Value of Information Methods in the Design and Analysis of Clinical Trials – Part A

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What is the Value of Information

Faced with making a decision based on current information, what is the expected value of additional information?

It is the amount by which the new information reduces the expected opportunity loss of making the decision

Okay, So What is the Opportunity Loss and How Does One find Its Expected Value?

The opportunity loss is the utility (net benefit) of the best decision *minus* the utility of the decision made

The opportunity loss is a function of the "truth" and one finds its expected value by using the prior density of the "truth" given by the current information

A.K.A. the expected value of perfect information, because if you had perfect information, you could avoid the opportunity loss

That all very well, but can we have an example please?

Suppose you are told the one of four boxes contains $1000, the rest are empty. You get to choose one box keep its contents.

Suppose further that you have the opportunity to have revealed to you two of the empty boxes, so that your choice would becomes one out of two boxes.

What is the expected value of this information?

Example Continued

Box	Contents	Opp. Loss	Prior Info.	EOL_{prior}	Post Info.	EOL_{post}
A	0	1000	0.25	250	0	
B	1000	0	0.25	0	0.5	0
C	0	1000	0.25	250	0.5	500
D	0	1000	0.25	250	0	
				750		500

$EVSI = EOL_{prior} - EOL_{post} = EVPI_{prior} - EVPI_{post} = 750 - 500 = 250$

EOL = expected opportunity loss
EVPI = expected value of perfect information
EVSI = expected value of sample information

$EVSI = (\text{Expected Value of Decision})_{post} - (\text{Expected Value of Decision})_{pre}$

$= 500 - 250 = 250$

Prostate Cancer Trial

Symptomatic hormone resistant prostate cancer

Treatment (*T*)*:* Mitoxantrone + Prednisone
versus
Standard (*S*): Prednisone alone

161 patients

No difference in survival

Better palliation with *Treatment*

Cost data on 114 patients from the 3 largest centres

Retrospective chart review; included hospital admissions, outpatient visits, investigations, therapies and palliative care

Quality-adjusted survival using EORTC QLQ-C30

Prostate Cancer Trial

Let e_j and c_j be the mean quality-adjusted survival time and cost for arm j (=T,S)

Then $\Delta_e = e_T - e_S$ and $\Delta_c = c_T - c_S$

Incremental Net Benefit (INB): $b(\lambda) = \Delta_e \lambda - \Delta_c$, where λ is the threshold value for the willingness-to-pay for unit of effectiveness

$$b(\lambda) = (e_T - e_S)\lambda - (c_T - c_S) = e_T\lambda - c_T - (e_S\lambda - c_S) = \text{NB}_T - \text{NB}_S$$
$$\therefore -b(\lambda) = \text{NB}_S - \text{NB}_T$$

Prostate Cancer Trial

	Treatment	*Standard*	
n_j	61	53	
$\hat{e}_j$	40.89	28.11	difference = $\hat{\Delta}_e$ = 12.8 (QALW)
$\hat{V}(\hat{e}_j)$	24.10	16.42	sum = $\hat{V}(\hat{\Delta}_e)$ = 40.5
$\hat{c}_j$	27,322	29,039	difference = $\hat{\Delta}_c$ = -1717 (CDN $)
$\hat{V}(\hat{c}_j)$	6,466,351	7,872,681	sum = $\hat{V}(\hat{\Delta}_c)$ = 14,339,032
$\hat{C}(\hat{e}_j,\hat{c}_j)$	2771	2876	sum = $\hat{C}(\hat{\Delta}_e,\hat{\Delta}_c)$ = 5647

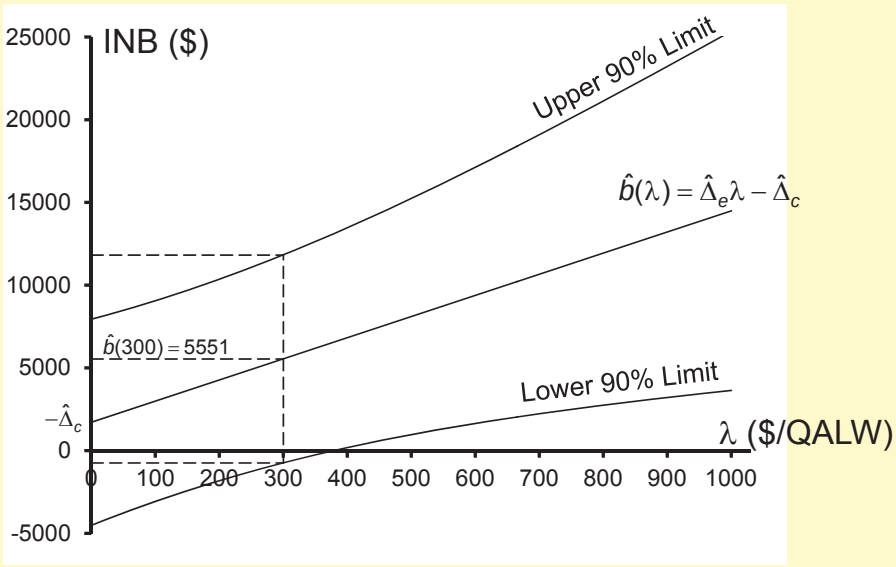
$$\hat{b}(\lambda) = \hat{\Delta}_e\lambda - \hat{\Delta}_c = 12.89\lambda + 1717$$

$$\hat{V}(\hat{b}(\lambda)) = \hat{V}(\hat{\Delta}_e)\lambda^2 + \hat{V}(\hat{\Delta}_c) - 2\hat{C}(\hat{\Delta}_e,\hat{\Delta}_c)\lambda$$
$$= 40.52\lambda^2 + 14339032 - 11294\lambda$$

90% confidence interval

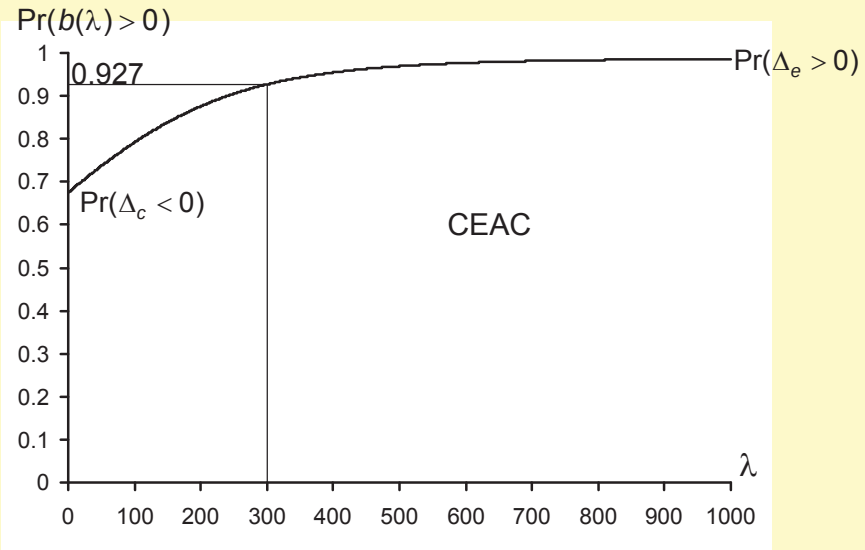
$$= \hat{b}(\lambda) \pm z_{0.95}\sqrt{\hat{V}(\hat{b})}$$
$$= \hat{b}(\lambda) \pm 1.65\sqrt{\hat{V}(\hat{b})}$$

Prostate Cancer Trial



Can reject H_0: $b(\lambda) \le 0$, at 5% level, for λ = 600, but not λ = 300

Prostate Cancer Trial



$\Pr(b(300) > 0)$ =0.927

significance for (H: $b(300) \le 0$ vs. A: $b(300) > 0$) = 1 – 0.927 = 0.073

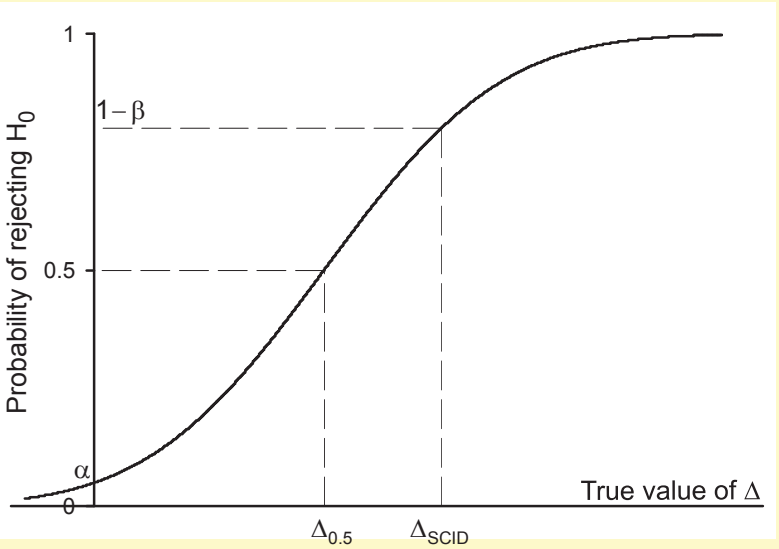
What to do for $\lambda = 300$?

Classical statistician: "Sorry folks, p = 0.073 > 0.05, there's no evidence that *Treatment* is better; stick with *Standard*.
Next project, please."

Bayesian statistician: "Whadayanuts!?
The probability that *Treatment* is cost-effective is 93%.
It's criminal to stick with *Standard*, adopt *Treatment*."

Informed (*i.e.* decision theory aware) clinical trial methodologist:
"Perhaps we need more information (*i.e.* another trial).
The size of trial (*n*/arm) should maximize the difference between the exp. value of doing the trial and the exp.cost of doing it."

Traditional Power Curve and Sample Size Determination



H_0: $\Delta \leq 0$, *i.e. Treatment* equal or inferior to *Standard*

Rejection of H_0 is argument for adopting *Treatment*

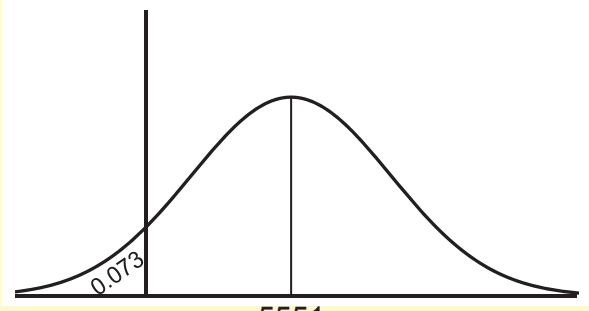
Decision Theory

For the threshold value of interest, let $b(\lambda) = b$ and let of the current mean and variance of b be denoted by b_0 and v_0, respectively.

For the Prostate trial

$$b_0 = \hat{b}(300) = \hat{\Delta}_e \times 300 - \hat{\Delta}_c = 12.8 \times 300 - (-1717) = 5557$$

$$v_0 = V\left\{\hat{b}(300)\right\} = V(\hat{\Delta}_e) \times 300^2 + V(\hat{\Delta}_c) - 2 \times 300 \times C(\hat{\Delta}_e, \hat{\Delta}_c)$$
$$= 14{,}595{,}832$$



Decision Theory

Optimal Decision Rule:

If no additional information is being sought, or expected, then adopt *Treatment* if, and only if, $b_0 > 0$

Optimal Decision Rule assumes cost of adoption = 0

Optimal Decision Rule maximizes expected net benefit for future patients

However, due to uncertainty *(i.e.* $v_0 > 0$) the Optimal Decision Rule may not be the optimal course of action. We must consider seeking additional information, *e.g.*conducting another trial.

Decision Theory Approach to Sampling

The size of trial (*n*/arm) should maximize the difference between the expected value of information from the trial and the expected cost of doing it.

The expected value of information from the trial is the amount by which the information reduces the total expected opportunity loss.

Let $OLpp_T(b)$ be the opportunity loss per patient of adopting *Treatment*

Opportunity Loss Function (per patient) for Adopting *Treatment*

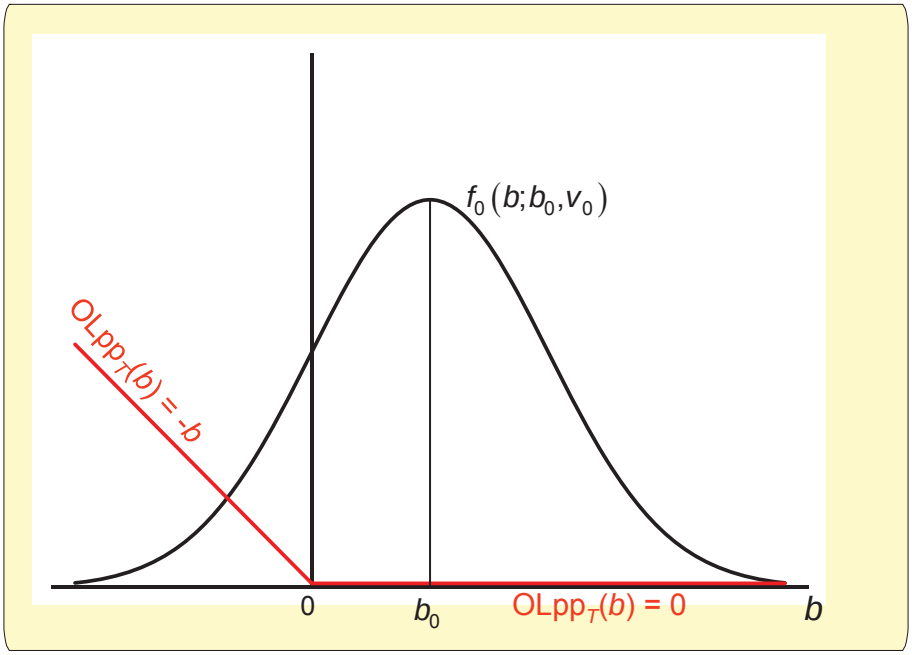
$OLpp_T(b) = NB(best) - NB(chosen) = NB(best) - NB_T$

$b > 0$: *Treatment* is best; $OLpp_T(b) = NB_T - NB_T = 0$

$b \leq 0$: *Standard* is best; $OLpp_T(b) = NB_S - NB_T = -b$

Recall that incremental net benefit = $NB_T - NB_S = b$

Prior Expected Opportunity Loss (per patient)



$$\text{EOLpp}_{T0} = \int_{-\infty}^{0} -b \cdot f_0(b)db = e^{-b_0^2/(2v_0)}\sqrt{v_0/(2\pi)} - b_0\Phi\left(-b_0/v_0^{\frac{1}{2}}\right) \equiv \mathcal{D}(b_0,v_0)$$

Decision Theory Approach to Sampling

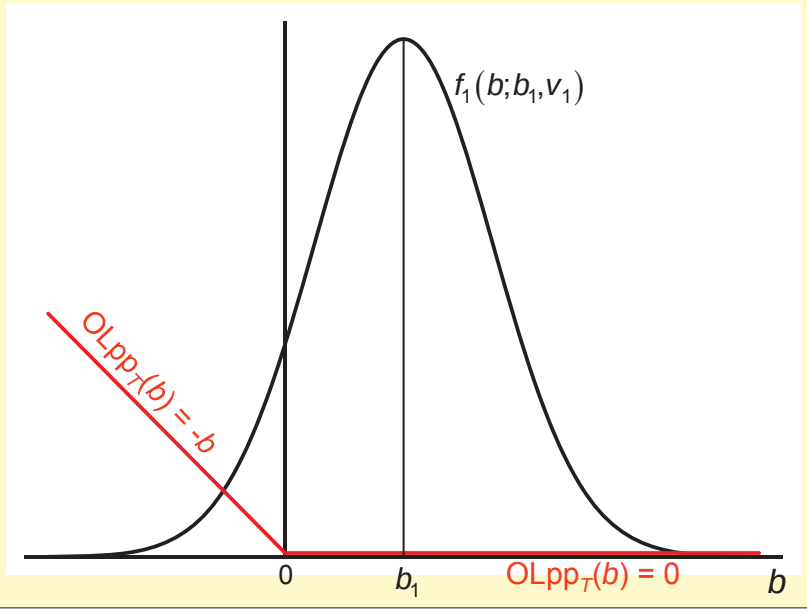
Suppose you plan to conduct a new trial of n patients per arm, and let $\hat{b}$ be the estimate of b from the trial data.

Combining the prior density for b with the new data using Bayesian methods yields a posterior density for b: $b \sim \text{N}(b_1, v_1)$

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

and σ_+^2 is the between-patient variance of NB for patients on *Standard* plus the between-patient variance of NB for patients on *Treatment*

Post Expected Opportunity Loss (per patient)



$$\text{EOLpp}_{T1} = E_{\hat{b}}\mathcal{D}(b_1,v_1) = \mathcal{D}(b_0,v_0) - \mathcal{K}(b_0,v_0,n,\sigma_+^2)$$

Expected Value of Sample Information (EVSI)

$$\text{EVSI}(n) = B(n)\left(\mathcal{D}(b_0,v_0) - E_{\hat{b}}\mathcal{D}(b_1,v_1)\right) = B(n)\mathcal{K}(b_0,v_0,n,\sigma_+^2)$$

$B(n)$ is the number of patients that can benefit from the new information,

i.e. $B(n) = hk - 2n$, where h is the time horizon in years

and k is the annual incidence.

Assumptions:

All patients are recruited into the trial

Trial results are know immediately

$$\mathcal{K}(b_0,v_0,n,\sigma_+^2) = \text{EVSI}_{\text{per-patient}} =$$

$$v_0 \exp\left(-b_0^2(v_0+\sigma_+^2/n)/(2v_0^2)\right)\Big/\sqrt{2\pi(v_0+\sigma_+^2/n)} - b_0\Phi\left(-b_0\sqrt{(v_0+\sigma_+^2/n)}/v_0\right)$$

Decision Theory Approach to Sampling

Expected Total Cost (ETC)

$\mathrm{ETC}(n) = C_f + 2nC_v + D(n)b_0$, where

C_f = fixed cost, C_v = variable cost per patient, and

$D(n)$ is the number of patients who are denied *Treatment*

(*i.e.* receive *Standard*) because the trial,

each of whom incur and expected opportunity cost of b_0.

$D(n) = n$

Assumptions:

All patients are recruited into the trial

Trial results known immediately after recruitment

Perfect implementation

Decision Theory Approach to Sampling

n^* is that value that maximizes Expected Net Gain (ENG)

$\mathrm{ENG}(n) = \mathrm{EVSI}(n) - \mathrm{ETC}(n)$

If $\mathrm{EVSI}(n^*) \leq \mathrm{ETC}(n^*)$, *i.e.* $\mathrm{ENG}(n^*) \leq 0$, then optimal sample size = 0,

i.e. current information is sufficient for decision making.

i.e. state of equipoise does not exists

Adopt *Treatment* based on current evidence (since $b_0 > 0$)

If $\mathrm{EVSI}(n^*) > \mathrm{ETC}(n^*)$, *i.e.* $\mathrm{ENG}(n^*) > 0$, then optimal sample size = n^*

i.e. state of equipoise exists

Willan AR, Pinto EM. *Statistics in Medicine* 2005; **24**:1791-1806.
(correction: *Statistics in Medicine* 2006; **25**:720.)

Prostate Cancer Trial

For λ = 300

$$b_0 = \hat{\Delta}_e \times 300 - \hat{\Delta}_c = 12.8 \times 300 - (-1717) = 5557$$

$$v_0 = \hat{V}(\hat{\Delta}_e) \times 300^2 + \hat{V}(\hat{\Delta}_c) - 2 \times 300 \times \hat{C}(\hat{\Delta}_e, \hat{\Delta}_c)$$
$$= 40.5 \times 300^2 + 14{,}339{,}032 - 2 \times 300 \times 5647 = 14{,}595{,}832$$

$$\sigma_+^2 = n_T \left\{ \hat{V}(\hat{e}_T)\lambda^2 + \hat{V}(\hat{c}_T) - 2\hat{C}(\hat{e}_T, \hat{c}_T) \right\} + n_S \left\{ \hat{V}(\hat{e}_S)\lambda^2 + \hat{V}(\hat{c}_S) - 2\hat{C}(\hat{e}_S, \hat{c}_S) \right\}$$
= 829,435,498

Prostate Cancer Trial

Assume:

Time horizon(h) = 20

Incidence(k) = 2500

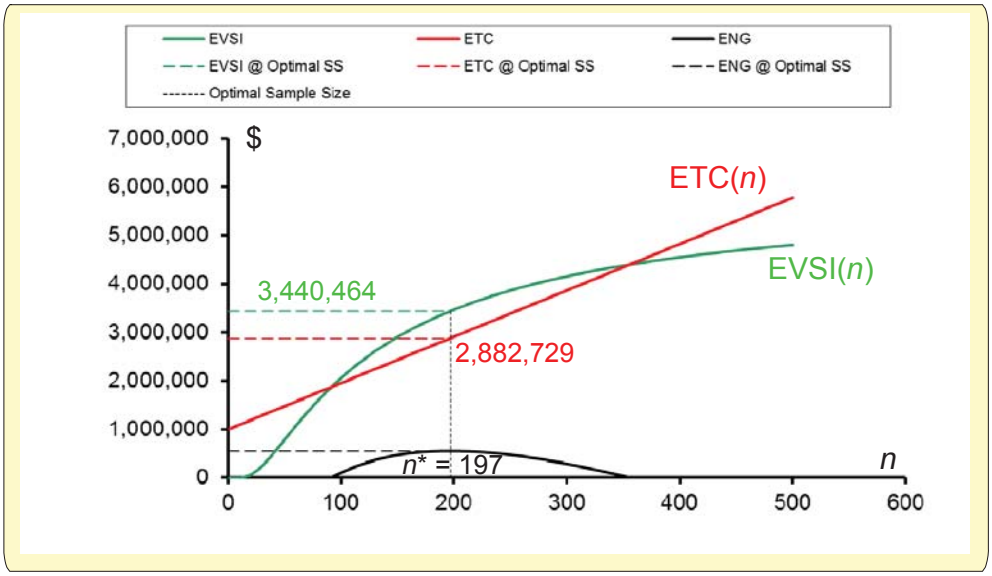
C_f = 1,000,000 and C_v = 2000

Therefore:

$$B(n) = hk - 2n = 50{,}000 - 2n$$

$$\text{ETC}(n) = C_f + 2nC_v + D(n)b_0$$
$$= 1{,}000{,}000 + 4000n + 5557n$$
$$= 1{,}000{,}000 + 9557n$$

Prostate Cancer Trial

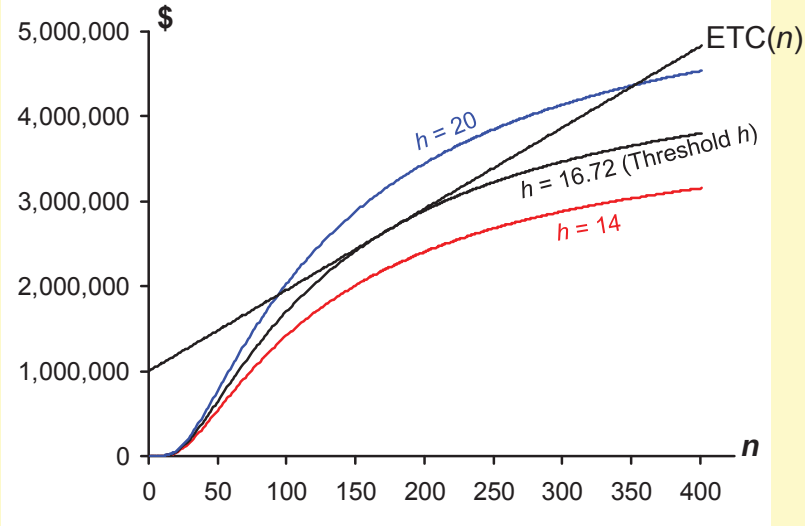


Financial cost =1,000,000 + 2*197*2000 = 1,788,000;

E(opportunity cost) = 197* 5557 = 1,094,729;

ETC(197) = 2,882,729; EVSI(197) = 3,440,464; ENG(197) = 577,735

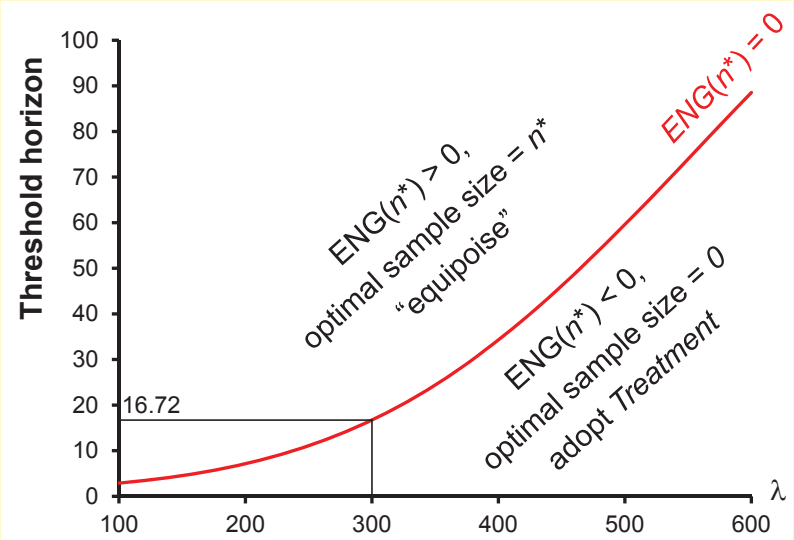
Prostate Cancer Trial



$$\mathrm{EVSI}(n) = (hk - 2n)\mathcal{K}(b_0, v_0, n, \sigma_+^2)$$

Willan AR. *Clinical Trials* 2007; **4**:279-285.

Prostate Cancer Trial



Combinations horizon (*h*) and λ for which ENG*(n*)* = 0

Early External Cephalic Version (ECV) Trial

Pilot RCT of 232 pregnant women presenting in breech position, with patients randomized between "early" ECV ($34^{0/7}$-$35^{6/7}$) (*Treatment*) and "late" ECV ($37^{0/7}$+) (*Standard*)

41/116 (35.34%) had non-caesarian delivery on *Treatment*

33/116 (28.45%) had non-caesarian delivery on *Standard*

2p = 0.32

New trial of 730 per arm, CIHR funded and recruiting patients

Designed to have an 80% power to achieve significance if arms differ by 7 percentage points, using two-sided, 5% type I error

Hutton E *et al*. *Am J Obs & Gyn* 2003; **189**:245-254.

Early External Cephalic Version Trial

	Treatment n = 116	Standard n = 116	
$\hat{e}_j$	0.3534	0.2845	difference = $\hat{\Delta}_e$ = 0.06897
$\hat{V}(\hat{e}_j)$	0.001970	0.001755	sum = $\hat{V}(\hat{\Delta}_e)$ = 0.003725
$\hat{c}_j$			0
$\hat{V}(\hat{c}_j)$			0
$\hat{C}(\hat{e}_j,\hat{c}_j)$			0

$$\hat{V}(\hat{e}_T) = \left\{\frac{0.3534 \times (1-0.3534)}{116}\right\}; \qquad \hat{V}(\hat{e}_S) = \left\{\frac{0.2845 \times (1-0.2845)}{116}\right\}$$

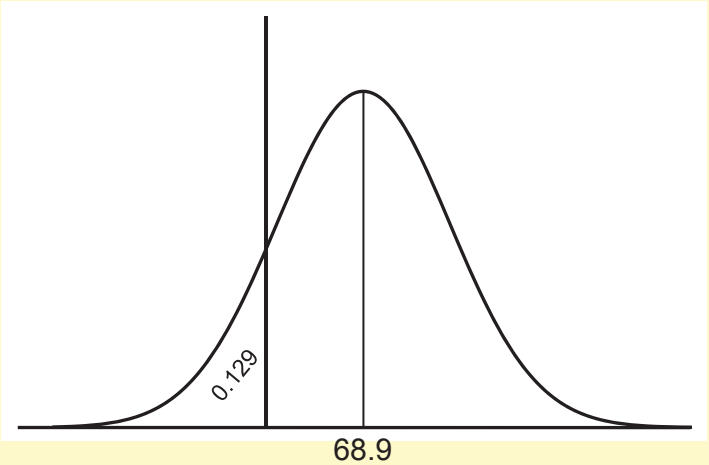
$$\lambda = 1000$$

Early External Cephalic Version Trial

$$b_0 = \lambda\Delta_e - \Delta_c = 1000 \times (0.3534 - 0.2845) - 0 = 68.97$$

$$v_0 = \lambda^2 \hat{V}(\hat{\Delta}_e) = 1000^2 \times 0.003725 = 3725$$

$$\sigma_+^2 = 1000^2 \{0.3534 \times (1-0.3534) + 0.2845 \times (1-0.2845)\}$$
$$\simeq 2(n_T \times n_S)/(n_T + n_S)v_0 = 432{,}075$$



Early External Cephalic Version Trial

Assume:

Time horizon(h) = 20

Incidence(k) = 50,000

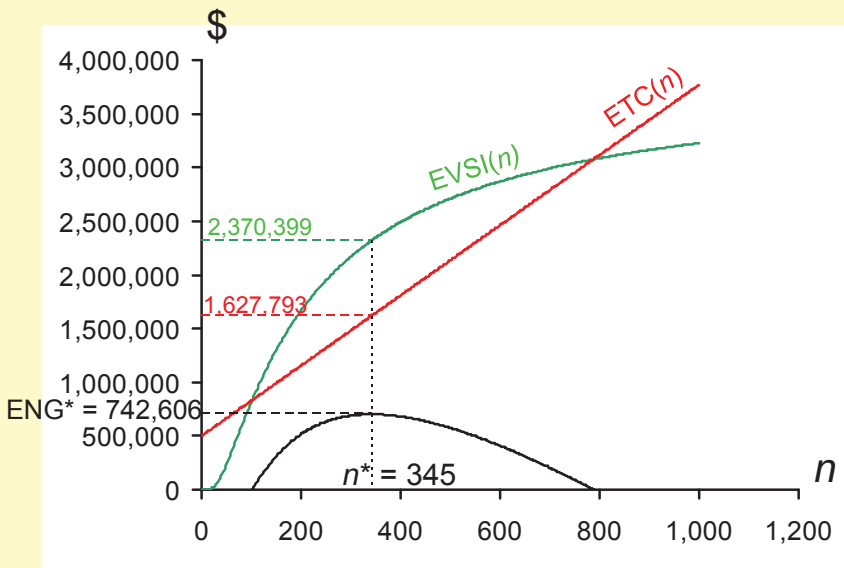
C_f = 500,000 and C_v = 1600

Therefore:

$$B(n) = hk - 2n = 1{,}000{,}000 - 2n$$

$$\begin{aligned} \text{ETC}(n) &= C_f + 2nC_v + D(n)b_0 \\ &= 500{,}000 + 3200n + 68.97n \\ &= 500{,}000 + 3268.97n \end{aligned}$$

Early External Cephalic Version Trial

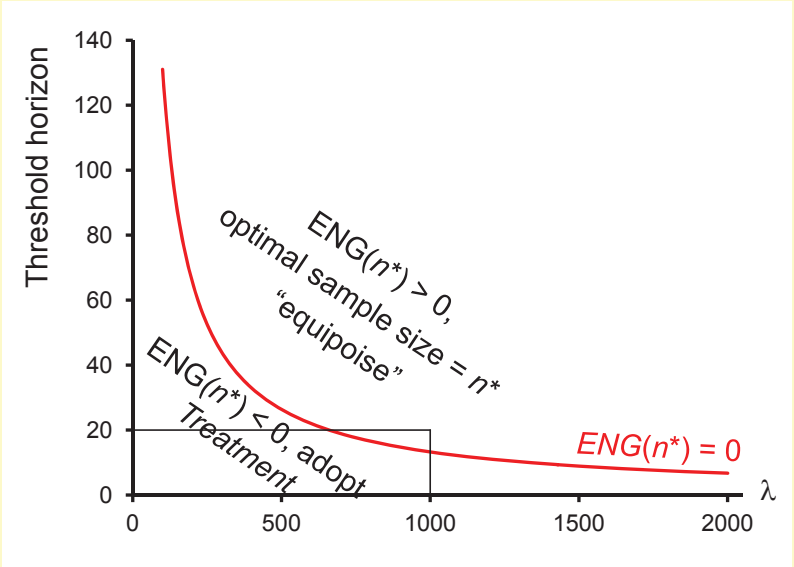


Financial cost =500,000 + 2*345*1600 = 1,604,000;

E(opportunity cost) = 345*68.97 = 23,793;

ETC(345) = 1,627,793; EVSI(345) = 2,370,399; ENG(345) = 742,606

Early External Cephalic Version Trial



Combinations of horizon (h) and λ for which ENG(n^*) = 0

Summary I

Standard approaches for sample size determination for randomized clinical trials are arbitrary and sub-optimal

The way forward is to use Bayesian decision theory based on incremental net benefit and to choose the sample size that maximizes expected net gain

Willan AR, Pinto EM. *Statistics in Medicine* 2005; **24**:1791-1806.
(correction: *Statistics in Medicine* 2006; **25**:720.

Willan AR. *Clinical Trials* 2007; **4**:279-285.

Summary II

Need to consider more realistic assumptions regarding the proportion of patients recruited, duration of follow-up/analysis, cost of adoption, the nature of decision rule, and the evidence from other jurisdictions

Eckermann S, Willan AR. *Health Economics* 2007; **16**:195-209
Eckermann S, Willan AR. *Value in Health* 2008; **11**:522-526
Eckermann S, Willan AR. *Medical Decision Making* 2008; **28**:300-305
Eckermann S, Willan AR. *Health Economics* 2009; **18**:203-216
Willan AR, Eckermann S. *Health Economics* 2010; **19**:549-561

Assumptions for Designing a Trial

1. The cost of adopting the new intervention is zero
2. All patients in the jurisdiction of interested are recruited into the trial
3. The results are available immediately after the last patient is randomized
4. Perfect implementation, *i.e.* if current evidence favours the new intervention and no new information is sought or expected, then the new intervention will be adopted for all future patients
5. The trial is a single-stage design, *i.e.* no interim “looks” at the data
6. Mean INB does not vary between trials (fixed-effect model)
7. Societal perspective
8. The discount rate is zero
9. Only research done within the jurisdiction of interest, has value

The ASsessment of the Safety and Efficacy of New Thrombolytic Regimens (ASSENT)-3 trial

6095 patients from 575 sites in 26 countries

with ST-elevated AMI randomized to 3 arms

- Heparin: full-dose tenecteplase + unfractionated heparin
- Enoxaparin: full-dose tenecteplase + enoxaparin
- Abciximab: half-dose tenecteplase + unfractionated heparin + abciximab

(duration of interest = 30 days)

Composite measure of effectiveness: "Success" defined as

freedom from (i) death, (ii) re-infarction and (iii) refractory ischemia

ASSENT-3 Trial

Abciximab (*Treatment*) vs Heparin (*Standard*)

$\hat{\Delta}_e$ = proportion of success on T – proportion of successes on S

= 0.0373 (p = 0.00022)

$\hat{\Delta}_c$ = average cost on T – average cost on S = 949 ($p < 0.0001$)

n_T = 2017; n_S = 2036

$$\text{ICER} = R = \frac{949}{0.0373} = 25{,}442$$

ASSENT-3 Trial

Abciximab (*Treatment*) vs Heparin (*Standard*)

$\hat{\Delta}_e = 0.0373$ $\quad\quad$ $\hat{\Delta}_c = 949$

$\hat{V}\left(\hat{\Delta}_e\right) = 0.0001124$ $\quad\quad$ $\hat{V}\left(\hat{\Delta}_c\right) = 23375$

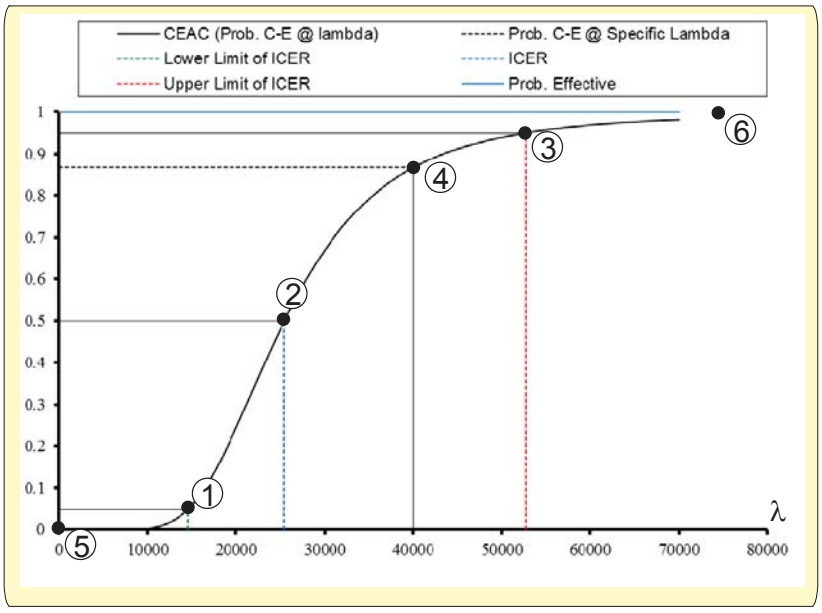
$\hat{C}\left(\hat{\Delta}_e, \hat{\Delta}_c\right) = -0.4410$

$\hat{b}(\lambda) = \hat{\Delta}_e\lambda - \hat{\Delta}_c = 0.0373\lambda - 949$ $\quad\quad$ $b_0 = \hat{b}(40{,}000) = 543$

$V\left(\hat{b}(\lambda)\right) = \hat{V}(\hat{\Delta}_e)\lambda^2 + \hat{V}(\hat{\Delta}_c) - 2\hat{C}(\hat{\Delta}_e, \hat{\Delta}_c)\lambda = 0.0001124\lambda^2 + 23375 + 0.882\lambda$

$v_0 = V\left(\hat{b}(40{,}000)\right) = 238{,}495$

Cost-effectiveness Acceptability Curve



Abciximab (*T*) vs Heparin (*S*)

$1 = (\mathrm{LL}_R, 0.05)$
$= (14616, 0.05)$

$2 = (\hat{R}, 0.5)$
$= (25442, 0.5)$

$3 = (\mathrm{UL}_R, 0.95)$
$= (52687, 0.95)$

$4 = \left(40000, \Pr(b(40000) > 0)\right)$
$= (40000, 0.87)$

$5 = \left(0, \Pr(\Delta_c < 0)\right) = (0, 0.27 \times 10^{-9})$
$6 = (\text{"}\infty\text{"}, \Pr(\Delta_e > 0) = (\text{"}\infty\text{"}, 0.9998)$

Some Assumptions

C_f = 250,000; C_v = 2000

λ = 40,000 (threshold value for a "success")

h = 25 years (time horizon)

k = 50,000 (annual incidence)

Therefore

$$B(n) = hk - 2n = 1{,}250{,}000 - 2n$$

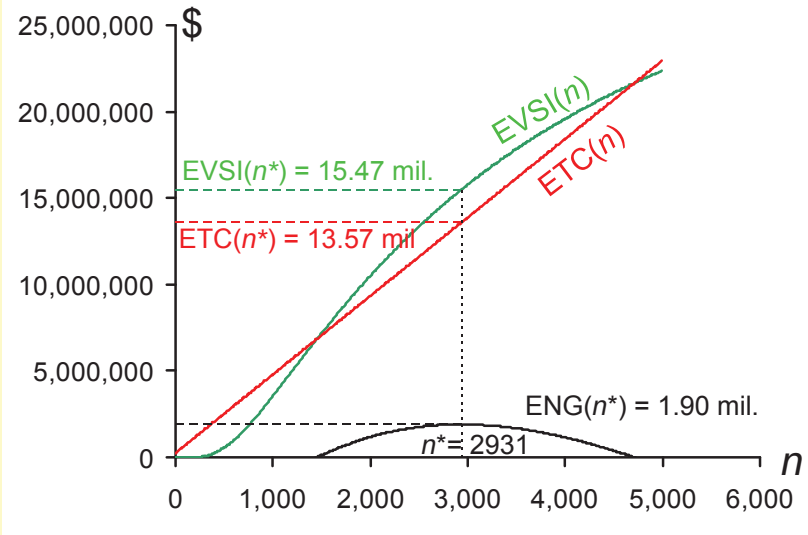
$$\begin{aligned} \text{ETC}(n) &= C_f + 2nC_v + D(n)b_0 \\ &= 250{,}000 + 4000n + 543n \\ &= 250{,}000 + 4543n \end{aligned}$$

$$i.e.\ D(n) = n$$

Unrealistic Assumptions

- C_A = 0
- a = 50,000 (*i.e.* $a = k$)
- τ= 0 (*i.e.* results are instantaneous)
- perfect implementation

ASSENT-3 Example



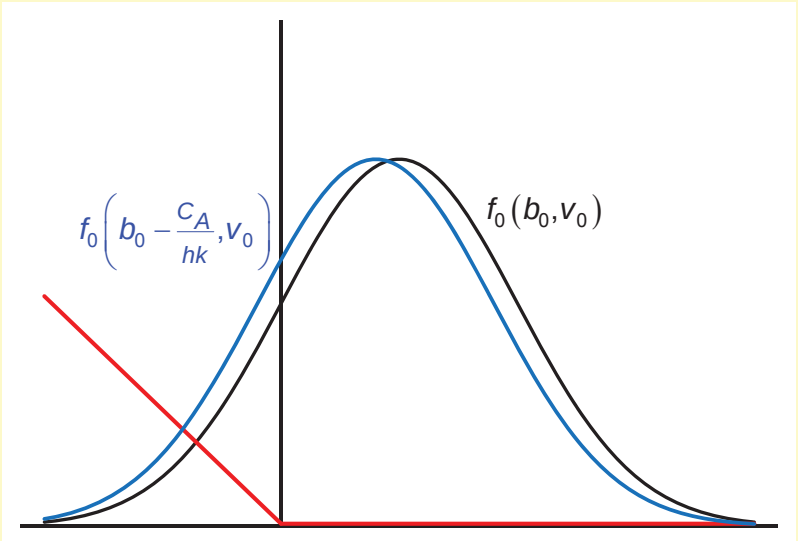
$B(n) = 1{,}250{,}000 - 2n$ Opportunity Cost $= 543n$

Previous Assumptions

1. The cost of adopting T is 0 (if relaxed, EOLpp↑; EVSIpp↑, EOC↓
2. All patients in the jurisdiction of interested are recruited into the trial (if relaxed, $B(n)\Downarrow$ & $D(n)\Uparrow$)
3. Trial results are instantaneous (if relaxed, $B(n)\Downarrow$ & $D(n)\Uparrow$)
4. Perfect implementation (if relaxed, EVSIpp$\Uparrow\Uparrow$ & $D(n)\Downarrow$)

How will relaxing these assumptions affect the formulations of EVSI and ETC, and how might that affect optimal sample size?

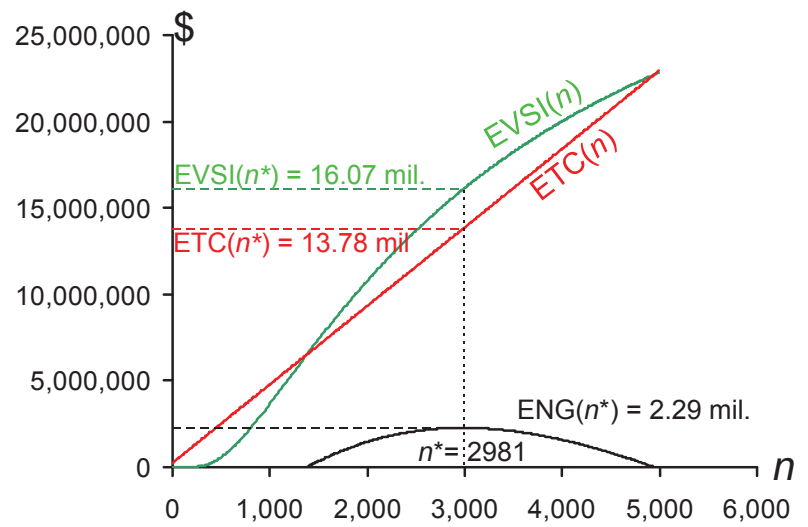
Relaxing Assumption 1 ($C_A > 0$)



$$\text{EVSI}(n) = B(n) \times \left[\mathcal{D}(b_0 - C_A/hk, v_0) - \mathrm{E}_{\hat{b}} \mathcal{D}\left(b_1 - C_A/B(n), v_1\right) \right]$$

Expected opportunity cost = $D(n)\{b_0 - C_A/(hk)\}$

ASSENT-3 Example (C_A = 5 mil.)



$B(n) = 1{,}250{,}000 - 2n$ Opportunity Cost $= 539n$

ASSENT-3 Example (C_A = 5 mil.)

The effect of the cost of adoption on optimal sample size and optimum ENG

Cost of Adoption	Optimal Sample Size	Optimum ENG	Reduction in ENG with a Trial of 2931 Patients per Arm
0	2931	1,900,581	0
5 Million	2981	2,285,132	0.07069%
10 Million	3027	2,680,729	0.2399%
25 Million	3166	3,934,181	1.002%

Relaxing Assumptions 2 and 3 ($a < k$, $\tau > 0$)

Let

h = time horizon (life expectancy of intervention)

k = annual incidence of the condition under study

a = annual accrual rate into the trial

τ = duration from last patient recruitment to results available

Therefore

- the duration of the trial is $t = 2n/a + \tau$
- $B(n) = (h - t)k = \left[h - (2n/a + \tau)\right]k = (hk - 2n) - \underbrace{\left[2n(k/a - 1) + \tau k\right]}_{\geq 0}$

If Assumptions 2 and 3 hold then $B(n)$ is maximized

Therefore, relaxing Assumptions 2 and 3 decreases EVSI

Relaxing Assumptions 2 and 3 ($a < k$, $\tau > 0$)

Further

the number of patients denied T during the trial is $D(n) = tk - n$

each one incurs an opportunity cost of b_0

Therefore

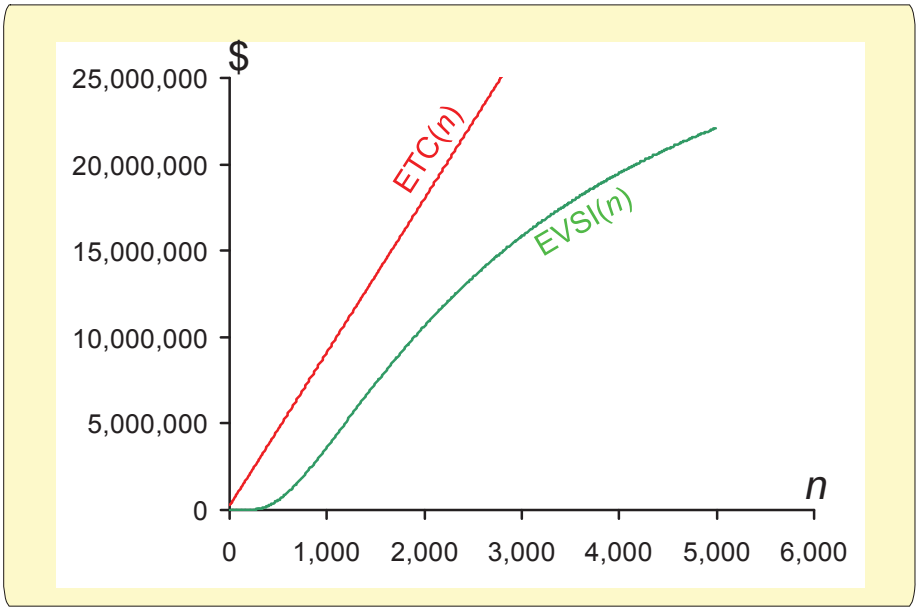
the opportunity cost becomes

$$D(n)b_0 = (tk - n)b_0 = \left[(2n/a + \tau)k - n\right]b_0 = nb_0 + \underbrace{\left[2n(k/a - 1) + \tau k\right]}_{\geq 0} b_0$$

If Assumptions 1 and 2 hold, then opportunity costs are minimized

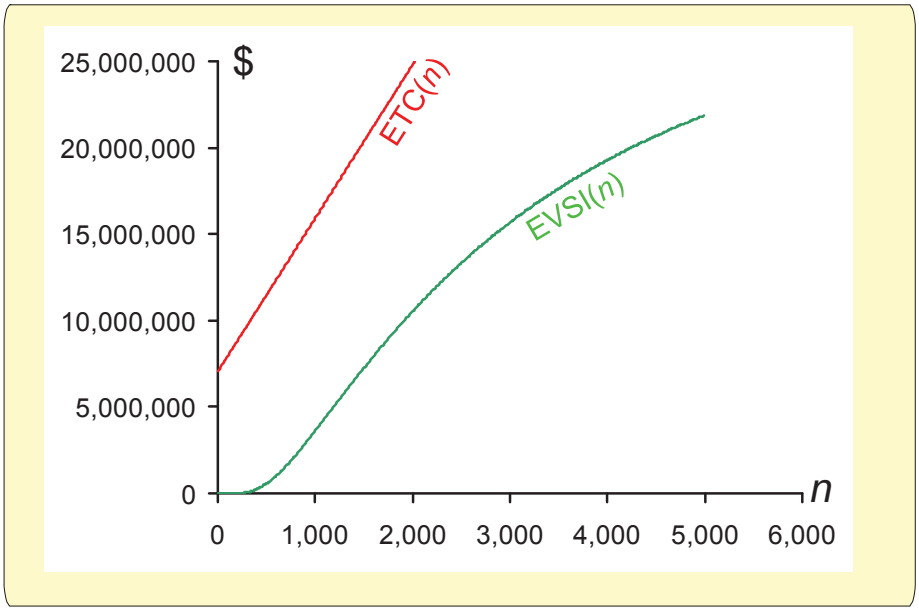
Therefore, relaxing Assumptions 2 and 3 increases opportunity costs

C_A = 5 mil.,a = 10,000 (=0.2*k); τ = 0



$B(n) = 1{,}250{,}000 - 10n$ Opportunity Cost $= 539 \times 9n$

C_A = 5 mil.,a = 10,000 (=0.2*k); τ = 0.25



$B(n) = 1{,}237{,}500 - 10n$ Opportunity Cost $= 539 \times (9n + 12{,}500)$

Dilemma

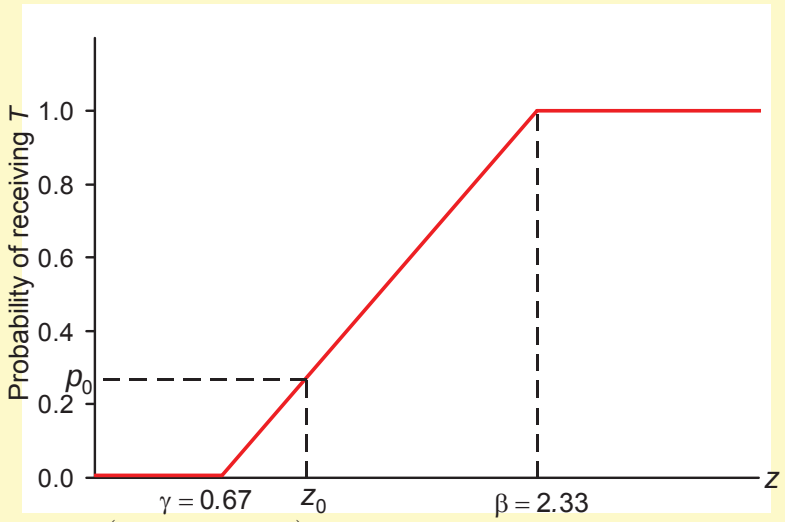
On the one hand, using a traditional approach the evidence is insufficient to justify adopting *Treatment*

On the other hand, using a VOI approach the ENG is negative regardless of the sample size

We are assuming that if no new information is sought or expected, a positive incremental net benefit is sufficient for adopting *Treatment*, *i.e.* perfect implementation.

Dilemma "Resolved" – Imperfect Implementation

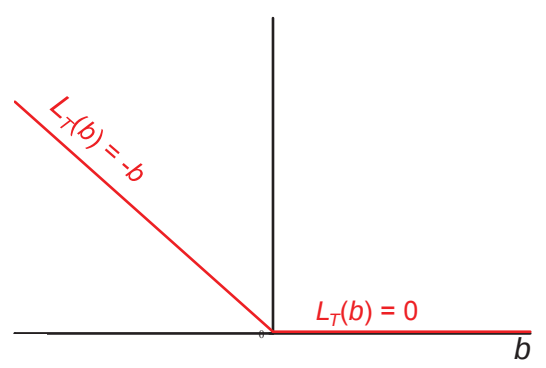
Assume that if no new information is sought or expected, the probability that a future patient will receive *T* is equal to $p_0 = \min\left(1, \max\left(0, (z_0 - \gamma)/(\beta - \gamma)\right)\right)$, where $z_0 = b_0 / \sqrt{v_0}$



Opportunity Loss Functions

$L(b)$ = NB(best) – NB(chosen)

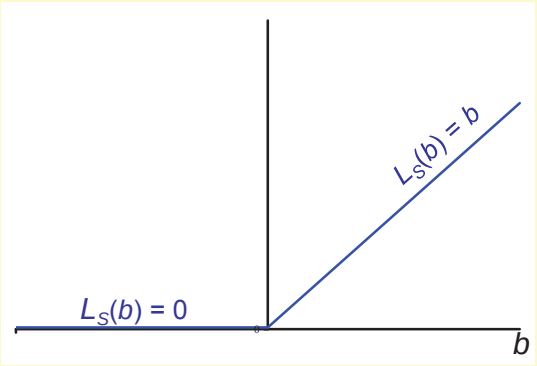
Opportunity Loss Function for Adopting *T*



$b \leq 0$: *S* is best; $L_T(b) = NB_S - NB_T = -b$

$b > 0$: *T* is best; $L_T(b) = NB_T - NB_T = 0$

Opportunity Loss Function for Retaining *S*

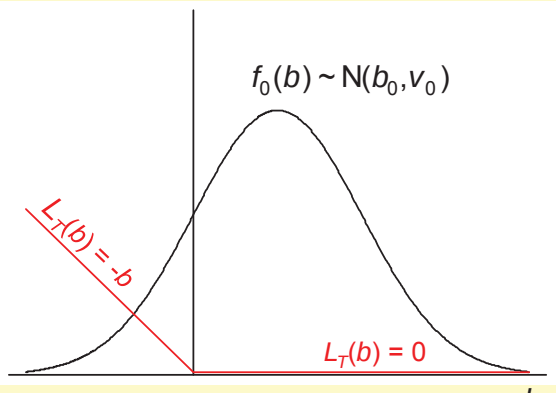


$b \leq 0$: *S* is best; $L_T(b) = NB_S - NB_S = 0$

$b > 0$: *T* is best; $L_T(b) = NB_T - NB_S = b$

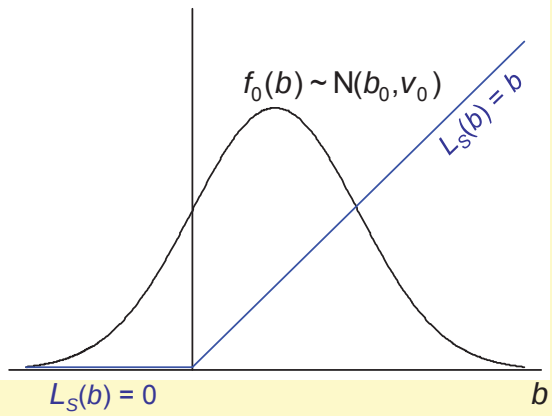
Pre-trial Expected Opportunity Loss Per Patient

EOLpp for Adopting *Treatment*



$$EOLpp_{T0} = \int_{-\infty}^{0} -bf_0(b)db = \mathcal{D}(b_0, v_0)$$

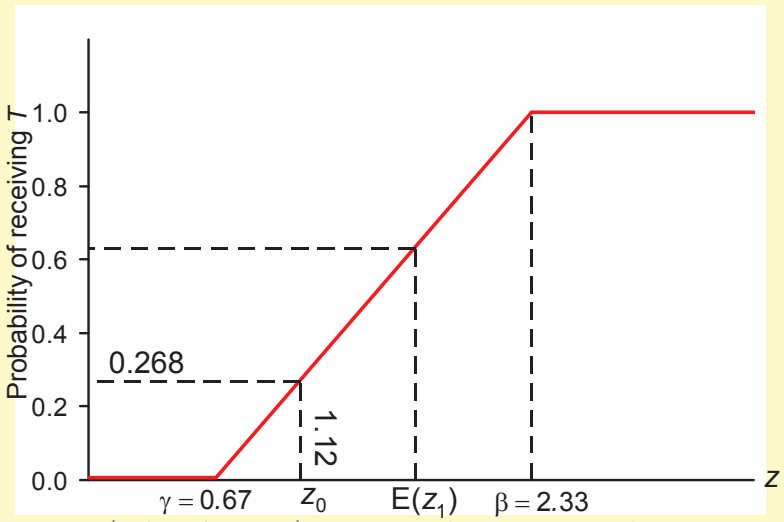
EOLpp for Retaining *Standard*



$$EOLpp_{S0} = \int_{0}^{\infty} bf_0(b)db = \mathcal{D}(b_0, v_0) + b_0$$

Imperfect Implementation

Since $E(z_1) > z_0$, it is expected that more patients will receive *T* post trial. And so fewer patients will be experiencing the higher EOL from receiving *Standard*, when INB > 0



Imperfect Implementation

$$EVSI(n) = B(n)\left\{\mathcal{D}(b_0, v_0) + (1-p_0)b_0 - E_{\hat{b}}\left[\mathcal{D}(b_1, v_1) + (1-p_1)|b_1|\right]\right\}$$

$b_0 = 543$; $v_0 = 238{,}489$; $z_0 = b_0/\sqrt{v_0} = 1.12$

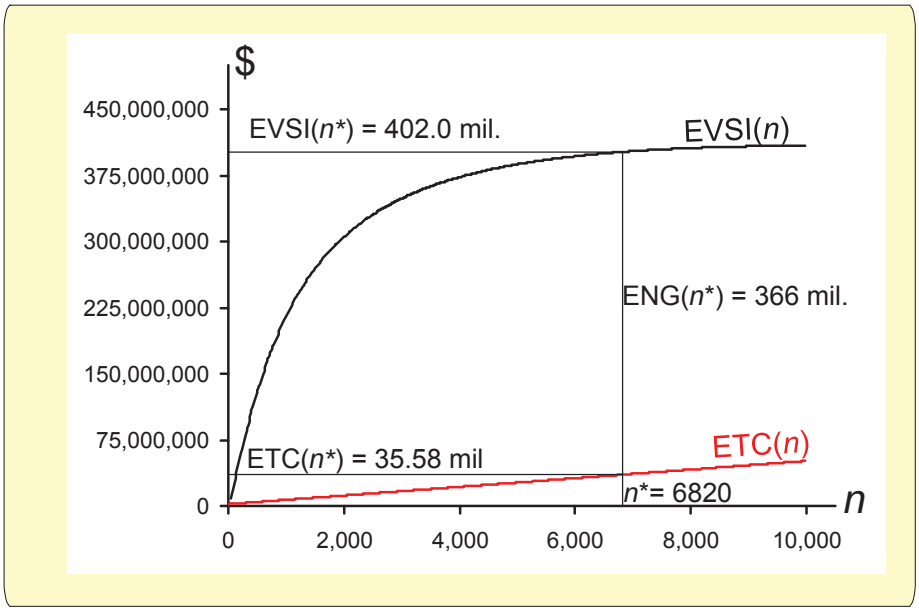
$p_0 = 0.268$

$\mathcal{D}(b_0, v_0) = 33.27$

Perfect implementation
pre-trial EOLpp $= \mathcal{D}(b_0, v_0) = 33.27$

Imperfect implementation
pre-trial EOLpp $= \mathcal{D}(b_0, v_0) + (1-p_0)b_0 =$
33.27 + (1 - 0.268) *x* 543 = 430.7

C_A = 5 mil.,a = 10,000 (=0.2*k); τ = 0.25; $\gamma = \Phi^{-1}(0.75)$; $\beta = \Phi^{-1}(0.99)$

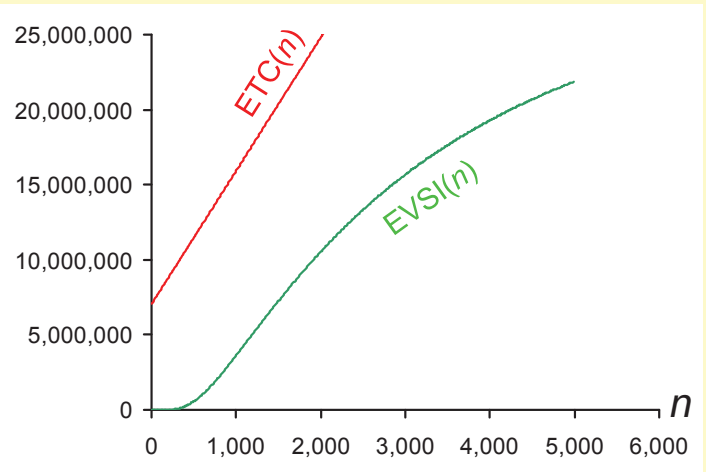


$B(n) = 1{,}237{,}500 - 10n$ Opportunity Cost $= 539 \times (1.68n + 3350)$

Based on Probability that *Treatment* is Effective

$\hat{\Delta}_e = 0.0373$; $V(\hat{\Delta}_e) = 0.0001124$; $z_{e0} = \hat{\Delta}_e \Big/ \sqrt{V(\hat{\Delta}_e)} = 3.518 > 2.33$

Therefore p_0 = 1, *i.e.* Pr(Effective) $= \Phi(3.518) = 0.99978 > 0.99$



Relaxing the Assumptions—Summary & References

1. Positive cost of adoption increases the EVSI, almost always

$$C_A > 0 \quad \Rightarrow \quad \text{EVSI} \uparrow$$

2. Accrual rate less than incidence

$$a < k \quad \Rightarrow \quad \text{EVSI} \Downarrow \text{ and Opportunity Cost } \Uparrow$$

3. Results not instantaneous

$$\tau > 0 \quad \Rightarrow \quad \text{EVSI} \Downarrow \text{ and Opportunity Cost } \Uparrow$$

Eckermann S, Willan AR. (2007) *Health Economics* **16**:195-209
Eckermann S, Willan AR. (2008) *Value in Health* **11**:522-526
Eckermann S, Willan AR. (2008) *Medical Decision Making* **28**:300-305

Relaxing the Assumptions—Summary & References

4. Imperfect implementation

$$p_0, p_1 < 1 \quad \Rightarrow \quad \text{EVSI} \Uparrow\Uparrow \text{ and Opportunity Cost } \Downarrow\Downarrow$$

Willan AR, Eckermann S. (2010) *Health Economics* **19**:549-561.

5. Multi-stage adaptive designs

$$\text{ENG} \Uparrow$$

Willan AR, Kowgier ME. (2008) *Clinical Trials* 5:289-300.

Chen HM, Willan AR. (2013) *Clinical Trials* **10**(1):54-62.

Relaxing the Assumptions—Summary & References

6. Mean INB varies between trials (random effects model)

EVSI ↑↑

Willan AR, Eckermann S. (2012) *Health Economics* **21**(10):1183–1195.

7. Industry Perspective

Willan AR, (2008) *Clinical Trials* **5**:587-594.

Chen HM, Willan AR. (2013) *Clinical Trials* **10**(1):54-62.

Willan AR, Eckermann S. (2012) *Pharmacoeconomics* **30**(6):447-459.

Relaxing the Assumptions—Summary & References

8. Positive discount rate

EVSI ⇓ > ETC ⇓

Willan AR, Pinto EM. (2005) *Statistics in Medicine* **24**:1791-1806.

9. Global Trials

Eckermann S, Willan AR. (2009) *Health Economics* **18**:203-216.

Value of Information Methods in the Design and Analysis of Clinical Trials – Part B

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Two Perspectives

Consider two interrelated perspectives:

1. A societal decision maker charged with the responsibility of deciding, in the face of uncertainty, whether or not a new health technology should be added to the formulary for reimbursement, and at what price.

2. The company that owns the patent and is requesting that the technology be added to the formulary for reimbursement.

Two Perspectives

Consider two interrelated perspectives:

1. The societal decision maker must determine, given the amount of uncertainty, what their maximum acceptable price is for reimbursement.

2. The company, given the decision maker's maximum acceptable price, needs to determine if they should to gather more evidence to reduce the uncertainty and thus increase the decision maker's maximum acceptable price.

Some Definitions

Suppose Δ_e is the increase in mean effectiveness provided by the new technology in comparison to the most appropriate standard (QALYs)

Let Δ_c be the increase in mean total cost due to using the new technology in comparison to the most appropriate standard, excluding the price of the technology ($)

Let *P* be the per-patient price of the new technology ($)

Let λ be the threshold value for a unit of effectiveness ($/QALY)

Wrong Question

Is the condition that the incremental net benefit greater than 0; (*i.e.* $\Delta_e\lambda - \Delta_c - P > 0$)

sufficient to approve for reimbursement?

Equivalently is the condition that the ICER = $\frac{\Delta_c + P}{\Delta_e} < \lambda$

sufficient to approve for reimbursement?

YES!

Trouble is: this is the ***right answer*** to the ***wrong question***

Right Question

The right question

Is the condition $\hat{\Delta}_e\lambda - \hat{\Delta}_c - P > 0$ sufficient to approve for reimbursement?

Equivalently, is the condition $\frac{\hat{\Delta}_c + P}{\hat{\Delta}_e} < \lambda$ sufficient to approve for reimbursement?

NO, because it ignores the uncertainty.

Optimal decision making in the face of uncertainty requires the application of decision theory and the associated value of information methods

Sufficient Conditions Under Uncertainty

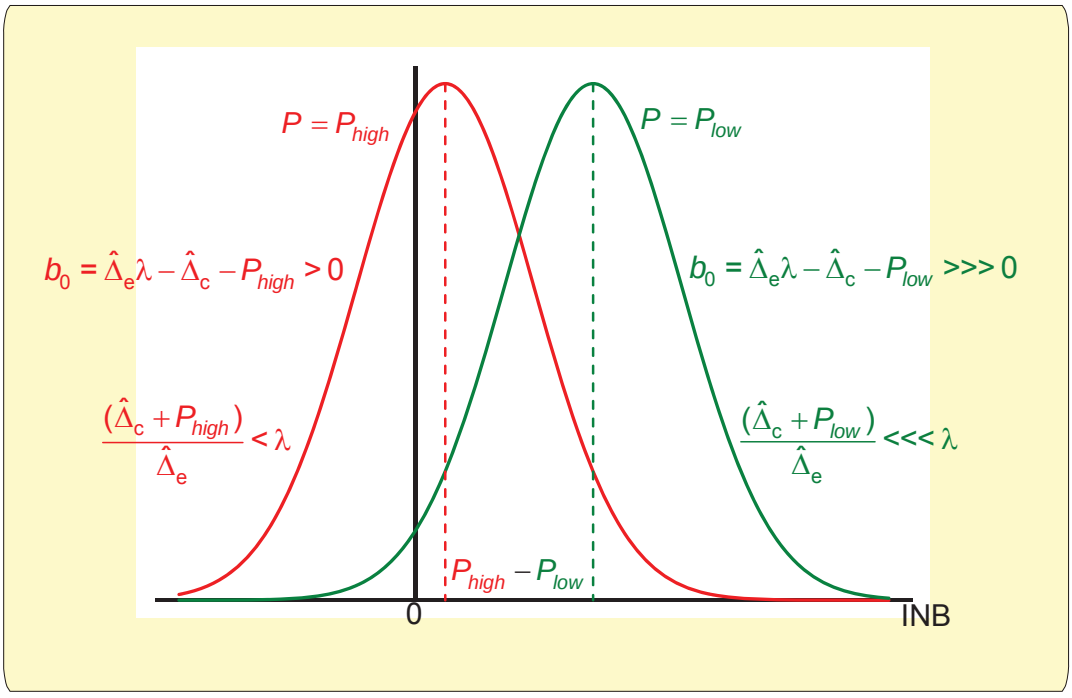
In the face of uncertainty, the sufficient conditions are:

$\hat{\Delta}_e\lambda - \hat{\Delta}_c - P > 0$ or equivalently $\frac{\hat{\Delta}_c + P}{\hat{\Delta}_e} < \lambda$

and

The cost of any new evidence exceeds its value, from the decision maker's perspective

Increasing Price



The Cost of Ignoring Uncertainty

The decision makers cannot ignore the uncertainty

If they do then the company can set the price so that the probability that the new technology is not cost-effective approaches 50%

So how is the uncertainty to be incorporated into the decision making process?

Certainly not *p*-values, confidence intervals and all that other nonsense associated with classical statistical approaches

The way forward is to apply Bayesian decision theory

Value and Cost of New Evidence to the Decision Maker

Bayesian decision theory can be used to determine the value of additional information (evidence) provided by a new study, referred to as the expected value of sample information ($EVSI_d(n)$), where n is the size of the study

Let $ETC_d(n)$ be the expect total cost of the new study

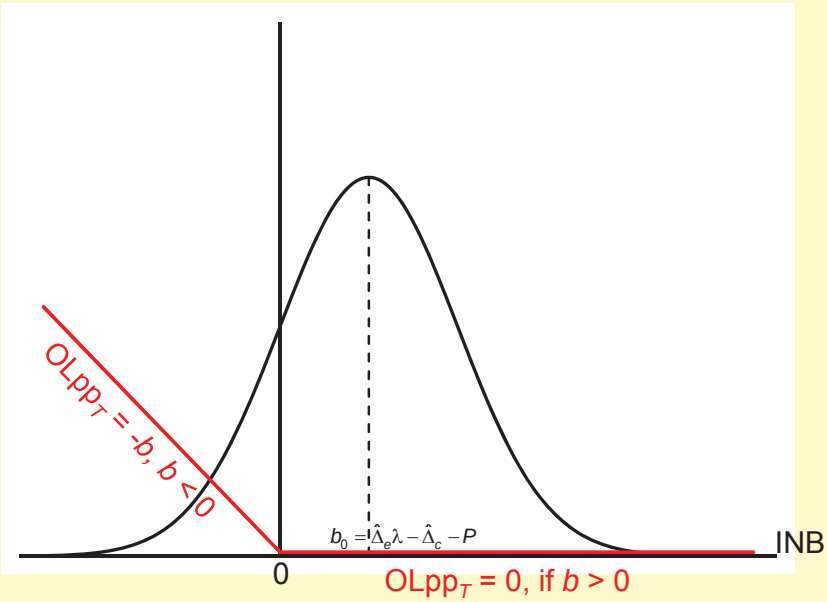
Let $ENG_d(n) = EVSI_d(n) - ETC_d(n)$

Let n_d^* maximize $ENG_d(n)$

If $ENG_d(n_d^*) \leq 0$ then the second condition is met and the new technology shold be approved for reimbursement

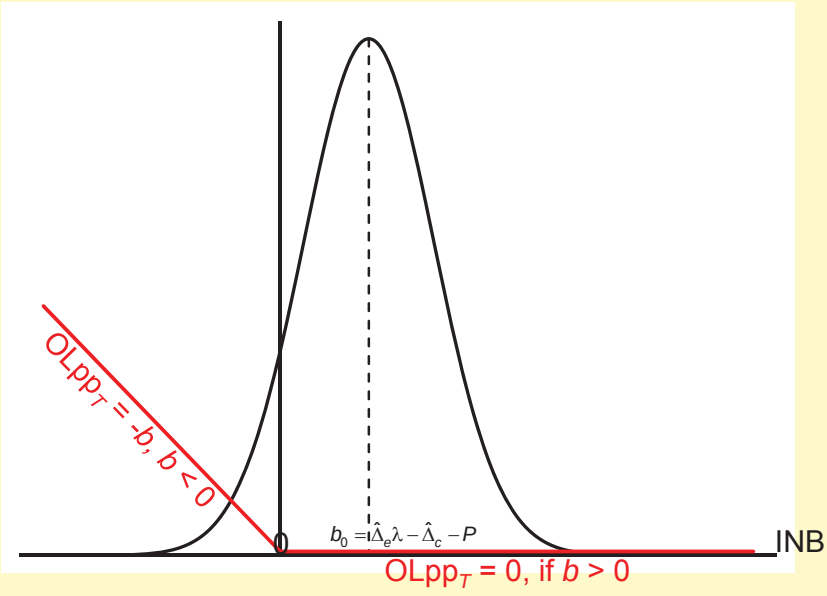
On the other hand, if $ENG_d(n_d^*) > 0$ then approval should be refused and additional evidence requested

$EVSI_d(n)$ is the amount by which the new study reduces the expected opportunity loss of the decision to approve for reimbursement



$EVSI_d(n)$ = Reduction of Expected OL/p *times* Number of patients $(B(n))$

$EVSI_d(n)$ increases as the price (P) goes up



Expected Cost of New Evidence to Decision Maker

Expected total cost to the decision maker of the new study is the opportunity cost of delaying the decision

$ETC_d(n)$ = the number of patients denied the new technology while the study is conducted *times* b_0

$$ETC_d(n) = D(n) \times b_0 = D(n) \times (\hat{\Delta}_e \lambda - \hat{\Delta}_c - P)$$

$ETC_d(n)$ decreases as the price (P) goes up

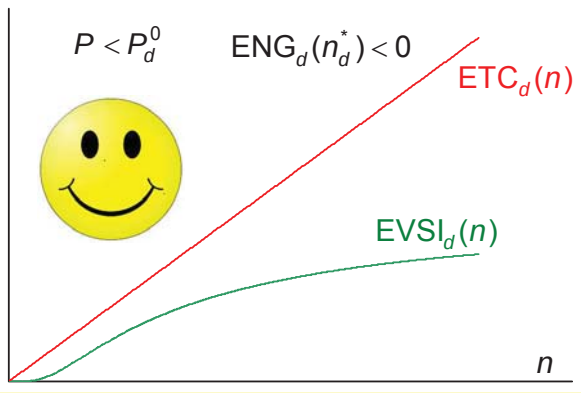
Decision Maker's Threshold Price

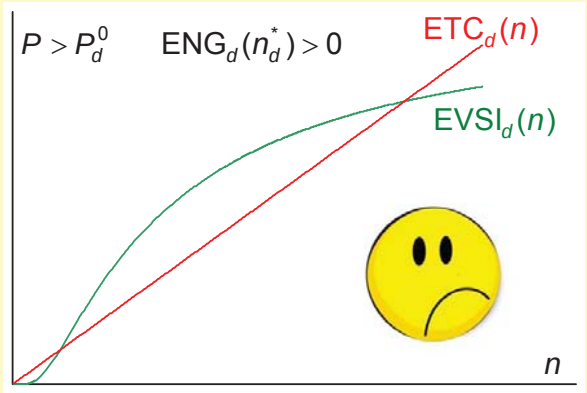
As P increases, $EVSI_d(n)$ increases and $ETC_d(n)$ decreases

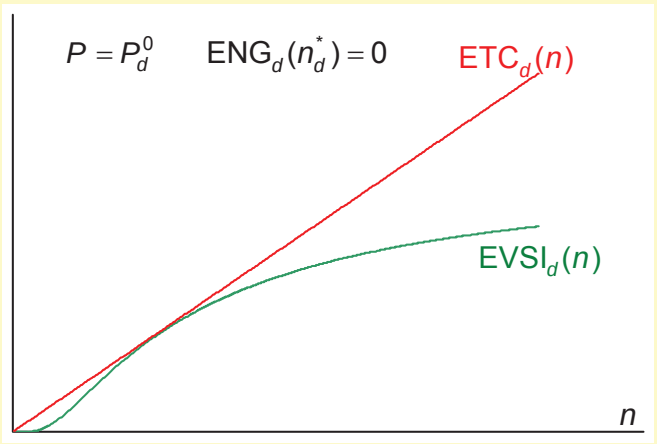
Therefore, as P increases, $ENG_d(n) = EVSI_d(n) - ETC_d(n)$ increases

Therefore, there exists a threshold price, denoted P_d^0, such that if $P > P_d^0$ then $ENG_d(n_d^*) > 0$ and the optimum decision for the decision maker is to delay the decision and request more evidence

On the other hand, if $P < P_d^0$ then $ENG_d(n_d^*) < 0$ and the optimum decision for the decision maker is to approve for reimbursement







Expected Net Gain for Company

For the company the ENG for another trial for a given price P

$$\text{EVSI}_c(n) = B(n)\left\{\text{E}(P_d^1) - P\right\}$$

where P_d^1 is the decision maker's post-study threshold price

$$\text{ETC}_c(n) = \textit{Financial}(n) + D(n)P$$

$$\text{ENG}_c(n) = \text{EVSI}_c(n) - \text{ETC}_c(n)$$

Let n_c^* maximize $\text{ENG}_c(n)$

Expected Net Gain for Company

$$\mathrm{EVSI}_c(n) = B(n)\left\{\mathrm{E}(P_d^1) - P\right\}$$

As P increases $\mathrm{EVSI}_c(n)$ decreases

$$\mathrm{ETC}_c(n) = \mathit{Financial}(n) + D(n)P$$

As P increases $\mathrm{ETC}_c(n)$ increases

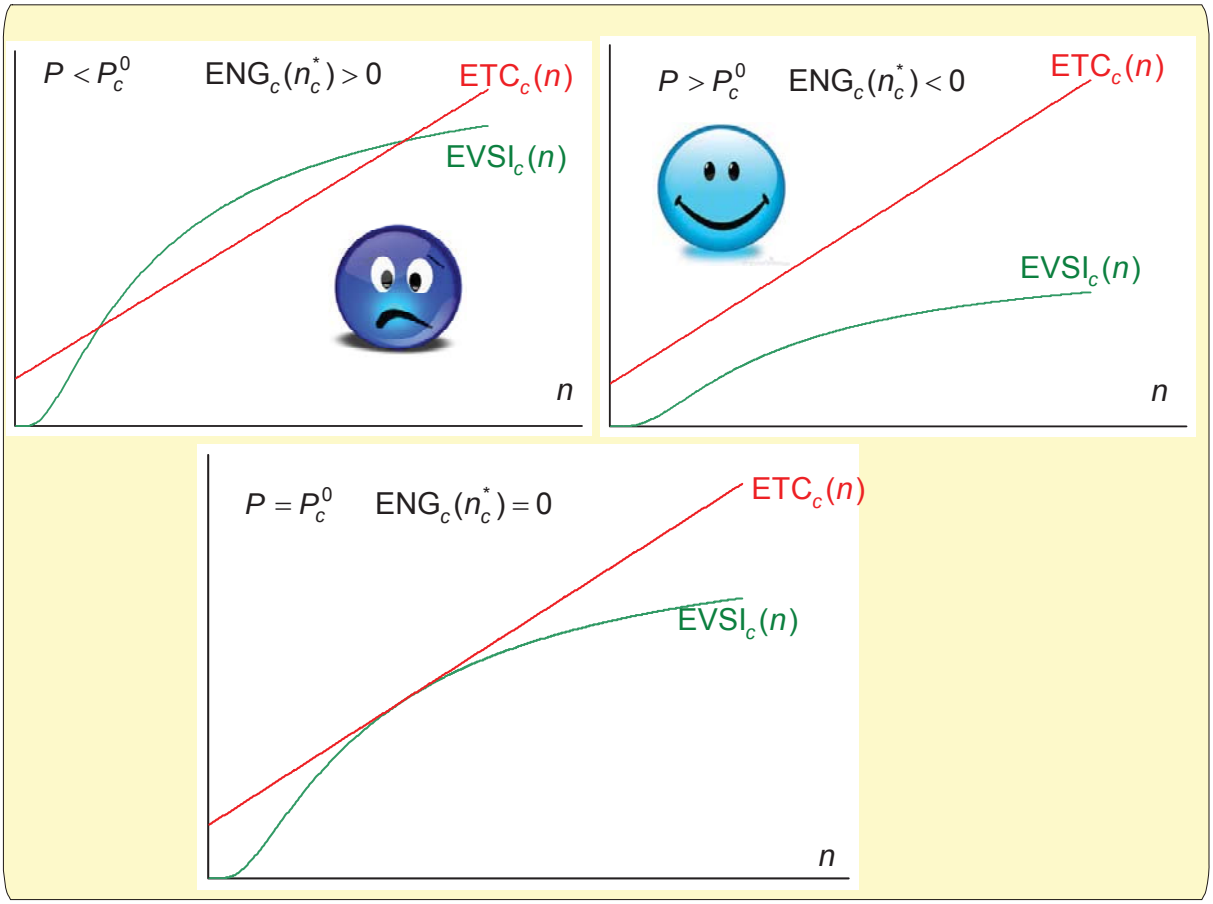
$$\mathrm{ENG}_c(n) = \mathrm{EVSI}_c(n) - \mathrm{ETC}_c(n)$$

As P increases $\mathrm{ENG}_c(n)$ decreases

Threshold Price to Company

Therefore, there exists a threshold price, denoted P_c^0, such that if $P < P_c^0$ then $\mathrm{ENG}_c(n_c^*) > 0$ and the optimum decision for the company is to not to submit for reimbursement approval,and perform study

On the other hand, if $P > P_c^0$ then $\mathrm{ENG}_c(n_c^*) < 0$ and the optimum decision for the company is to submit for reimbursement approval



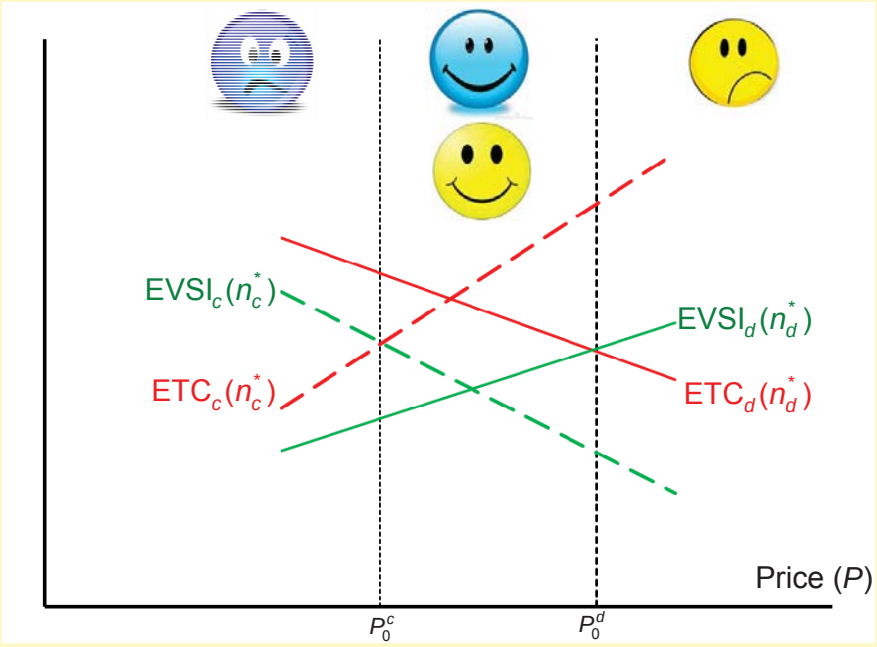
The Threshold Prices Interact

P_d^0 is the maximum price acceptable to the decision maker

P_c^0 is the minimum price acceptable to the company

If $P_d^0 \geq P_c^0$ then any price between P_c^0 and P_d^0 is acceptable to both

CADET-Hp Trial



$EVSI_c(n_c^*) < ETC_c(n_c^*)$

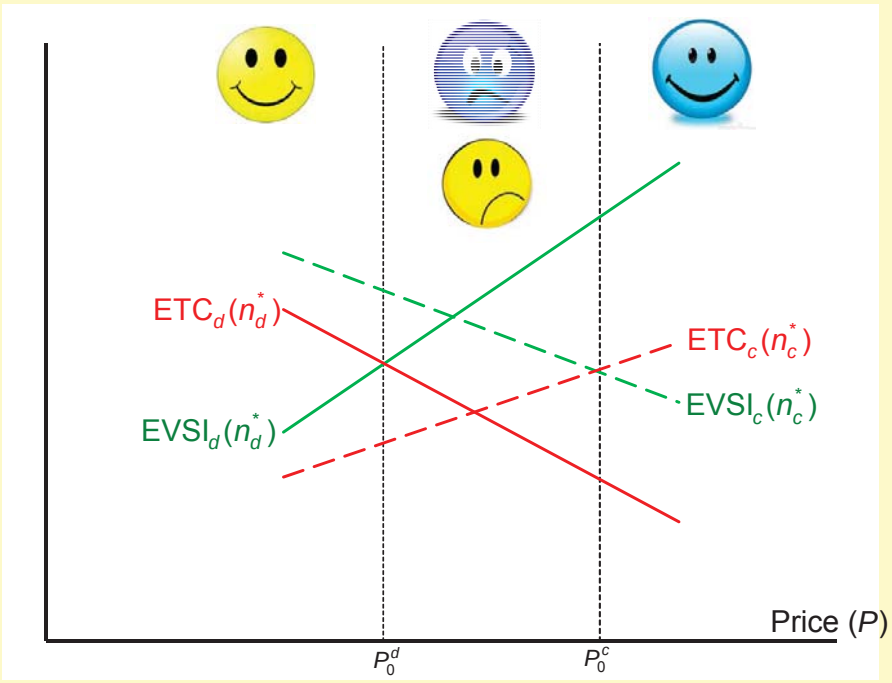
The Threshold Prices Interact

P_d^0 is the maximum price acceptable to the decision maker

P_c^0 is the minimum price acceptable to the company

On the other hand, if $P_d^0 < P_c^0$ then no price is acceptable to both, and at the maximum price the company can get (*i.e.* P_d^0), $ENG_c(n_c^*) > 0$. Therefore optimal decision for the company is to delay submission and perform study of size n_c^*

CADET-Hp Trial



$EVSI_c(n_c^*) > ETC_c(n_c^*)$

CADET-Hp Trial

Double-blind, placebo-controlled, parallel-group, multi-centre, randomized controlled trial.

Patients with uninvestigated dyspepsia of at least moderate severity were randomized between

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

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

Treatment success was defined as the presence of no or minimal dyspepsia symptoms at one year.

Total costs were determined from the societal perspective and are given in Canadian dollars.

CADET-Hp Trial

	Treatment (n_T = 142)	Standard (n_S = 146)	
$\hat{e}_j$	0.5070	0.3699	difference = $\hat{\Delta}_e$ = 0.1371
$\hat{V}(\hat{e}_j)$	0.001760	0.001596	sum = $\hat{V}(\hat{\Delta}_e)$ = 0.003356
$\hat{c}_j$	455.47	529.98	difference = $\hat{\Delta}_c$ = -74.51 (-53.01)
$\hat{V}(\hat{c}_j)$	2167	2625	sum = $\hat{V}(\hat{\Delta}_c)$ = 4792
$\hat{C}(\hat{e}_j, \hat{c}_j)$	-0.2963	-0.4166	sum = $\hat{C}(\hat{\Delta}_e, \hat{\Delta}_c)$ = -0.7129

$$b_0 = \hat{\Delta}_e\lambda - \hat{\Delta}_c - P = 0.1371\lambda + 74.51 - P$$

$$v_0 = \hat{V}(\hat{\Delta}_e)\lambda^2 + \hat{V}(\hat{\Delta}_c) - 2\lambda\hat{C}(\hat{\Delta}_e, \hat{\Delta}_c) v_0 = 0.003356\lambda^2 + 4792 - 2\lambda(-0.7129)$$

CADET-Hp Trial

threshold value of outcome (λ)	\$500
time horizon (h)	10 years
incidence (k)	80,000 / year
accrual rate (a)	800 / year
follow-up (τ)	1.5 years
fixed cost (C_f)	\$800,000
variable cost (C_v)	\$2000

$$b_0 = \hat{\Delta}_e\lambda - \Delta_c - P = 143.06 - P$$

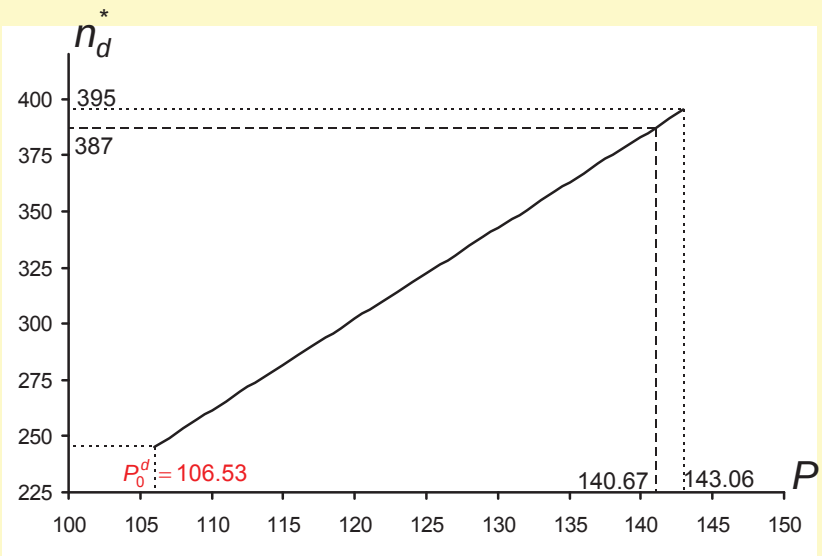
$$v_0 = 6344$$

CADET-Hp Trial

P	Prob(C-E)	ICER	b_0	
0	0.96	-543.47	143.06	$\text{ENG}_d(n_d^*) < 0$
25	0.93	-361.12	118.06	
50	0.88	-178.77	93.06	
75	0.80	3.57	68.06	
100	0.71	185.92	43.06	
$P_d^0 = 106.53$	0.68	233.55	36.53	
125	0.59	368.27	18.06	$\text{ENG}_d(n_d^*) > 0$
143.06	0.5	500	0	

Approve if $P \leq 106.53$
or Prob(C-E) ≥ 0.68
or ICER ≤ 233.55
or $b_0 \geq 36.53$

CADET-Hp Trial



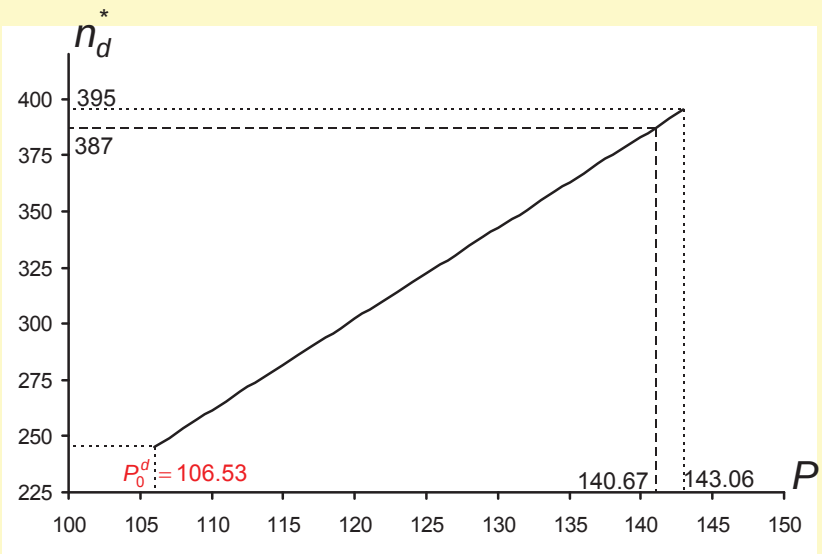
$$\text{INB}_0 = \hat{\Delta}_e \lambda - \hat{\Delta}_c - P = 143.06 - P$$

CADET-Hp Trial

for $P = P_0^d = 106.53$ $\qquad P_0^d < P_0^c \Leftrightarrow ENG_c(n_n^* \mid P = P_0^d) > 0$

Sample Size Per Arm (n)	$EVSI_c$	ETC_c	ENG_c	$E(P_d^1)$
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

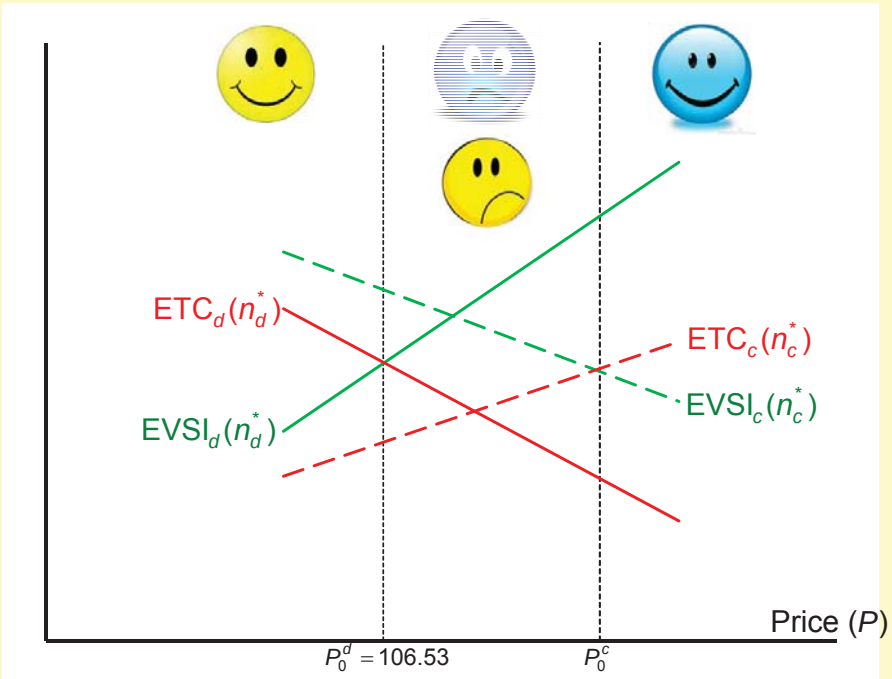
CADET-Hp Trial



$$INB_0 = \hat{\Delta}_e \lambda - \hat{\Delta}_c - P = 143.06 - P$$

CADET-Hp Trial

$P_0^d < P_0^c \Leftrightarrow ENG_c(n_n^* \mid P = P_0^d) > 0$



Other Issues

- Risk neutral versus risk aversion
- Bias
- Random effects
- Global Trials

Summary I

Additional evidence has value to both:

Decision maker: reduces expected opportunity loss.

The company: increases “acceptable” price to the decision maker.

Additional evidence has cost to both:

Decision maker: opportunity costs.

The company: financial costs and lost revenue.

Summary II

Given current level of evidence the decision maker and the company each have a threshold price

If the decision maker’s exceeds the company’s then current evidence is sufficient for reimbursement

Otherwise, the company should get more evidence prior to submitting for reimbursement approval, or the decision maker should request more evidence prior to approval

References—VOI and Reimbursement

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