Value and Uncertainty in the Pricing of New Health Interventions

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Two Perspectives

Consider two interrelated perspectives:

1. A societal decision maker charged with the responsibility of deciding, based on current evidence (*i.e.* in the face of uncertainty), whether or not to add a new health technology 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.

Motivating Example 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.

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

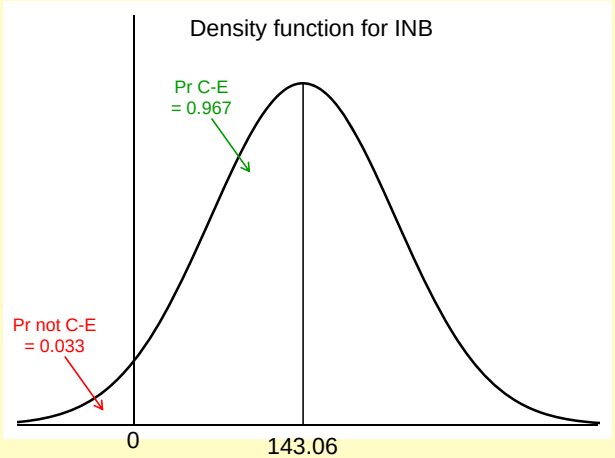
	Treatment (n_T=142)	*Standard* (n_S=146)	
$\hat{e}_j$	0.5070	0.3699	difference = $\hat{\Delta}_e$ = 0.1371
$\hat{c}_j$	455.47	529.98	difference = $\hat{\Delta}_c$ = -74.51
$\hat{V}(\hat{e}_j)$	0.001760	0.001596	sum = $\hat{V}(\hat{\Delta}_e)$ = 0.003356
$\hat{V}(\hat{c}_j)$	2167	2625	sum = $\hat{V}(\hat{\Delta}_c)$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

Mean Incremental net benefit: $b_0 = \hat{\Delta}_e\lambda - \hat{\Delta}_c - P = 0.1371\times\lambda + 74.51 - P$

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

For λ = 500; $b_0 = 143.06 - P$ *and* $v_0 = 6344$

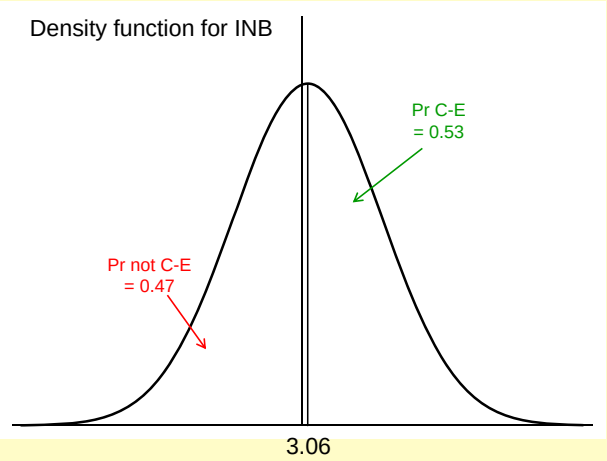
P = 0



INB = 143.06 – 0
= 143.06

ICER
= (-74.51 – 0)/0.1371
< 500

P = 140



INB = 143.06 – 140
= 3.06

ICER
= (-74.51+140)/0.1371
= 478 < 500

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.

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

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 and 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

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

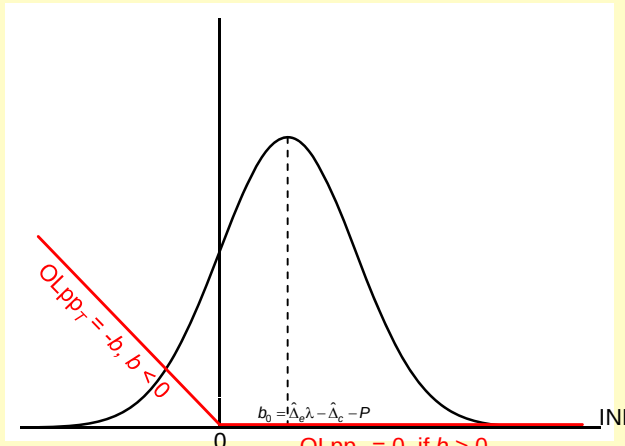
Let $ENG_d(n) = EVSI_d(n) - ETC_d(n)$

Let n_d^* maximize $ENG_d(n)$

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

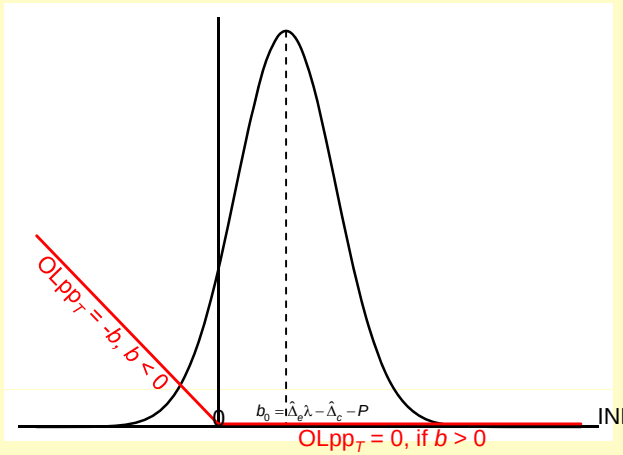
On the other hand, if $ENG(n_d^*) > 0$ then approval should be refused and additional evidence requested

$EVSI_d(n)$ 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

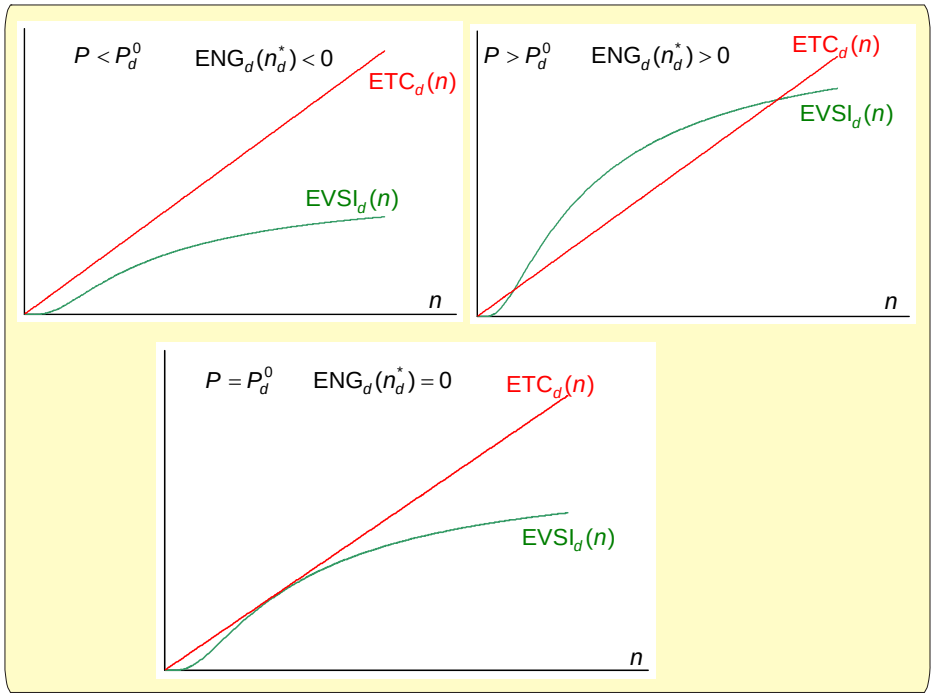
Decision Maker's Threshold Price

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

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

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

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

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

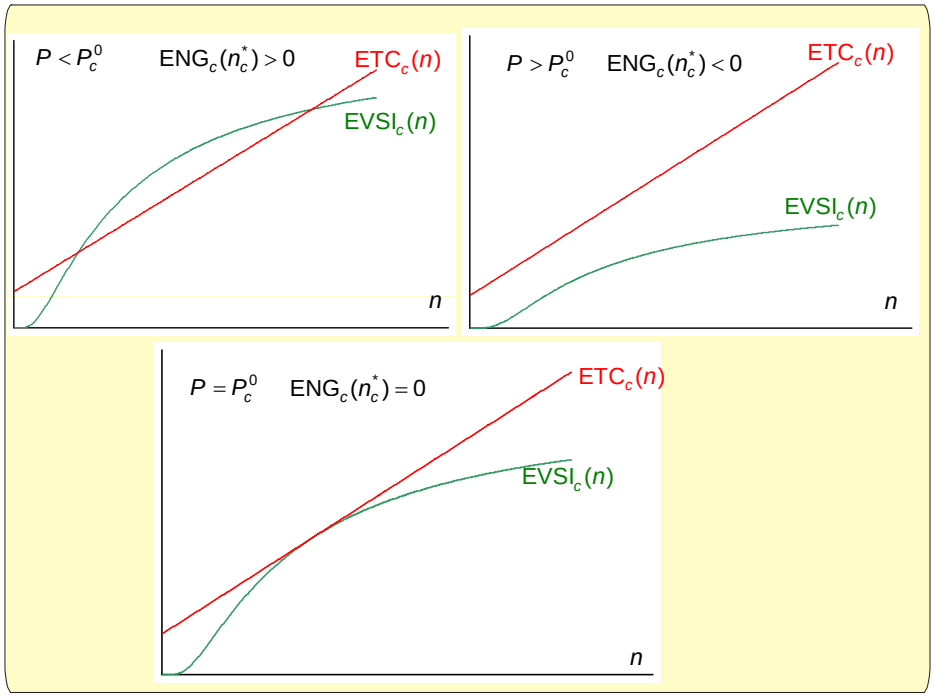
$$\text{ENG}_c(n) = \text{EVSI}_c(n) - \text{ETC}_c(n)$$

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

Threshold Price to Company

Therefore, there exists a threshold price, denoted P_c^0, such that if $P < P_c^0$ then $\text{ENG}_c(n_c^*) > 0$ 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 $\text{ENG}_c(n_c^*) < 0$ 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

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), $\text{ENG}_c(n_c^*) > 0$. Therefore optimal decision for the company is to delay submission and perform study of size n_c^*

CADET-Hp Trial

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

$$\text{Mean } INB = \hat{\Delta}_e \lambda - \Delta_c - P = 143.06 - P$$

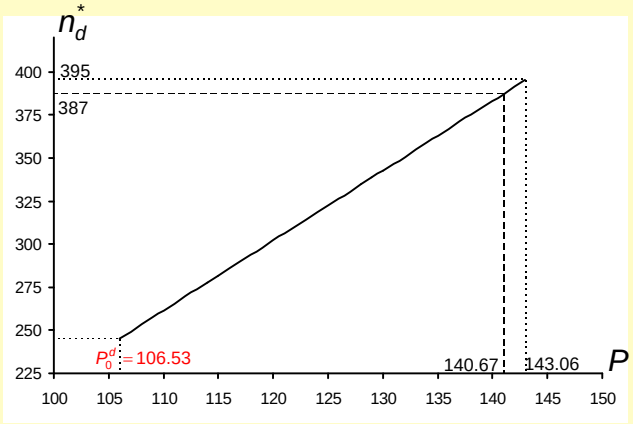
$$\text{Var(INB)} = 6344$$

CADET-Hp Trial

P	Prob(C-E)	ICER	INB
0	0.96	-543.47	143.06
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
143.06	0.5	500	0

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

CADET-Hp Trial



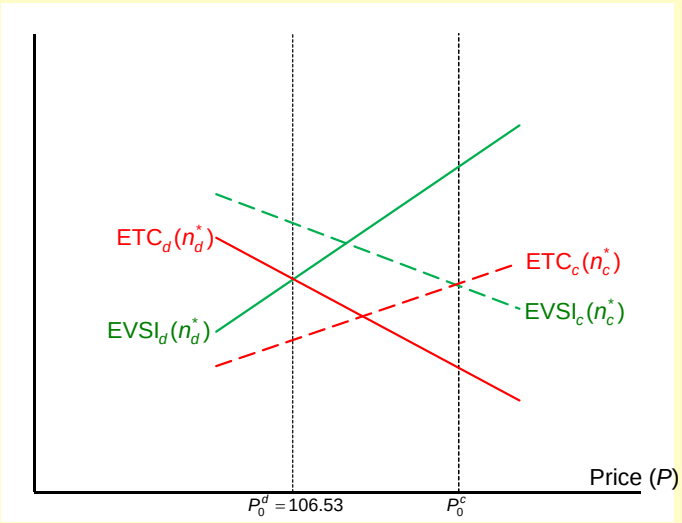
$$\text{INB}_0 = \hat{\Delta}_e\lambda - \hat{\Delta}_c - P = 143.06 - P$$

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



Other Issues

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

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

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

Slides: www.andywillan.com/talks