ be the (clinical) effectiveness for patient *i* receiving intervention *j* and let c_{ji}, $j = T, S$ be the total health care cost for patient *i* receiving intervention *j*. The cost c_{Ti} includes the price of the new intervention for patients receiving *Treatment*. Let $e_j = \mathrm{E}(e_{ji})$, $c_j = \mathrm{E}(c_{ji})$, $\Delta_e = e_T - e_S$ and $\Delta_c = c_T - c_S$, where $\mathrm{E}(\cdot)$ is the expected value function. If λ is the decision maker's threshold value for a unit of effectiveness, then $b \equiv \Delta_e\lambda - \Delta_c$ is the incremental net benefit. Now, if we separate out the price of the new intervention from other costs in the notation we can explore the consequences of allowing it to vary. If the per-patient price of the new intervention (*i.e.* revenue per patient to the company) equals *R*, then $c_{Ti}^- \equiv c_{Ti} - R$ is the health care cost for patient *i* receiving *Treatment*, excluding the price of the new intervention, where price is assumed to be the same for all patients. Further, let $c_T^- = c_T - R$, $\Delta_c^- = \Delta_c - R$ and $b^- = \Delta_e\lambda - \Delta_c^-$. We assume that the decision maker's threshold value is known to the company.

Suppose that a societal decision maker is charged with the task of deciding whether or not to approve a submission from a company to have the new intervention added to the formulary for reimbursement at a price of *R*. The current evidence in support of the new intervention, relative to the appropriate comparator, is expressed as a normal probability distribution function for the incremental net benefit, with mean b_0 and variance v_0. That is, $b_0 = \Delta_{e0}\lambda - \Delta_{c0}$ and $v_0 = v_{e0}\lambda^2 + v_{c0} - 2\lambda c_{ec0}$, where, based on current evidence, Δ_{e0} and Δ_{c0} are the means and v_{e0}

and v_{c0} the variance of Δ_e and Δ_c, respectively, and c_{ec0} is the covariance between Δ_e and Δ_c. Let $b_0^- = b_0 + R$. The assumption of normality is applied to incremental net benefit and not to the individual patient observations, as illustrated in the Section 3 example, where binomial and gamma models are assumed for effectiveness and cost, respectively. If $b_0 \le 0$, it is optimal for the decision maker to refuse approval or request a price reduction. If $b_0 > 0$, potentially optimal decisions are to approve reimbursement, request a price reduction prior to approval, or request additional research.

Assuming that the additional evidence is from a randomized clinical trial in which the cost and effectiveness are observed on *n* patients per arm (*Treatment* and *Standard*), the expected value of sample information ($EVSI^d$) of the trial to the societal decision maker is given by Willan and Pinto[20] and Eckermann and Willan[7] as

$$\mathrm{EVSI}^d(n) = N(n)\{\mathcal{D} - \mathcal{F}(n)\},$$

where

$N(n)$ is the number of patients to whom the decision applies;

$$\mathcal{D} = \sqrt{v_0/(2\pi)}\exp\left[-b_0^2/(2v_0)\right] - b_0\left[\Phi(-b_0/\sqrt{v_0}) - I\left(b_0 \le 0\right)\right];$$

$$\begin{aligned}\mathcal{F}(n) = {} & \sqrt{v_0/(2\pi)}\,\sigma_+^2\exp\left(-b_0^2/2v_0\right)\Big/(nv) \\ & - b_0\Phi\left(-b_0/\sqrt{v_0}\right) + v_0^{3/2}\exp\left(-b_0^2/2v_0\right)\Big/\left(v\sqrt{2\pi}\right) \\ & + b_0\Phi\left(-b_0\sqrt{v}/v_0\right) - v_0\exp\left(-b_0^2 v/(2v_0^2)\right)\Big/\sqrt{2\pi v};\end{aligned}$$

$\sigma_+^2 = \mathrm{V}(e_{Ti}\lambda - c_{Ti}) + \mathrm{V}(e_{Si}\lambda - c_{Si})$ is the sum over treatment groups of the between-patient variance of net benefit;

$v = v_0 + \sigma_+^2/n$;

$\Phi(\cdot)$ is the cumulative distribution function for the standard normal random variable; and $I(\cdot)$ is the indicator function.

The terms $\mathcal{D}$ and $\mathcal{F}(n)$ are the pre- and post-trial per-patient expected opportunity loss, respectively. Their difference is the amount by which the per-patient expected opportunity loss is reduced by the trial evidence and, when multiplied by the number of patients who can benefit, yields the expected value of sample information. Where $b_0 > 0,$ the difference $\mathcal{D} - \mathcal{F}(n),$ which is the per-patient expected value of sample information ($\text{EVSI}_{\text{pp}}(n)$), simplifies to

$$\text{EVSI}_{\text{pp}}(n) = v_0 \exp\left(-b_0^2 v / (2v_0^2)\right) \Big/ \sqrt{2\pi v} - b_0 \Phi\left(-b_0 \sqrt{v} / v_0\right).$$

If *h*, expressed in years, is the time horizon for the new intervention, *k* the annual incidence of the health condition in question, *a* the annual patient accrual rate and τ, expressed in years, the duration from when the last patient is recruited until the evidence is updated, then, as given in Eckermann and Willan[7], the number of patients to whom the decision applies is given by $N(n) = \{h - (\tau + 2n/a)\} k.$

If the trial is undertaken by the company, the only cost to the decision maker is the expected opportunity cost (EOC^d) incurred by those patients who are denied the intervention while the trial is performed and the evidence is updated, given by Eckermann and Willan[7] as

$$\text{EOC}^d(n) = \{(\tau + 2n/a)k - n\} b_0 .$$

Therefore, the expected net gain (ENG^d) to the decision maker of another trial of *n* patients per arm, defined as $\text{EVSI}^d - \text{EOC}^d$, is given by

$$\mathrm{ENG}^{d}(n) = \{h - (\tau + 2n/a)\}\, k\, \{\mathcal{D} - \mathcal{F}(n)\} - \{(\tau + 2n/a)k - n\}\, b_0 . \qquad (1)$$

Let $\mathrm{ENG}^{d}(n)$ be maximized at n_R^*. If $\mathrm{ENG}^{d}(n_R^*)$ is positive then the optimal decision is to delay approval and request another trial with n_R^* patients per arm. On the other hand, if $\mathrm{ENG}^{d}(n_R^*)$ is negative then, if b_0 is positive, the optimal decision is to approve the intervention for reimbursement at a price of *R*. The subscript *R* in the notation for optimal sample size is a reminder that the optimal sample size depends on the submitted price.

Griffin *et al*.[29] provide a criterion similar to Equation 1 for choosing between adoption and rejection which allows for uncertainty as to whether or not additional research will be conducted. However, they use the current expected value of perfect information (EVPI), rather than the expected value of sample information, as the value of additional research. EVPI does not allow for optimal decision making, since it overestimates value of research and has no defined relationship to EVSI, let alone ENG which is required f optimal decision making. Hence, Eckermann, Karnon and Willan (2010) show that use of EVPI in prioritizing research can easily lead to support for research with negative ENG, while also failing to support research with high research return despite small EVPI.

2.2. Decision maker's threshold price

By substituting $b_0^- - R$ for b_0, where $b_0 > 0$, the expected net gain can be seen as a function of *n* and *R*, given as

$$\begin{aligned}\mathrm{ENG}^d(n,R) &= \mathrm{EVSI}^d(n,R) - \mathrm{EOC}^d(n,R) \\ &= \{h - (\tau + 2n/a)\}\, k\, \mathrm{EVSI}_{\mathrm{pp}}(n,R) - \{(\tau + 2n/a)k - n\}(b_0^- - R),\end{aligned} \tag{2}$$

where

$$\mathrm{EVSI}_{\mathrm{pp}}(n,R) = v_0 \exp\left(-(b_0^- - R)^2 v/(2v_0^2)\right)\Big/\sqrt{2\pi v} - (b_0^- - R)\Phi\left(-(b_0^- - R)\sqrt{v}/v_0\right).$$

Since, if all other variables are held constant, the EVSI^d is an increasing function of R and EOC^d is a decreasing function of R, there exists a decision maker's threshold price, denoted $\tilde{R}_0^d$, such that if $R < \tilde{R}_0^d$, $\mathrm{ENG}^d(n_R^*)$ is negative, while if $R > \tilde{R}_0^d$, $\mathrm{ENG}^d(n_R^*)$ is positive. Therefore, if $R \le \tilde{R}_0^d$, the expected net gain for another trial is negative, regardless of its size, and the optimal decision for the decision maker is to approve the intervention for reimbursement at a price of R. On the other hand, if $R > \tilde{R}_0^d$, the optimal decision is to request evidence from another trial, with n_R^* per arm, or to request a reduction in the price to no more than $\tilde{R}_0^d$.

Since $\tilde{R}_0^d$ is the maximum price acceptable to the decision maker then $b_0^d = b_0^- - \tilde{R}_0^d$ is the minimum acceptable incremental net benefit, referred to as the threshold incremental net benefit. Therefore, because of the uncertainty, the criterion for adoption should be $b_0 > b_0^d$ rather than $b_0 > 0,$ where b_0 is the estimate of incremental net benefit based on some price R, *i.e.* $b_0 = b_0^- - R.$ Note that $b_0 > b_0^d$ is equivalent to $R < \tilde{R}_0^d$.

2.3. Company's threshold Price

The maximum price the company can receive following a trial of *m* patients per arm is $\tilde{R}_m^d$, the post-trial threshold price for the decision maker. Therefore, for a company facing a price of *R*, the expected value of the sample information is the increase in the post-trial revenue per patient, given by

$$\text{EVSI}^c(m,R) = \{h - (\tau + 2m/a)\}\, k \left\{ \text{E}(\tilde{R}_m^d) - R \right\},$$

which is simply the post-trial time horizon multiplied by the incidence and the expected increase in price. All other variables constant, $\text{EVSI}^c(m,R)$ is a decreasing function of *R*.

The financial cost to the company of performing a trial with *m* patients per arm is given by $C_f + 2mC_v$, where C_f is the fixed cost and C_v the per-patient variable cost of performing the trial. The expected opportunity cost of foregone revenue experience by the company, facing a price of *R*, is given by $(\tau + 2m/a)kR$, which is simply the duration of the trial multiplied by the incidence and the price. Therefore, the expected total cost for the company (ETC^c) is given by

$$\text{ETC}^c(m,R) = C_f + 2mC_v + (\tau + 2m/a)kR\,.$$

All other variables held constant, $\text{ETC}^c(m,R)$ is an increasing function of *R*. The expected net gain to the company (ENG^c) of a trial with *m* patients per arm is given by

$$\begin{aligned}
\text{ENG}^c(m,R) &= \text{EVSI}^c(m,R) - \text{ETC}^c(m,R) \\
&= \{h - (\tau + 2m/a)\}\, k \left\{ \text{E}(\tilde{R}_m^d) - R \right\} - \left\{ C_f + 2mC_v + (\tau + 2m/a)kR \right\} \\
&= \{h - (\tau + 2m/a)\}\, k\, \text{E}(\tilde{R}_m^d) - hkR - (C_f + 2mC_v)\,.
\end{aligned}$$

Let $\mathrm{ENG}^c(m,R)$ be maximized at m_R^*. Since $\mathrm{EVSI}^c(m_R^*,R)$ is a decreasing function of *R* and $\mathrm{ETC}^c(m_R^*,R)$ is a increasing function of *R*, there exists a company threshold price, denoted $\tilde{R}_0^c$, such that if $R<\tilde{R}_0^c$, $\mathrm{ENG}^c(m_R^*,R)$ is positive, while if $R>\tilde{R}_0^c$, $\mathrm{ENG}^c(m_R^*,R)$ is negative. The threshold price can be determined by setting $\mathrm{ENG}^c(m_R^*,R)=0$ and solving for *R*, yielding

$$\tilde{R}_0^c=\frac{\left\{h-(\tau+2m_R^*/a)\right\}k\,\mathrm{E}(\tilde{R}^d_{m_R^*})-(C_f+2m_R^*C_v)}{hk}.$$

The threshold price $\tilde{R}_0^c$ depends on *R*, the price the company faces, and, substituting the maximum pre-trial price the company faces, *i.e.* $\tilde{R}_0^d$, the company threshold price is

$$\tilde{R}_0^c=\frac{\left\{h-(\tau+2m^*_{\tilde{R}_0^d}/a)\right\}k\,\mathrm{E}(\tilde{R}^d_{m^*_{\tilde{R}_0^d}})-(C_f+2m^*_{\tilde{R}_0^d}C_v)}{hk}. \qquad (3)$$

If the decision maker's threshold price is greater than the company's, *i.e.* $\tilde{R}_0^d>\tilde{R}_0^c$, the maximum expected net gain for another trial is negative and the optimal decision for the company is to submit for approval at an expected price of $\tilde{R}_0^d$. On the other hand, if $\tilde{R}_0^d<\tilde{R}_0^c$, the maximum expected net gain for another trial is positive and the optimal decision for the company is to perform another trial with a sample size of $m^*_{\tilde{R}_0^d}$ and submit for approval at a price of $R=\tilde{R}^d_{m^*_{\tilde{R}_0^d}}$ when the evidence is updated.

3. Example—The Cadet-Hp Trial

The CADET-Hp Trial was a double-blind, placebo-controlled, parallel-group, multi-centre, randomized controlled trial performed in 36 family practitioner centres across Canada. The results are published in Chiba *et al*.[30,31] and Willan[32]. Patients 18 years and over with uninvestigated dyspepsia of at least moderate severity presenting to their family physicians were eligible for randomization, provided they did not have any alarm symptoms and were eligible for empiric drug therapy. Patients 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 288 patients were randomized, 142 (= n_T) to *Treatment* and 146 (= n_S) to *Standard*. The new intervention (*i.e. Treatment*) is the regimen of metronidazole 500 mg and clarithromycin 250 mg. Both regimens were given twice daily for seven days. The binary measure of effectiveness was treatment success, defined as the presence of no or minimal dyspepsia symptoms at one year. Costs were determined from the societal perspective and are given in Canadian dollars. A summary of the trial results are given in Table I.

Treatment was observed to increase the probability of treatment success by 13.71 percentage points and reduce total cost by $75.30 per patient, excluding the price of metronidazole and clarithromycin. If we assume a normal flat prior for incremental net benefit, and assume that the estimator of incremental net benefit from this trial is normally distributed then the current evidence in favour of *Treatment* will be based solely on the data from this trial, and will be characterized by a normal distribution for incremental net benefit with mean

$$b_0 = \hat{\Delta}_e \lambda - (\hat{\Delta}_c^- + R) = 0.1371\lambda - (-75.30 + R) = 0.1371\lambda + 75.30 - R$$

and variance

$$v_0 = \hat{V}(\hat{\Delta}_e)\lambda^2 + \hat{V}(\hat{\Delta}_c^-) - 2\lambda\hat{C}(\hat{\Delta}_e, \hat{\Delta}_c^-) = 0.003356\lambda^2 + 4320 - 2\lambda(-0.6870),$$

where λ is the threshold value for the willingness-to-pay for a treatment success. Assume a time horizon (*h*) of 10 years, an annual incidence (*k*) of 80,000, an annual accrual rate (*a*) of 800 and a duration of 1.5 years for follow-up and data analysis (τ). A plot of the decision maker's threshold price $(\tilde{R}_0^d)$ as a function of the threshold value of a treatment success (λ) is given in Figure 1. The quantity $\tilde{R}_0^d$ is the maximum price at which the decision maker would approve now in preference to requesting another trial, and increases with the threshold value for a treatment success. Also given in Figure 1 is the plot of the threshold incremental net benefit, *i.e.* $b_0^d = b_0^- - \tilde{R}_0^d$. For λ = 500, the threshold decision maker's price is $106.53, and the threshold incremental net benefit is $37.32. Thus the decision maker would approve for reimbursement if the submitted price is less than $106.53 or, equivalently, if the mean incremental net benefit is greater than $37.32.

A plot of the decision maker's optimal sample size $(= n_R^*)$ as a function of price (*R*) is given in Figure 2 for λ = 500. At a price less than or equal to $106.53 $(= \tilde{R}_0^d)$, *Treatment* would be approved for reimbursement, see Figure 1. At the other end of the scale, if the price exceeds $143.85, approval would be refused since mean incremental net benefit (b_0) would be negative. For a price between $106.53 and $143.85 the decision maker would request another trial, with the size of the trial increasing with *R* over this range, as the incremental net benefit falls towards zero at *R* = $143.85. For example, at a submitted price of $140.67, the decision maker would

request a trial of 387 patients per arm. Given the societal decision maker's threshold price with current evidence, the company's optimal behaviour is to submit a request with the price set to \$106.53 $(= \tilde{R}_0^d)$, unless there exists a sample size such that their expected net gain (ENG^c) is positive.

For $\lambda = 500$ and fixed (C_f) and variable (C_v) cost of \$800,000 and \$2000 respectively, Table II contains, from the company's perspective, the expected value of sample information ($EVSI^c$), the total cost (TC^c) and the expected net gain (ENG^c) for various sample sizes. Also given in Table II is the post-trial expected threshold price for the decision maker $\left(\mathrm{E}(\tilde{R}_m^d)\right)$, which was determined by numerical integration, see the Appendix. The optimal sample size lies between 100 and 200 patients per arm. A more exhaustive search reveals that the optimal sample size is 137 patients per arm, corresponding to a pre-trial threshold price to the company $(\tilde{R}_0^c)$ of \$113.06 and an expected net gain to the company of \$6,451,162. The expected threshold price for the decision maker following a trial of 137 patients per arm $\left(\mathrm{E}(\tilde{R}_{137}^d)\right)$ is \$140.67. By contrast, a pre-trial submission by the company at a price of \$140.67 would precipitate a request from the decision maker for a trial with 387 patients per arm, see Figure 2, which is associated with an expected net gain to the company of only \$1,170,179, see Table II.

4. Extensions

4.1. Partial revenue per patient

In Sections 2 and 3, it was assumed that the revenue per patient received by the company is equal to the price. It is more realistic to assume that the revenue per patient to the company is, instead,

a fraction, *U*, of the price, in which case the expected net gain and the threshold price to the company become:

$$\mathrm{ENG}^c(m) = \left[\left\{h - (\tau + 2m/a)\right\} k\,\mathrm{E}(\tilde{R}_m^d) - hk\tilde{R}_0^d\right] U - (C_f + 2mC_v)$$

$$\tilde{R}_0^c = \frac{\left\{h - (\tau + 2m^*_{\tilde{R}_0^d} \,*/a)\right\} k\,\mathrm{E}(\tilde{R}^d_{m^*_{\tilde{R}_0^d}})U - (C_f + 2m^*_{\tilde{R}_0^d} C_v)}{hk}.$$

4.2. Discounting

In Sections 2, 3 and 4.1 above, a discount rate of zero is assumed. A discount rate of $r > 0$ requires the following adjustments to the formulations for the expected net gain for the decision maker and company (ENG^d and ENG^c respectively) and threshold price to the company $(\tilde{R}_0^c)$, as given below.

$$\mathrm{ENG}^d(n,R) = \left\{(t^U - t)(1+r)^{-t^L} + \sum_{i=t^U}^{h-1}(1+r)^{-i}\right\} k\left\{\mathcal{D}(R) - \mathcal{F}(n,R)\right\}$$

$$-\left\{(t - t^L)(1+r)^{-t^L} + \sum_{i=0}^{t^L-1}(1+r)^{-i}\right\} k(b_0^- - R)$$

$$+\left\{(t_a - t_a^L)(1+r)^{-t_a^L} + \sum_{i=0}^{t_a^L-1}(1+r)^{-i}\right\}(a/2)(b_0^- - R),$$

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 patient accrual; and, t_a^L is the integer part of t_a.

$$\mathrm{ENG}^c(n) = \left\{(t^U - t)(1+r)^{-t^L} + \sum_{i=t^U}^{h-1}(1+r)^{-i}\right\} k\mathrm{E}(\tilde{R}_m^d)U - \left\{\sum_{i=0}^{h-1}(1+r)^{-i}\right\} k\tilde{R}_0^d U$$

$$-\left\{C_f+\left[(t_a-t_a^L)(1+r)^{-t_a^L}+\sum_{i=0}^{t_a^L-1}(1+r)^{-i}\right]aC_v\right\}.$$

$$\tilde{R}_0^c=\frac{\left\{(t^{*U}-t^*)(1+r)^{-t^{*L}}+\sum_{i=t^{*U}}^{h-1}(1+r)^{-i}\right\}k\mathrm{E}(\tilde{R}^d_{m^*_{\tilde{R}_0^d}})U-\left\{C_f+\left[(t_a^*-t_a^{*L})(1+r)^{-t_a^{*L}}+\sum_{i=0}^{t_a^{*L}-1}(1+r)^{-i}\right]aC_v\right\}}{\left\{\sum_{i=0}^{h-1}(1+r)^{-i}\right\}kU},$$

where $t^*=2m^*_{\tilde{R}_0^d}\big/a+\tau$ is the optimal trial duration; t^{*L} is the integer part of t^*; $t^{*U}=t^{*L}+1$; $t_a^*=2m^*_{\tilde{R}_0^d}\big/a$ is the duration of patient accrual; and t_a^{*L} is the integer part of t_a^*.

4.3 Positive cost of adoption

In Sections 2, 3, 4.1 and 4.2 above, the cost of adopting the new intervention is assumed to be zero. 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 up-front costs, such as those associated with conveying public health messages, training and learning by doing as well as capital equipment. For a positive C_A, it can be shown that the formulations for $\mathcal{D}(R)$, $\mathcal{F}(n,R)$ and $\mathrm{EOC}^d(n)$ become:

$$\mathcal{D}(R)=\sqrt{v_0/(2\pi)}\exp\left[-\left\{b_0^- -R-C_A/(hk)\right\}^2\Big/(2v_0)\right]$$
$$-\left\{b_0^- -R-C_A/(hk)\right\}\left[\Phi\left(-\left\{b_0^- -R-C_A/(hk)\right\}\Big/\sqrt{v_0}\right)-I\left(b_0^-\le R+C_A/(hk)\right)\right];$$

$$\mathcal{F}(n,R) = \sqrt{v_0/(2\pi)}\,\sigma_+^2 \exp\left(-\left\{b_0^- - R - C_A/N(n)\right\}^2 \Big/ 2v_0\right)\Big/(nv)$$
$$-\left\{b_0^- - R - C_A/N(n)\right\}\Phi\left(-\left\{b_0^- - R - C_A/N(n)\right\}\Big/\sqrt{v_0}\right)$$
$$+v_0^{3/2}\exp\left(-\left\{b_0^- - R - C_A/N(n)\right\}^2 \Big/ 2v_0\right)\Big/\left(v\sqrt{2\pi}\right)$$
$$+\left\{b_0^- - R - C_A/N(n)\right\}\Phi\left(-\left\{b_0^- - R - C_A/N(n)\right\}\sqrt{v}\Big/v_0\right)$$
$$-v_0\exp\left(-\left\{b_0^- - R - C_A/N(n)\right\}^2 v\Big/(2v_0^2)\right)\Big/\sqrt{2\pi v}\,;$$

and

$$\mathrm{EOC}^d(n) = \left\{(\tau + 2n/a)k - n\right\}\left\{b_0^- - R - C_A/(hk)\right\}.$$

5. Discussion

Previous application of value of information methods to optimal trial design have predominantly taken a societal decision making perspective, implicitly assuming that society commissions prospective trials and decides whether or not to adopt new health interventions. Eckermann and Willan[6-9] demonstrate that optimal societal decision making and trial design requires joint consideration of whether to commission another trial or adopt the new intervention, given that the value, cost and feasibility of performing another trial are determined by whether or not the new intervention is adopted. Optimal decision making is shown to require a comparison of expected net gain for delaying the decision regarding adoption and performing another trial versus adopting immediately with no trial within jurisdiction, with the additional consideration of expected net gain for adopting and trialing, where feasible, across jurisdictions.

Griffin, Claxton and Sculpher[29] suggest that, where societal decision making is restricted to adopting or rejecting, the decision could influence manufacturers through a tradeoff between the

price of, and level of evidence for, a new intervention. The tradeoff they suggest is between expected value of perfect information and incremental net benefit, where expected value of perfect information is suggested as the opportunity cost of adopting and incremental net benefit the opportunity cost of delaying. However, the populations to which the value of information and the opportunity costs apply are different. Value of information (the option value of delay) arises for all patients beyond the point that evidence is updated, while an opportunity cost of incremental net benefit arises for all patients except those on the treatment arm of the trial, until evidence is updated[6-8]. Consequently, a tradeoff between value of information and opportunity cost needs to consider time and population differences. Further, value of information from delaying should be the expected value of sample information of an optimal trial, rather than expected value of perfect information, given evidence. The expected opportunity loss of adoption is the expected value of sample information provide by an optimal trial, not the expected value of perfect information. Griffin *et al*.[29] extend their methods to account for changing populations and consider the role of additional research. However, they still quantify the value of additional research as the expected value of perfect information, rather than the expected value of sample information as required by optimal decision making, which we have addressed as part of this paper.

In this paper we have established and illustrated the appropriate tradeoff between pricing and the level of evidence relevant to the societal decision of whether to approve health care interventions for reimbursement when companies have sole remit to commission trials. For a given level of evidence, it has been illustrated that there exists a maximum threshold price “acceptable” to the

societal decision maker. For prices above this threshold, the expected net gain for the decision maker from another trial is positive and requesting another trial is their optimal strategy.

Further, we have shown that the optimal response of manufacturers to the societal threshold price of whether to undertake further research or lower their price depends on their expected value and cost of research and current evidence. Given current evidence, there exists a minimum threshold price "acceptable" to the company, meaning that for prices below the threshold, the expected net gain for the company from another trial is positive and performing another trial is their optimal strategy. The company's threshold price exceeds that of the decision maker if, and only if, there exists a sample size for which the company's expected net gain is positive.

The optimal strategy for a company is to submit for approval at the decision maker's threshold price when the company's expected net gain is negative for all sample sizes at this price, or to perform another trial when the maximum expected net gain for the company is positive. From the company perspective, the optimal sample size of the trial will be that which maximizes their expected net gain, given the value and cost of trials and revenue foregone. In general, it is sub-optimal for the company to submit for approval at a price greater than the decision maker's threshold, since, at best, it will precipitate a request for another trial with, from their perspective, sub-optimal sample size.

Thus, the incentives implicit in the framework presented here discourage the company from submitting for approval until there is sufficient evidence to support the submitted price. This reduces administrative and analytic burden on decision makers and companies alike, in turn

reducing the associated transaction costs of the approval process. Other considerations, such as the value of being the first to market, the competing uses of research funding, or uncertainty in relation to the threshold value of outcomes in a jurisdiction may also influence the expected revenue and cost of research trade-off faced by companies in undertaking decision making. Hence, the framework presented here could be generalized to account for these additional factors where appropriate. Nevertheless, in general, the framework enables optimal tradeoffs between the value and cost of further research from both societal and company perspectives and establishes how these tradeoffs interact and play out in practice, where companies have control of prospective research and society has control of reimbursement within a jurisdiction.

The analysis presented has been strictly within jurisdiction. Moving beyond a strictly within jurisdiction analysis, options arise in relation to adopting and trialing, with the associated advantages in avoiding opportunity cost of delay, and the potential for improving risk sharing arrangements between companies and societal decision makers[9,10]. Hence, further research is suggested to extend the within jurisdiction framework presented here and explore optimal mechanisms for researching and pricing across jurisdictions, given interactions between decision makers and manufacturers and the potential to adopt and trial. This could, for example, consider incorporating contractual agreements to adjust pricing in jurisdictions where such adoption is optimal while additional evidence is collected in other jurisdictions in which delaying and trialing is optimal.

To apply a framework for optimal decision making and interaction between societal decision makers and companies, within or across jurisdictions, it is critical to establish economically and

meaningful societal threshold values for health outcomes. Threshold values are required to determine the prior distribution of incremental net benefit, the expected value of sample information and opportunity cost, as well as the consequent threshold prices and optimal research decisions. There is wide agreement that the threshold value for health outcomes in societal decision making should reflect the opportunity cost of funding new interventions within a fixed budget and the current use of existing interventions. Recently, it has been suggested that, if the societal objective is restricted to health maximisation, the threshold value for outcomes can be estimated as the shadow price of the least cost-effective (worst performing) interventions to be displaced[33,34-36]. However, even if the objective is restricted to health maximization, the shadow price of contracting or displacing the least cost-effective interventions will only coincide with that from the best expansion of current interventions (represented by the opportunity cost from financing new interventions) when there is complete allocative efficiency across all activities and interventions[37,38]. Hence, with allocative inefficiency in the current health care system, the opportunity cost and threshold price of, *e.g.*, incremental dollars per QALY gained will be lower than that of displacing the least cost effective services. Consequently, evidence of the most cost effective expansion of existing technology is required to estimate the true opportunity cost and threshold values for incremental net benefit so that value of information methods can be appropriately applied.

Throughout the paper we have assumed that the parameters h, k, a and τ are fixed, mostly to focus the attention on the uncertainty regarding incremental net benefit. However, the uncertainty of such parameters could be added to the model. The parameters h, a and τ would be amenable to sensitivity analyses, since they are somewhat in the control of the investigators. On

the other hand, the uncertainty regarding *k* might be best incorporated by using a Bayesian approach since its estimate would be typically based on empirical evidence. We have assumed that the prior- and post-study distributions for incremental net benefit are derived from randomized clinical trials data. However, it is often the case, as in decision-analytic models, for example, that incremental net benefit is a complex function of many parameters, the information for which may come from a variety of study types, see Ades, Lu and Claxton[1]. This is illustrated in Welton *et al*.[19] who examine the evidence in support of interventions for improving the uptake of breast cancer screening, and by Brennan and Kharroubi[39] who explore methods for EVSI determination for models with Weibull survival parameters. Consequently value is suggested to extending the methods presented in this paper for randomized clinical trials to other research designs. Nonetheless, the principle of applying value of information methods for the pricing of new health interventions illustrated in this paper is the same, regardless of the derivation of incremental net benefit.

The case for assuming normality for mean incremental net benefit based on individual patient data has been made by numerous authors, and has been generally accepted. The parametric assumption of bivariate normality for mean cost and effectiveness (and hence, mean incremental net benefit) has been shown to perform well[40-43]. Alternative distributional assumptions for incremental net benefit do not, in general, lead to closed form solutions for the expected value of sample information, requiring the use of numerical integration or Markov Chain-Monte Carlo methods. Consequently, the computer intensiveness of methods required with alternative assumptions may prove to be particularly challenging[1].

We have assumed that the company is risk-neutral, implying that if the company's threshold price exceeds the decision maker's then it is optimal for the company to do additional research. However, if the company is somewhat risk-averse then they should be more willing at the margin to accept the decision maker's threshold price based on current evidence. Hence, while expected revenue associated with an expected increase in the decision maker's threshold price with additional evidence may be greater than the companies direct and opportunity costs, the risk-averse company may not be willing to risk that actual net revenue could be reduced due to a potential price reduction with additional evidence.

Appendix

$\tilde{R}_m^d$ is the decision maker's threshold price following a trial of *m* patients per arm. That is, $\tilde{R}_m^d$ is that value of *R*, such that $\left|\max_n\{\mathrm{ENG}_m(n,R)\}\right| = 0,$ where $\mathrm{ENG}_m(n,R)$ is the expected net gain of performing a trial of *n* patients per arm, once the evidence is updated with data from the trial of *m* patients per arm. Numerical integration with respect to the distribution *f* is used to determine the expected value of $\tilde{R}_m^d,$ where *f* is the pdf for the observed incremental net benefit from the trial of *m* patients per arm, which, under the assumptions we have made, is normal with mean b_0 and variance $v = v_0 + \sigma_+^2 / m.$

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Table I. Parameter estimates for the CADET-Hp Trial

	Treatment	*Standard*	
Sample size $(=n_j)$	142	146	
Proportion of successes $(=\hat{e}_j)$	0.507	0.3699	difference = 0.1371 $(=\hat{\Delta}_e)$
Estimate of mean cost minus cost of metronidazole and clarithromycin (using gamma model)	459.50	534.80	difference = -75.30 $(=\hat{\Delta}_c^-)$
Estimated variance of proportion of successes $(=\hat{e}_j(1-\hat{e}_j)/n_j)$	0.00176	0.001596	sum = 0.003356 $(=\hat{V}(\hat{\Delta}_e))$
Estimated variance of average cost (using gamma model)	1,825	2,495	sum = 4,320 $(=\hat{V}(\hat{\Delta}_c^-))$
Estimated covariance between proportion of successes and average cost (using gamma model)	-0.2837	-0.4033	sum = -0.6870 $(=\hat{C}(\hat{\Delta}_e, \hat{\Delta}_c^-))$

note: $\hat{\theta}$ is an estimate of θ

Table II. From the company's perspective, the expected value of sample information ($EVSI^c$), total cost (TC^c), expected net gain (ENG^c) and the decision maker's expected threshold price ($E(\tilde{R}_m^d)$) as a function of sample size, for the CADET-Hp Trial

Sample Size Per Arm (m)	$EVSI^c$	TC^c	ENG^c	$E(\tilde{R}_m^d)$
50	18,252,845	14,650,000	3,602,845	132.24
100	20,539,382	15,900,000	4,639,382	136.12
137§	23,276,162	16,825,000	6,451,162	140.67
150	22,530,291	17,150,000	5,380,291	139.66
200	24,796,479	18,400,000	6,396,479	143.74
250	23,679,076	19,650,000	4,029,076	142.59
300	24,283,713	20,900,000	3,383,713	144.17
350	23,325,027	22,150,000	1,175,027	143.24
387§§	24,245,179	23,075,000	1,170,179	145.23
400	24,126,392	23,400,000	726,392	145.21
450	23,085,097	24,650,000	-1,564,903	144.13

§ $137 = m^*_{\tilde{R}_0^d} = m^*_{106.53}$

§§ $387 = n^*_{\tilde{R}^c_{137}} = n^*_{140.67}$

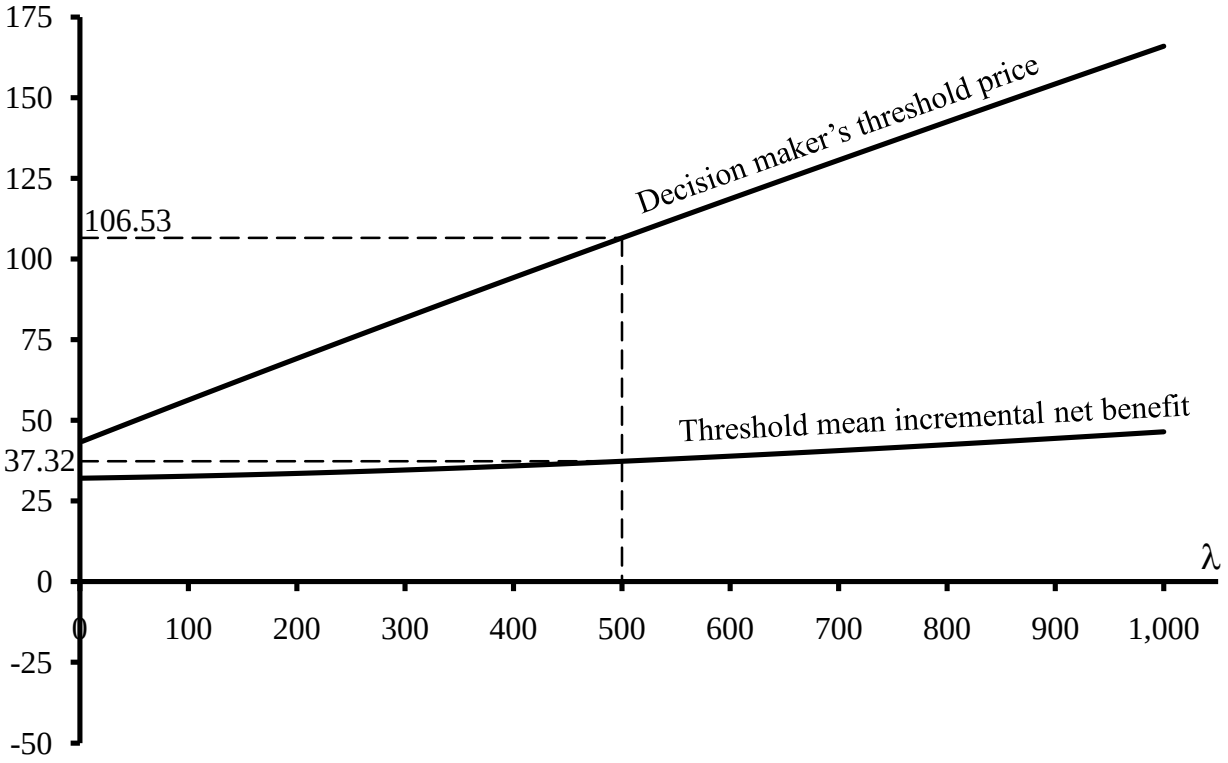

Figure 1. The decision maker's threshold price ($\tilde{R}_0^d$) and threshold mean incremental net benefit $b_0^d = (b_0^- - \tilde{R}_0^d)$ as a function of the threshold value for treatment success (λ), for the CADET-Hp Trial. At a threshold value for treatment success of $500, the decision maker's threshold price and threshold mean incremental net benefit are $106.53 and $37.32, respectively.

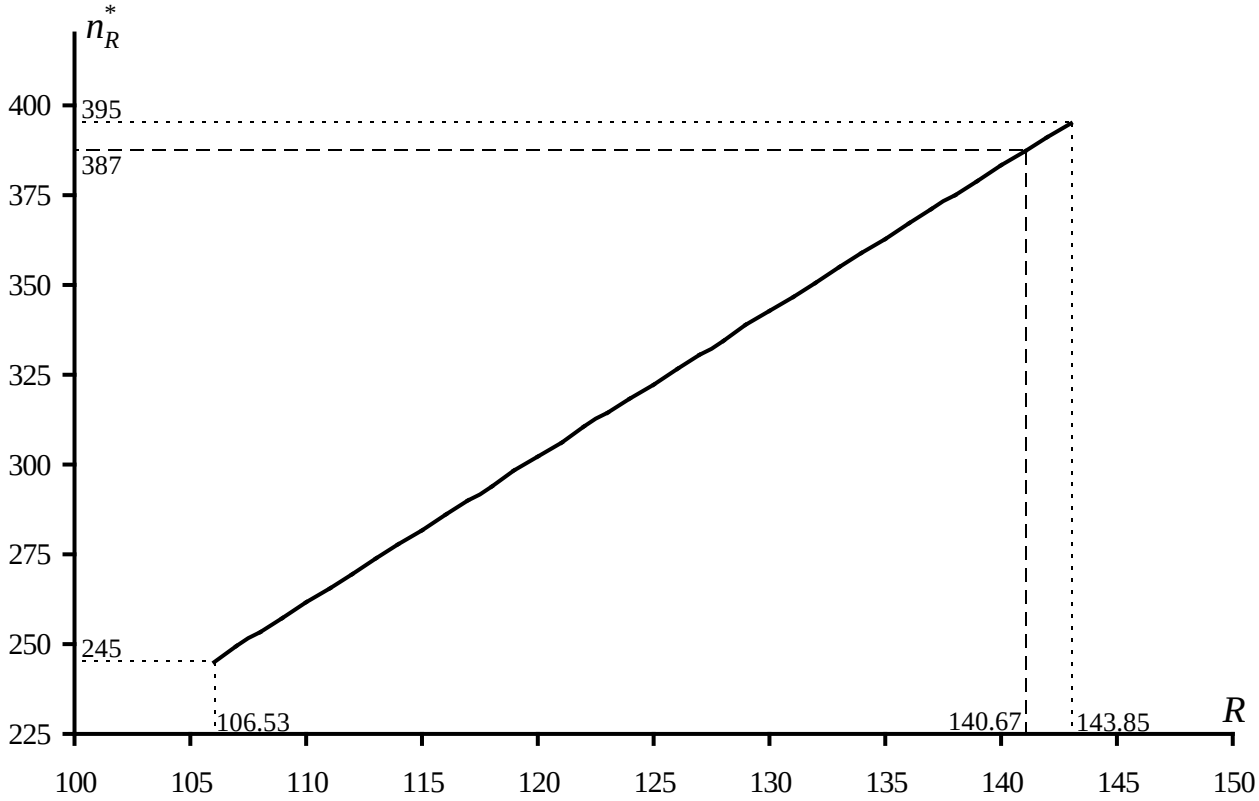

Figure 2. Optimal sample size (n_R^*) as a function of price (R) for a threshold value for treatment success (λ) of 500. The decision maker approves for $R < 106.53$; refuses approval for $R > 143.85$; and, requests another trial for $106.53 \leq R \leq 143.85$.