Determination of trial size: How large should our RCT be?

Economics Perspective

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Brief Outline

- Introduce Incremental Cost-effectiveness Ratios (ICERs)
- Examine a couple of approaches based on ICERs
- Introduce Incremental Net Benefit (INB)
- Relate INB to Value of Information (VOI) methods for optimal sample size determinations
- Provide example

Consider a trial for comparing two health care interventions, ***Treatment*** **(*T*) vs** ***Standard*** **(*S*), with respect to cost-effectiveness**

Collect patient-level health-care costs
Not just costs related to the interventions
Might include non-health care costs, such as time lost from work

Δ_e : difference ($T - S$) in effectiveness

e.g. difference in the probability of surviving
difference in mean survival
difference in quality-adjusted mean survival

Δ_c : difference ($T - S$) in mean costs

Incremental Cost-effectiveness Ratio (ICER)

$$\text{ICER} = \frac{\Delta_c}{\Delta_e} = \Delta_c \frac{1}{\Delta_e} = \Delta_c \text{NNT}$$

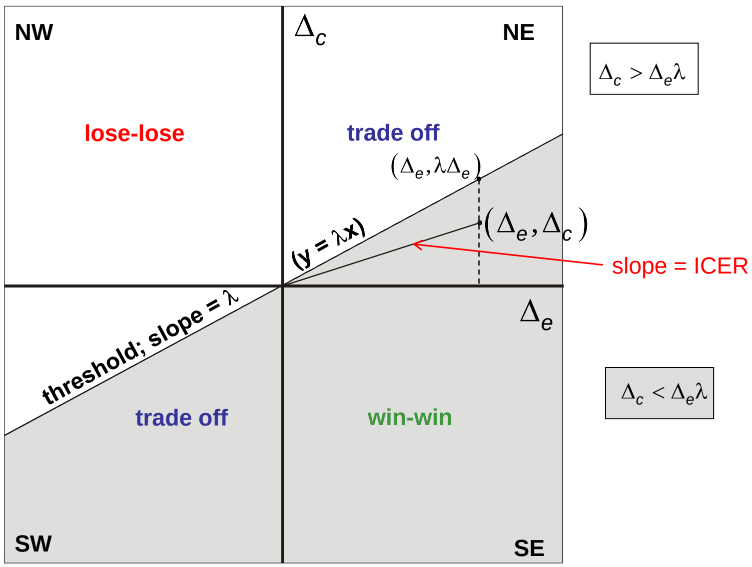
$\therefore$ ICER is the cost of achieving an additional unit of effectiveness from adopting T in replacement of S

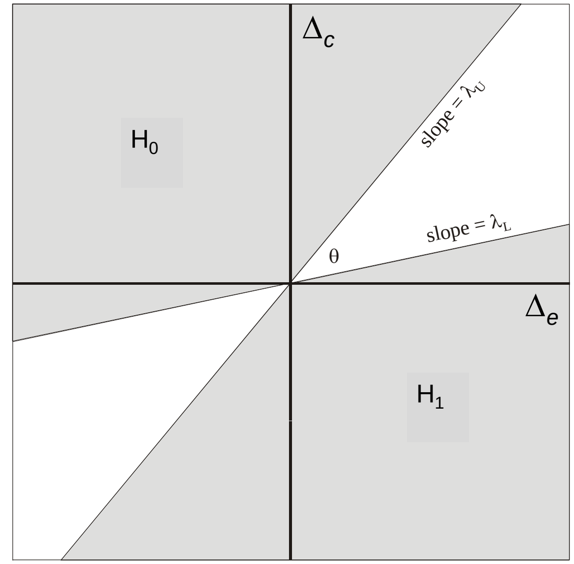
e.g. cost of saving a life
cost of a year of life
cost of a quality-adjusted life-year

T is cost-effect iff $\Delta_c \le \lambda \Delta_e$,
where λ threshold value for a unit of effectiveness

$\therefore$ T is cost-effect iff ICER $\le \lambda$ ($\Delta_e > 0$)
or iff ICER $\ge \lambda$ ($\Delta_e < 0$)

Cost-effectiveness Plane



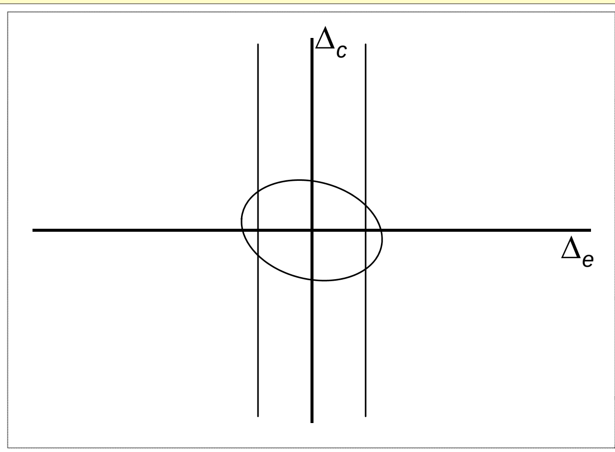


$\Pr(\text{adopting } T \mid H_0) \le \alpha$

$\Pr(\text{adopting } T \mid H_1) \ge 1-\alpha$

Achieved by having a sufficiently large sample so that the angle between the upper and lower limit for the $100(1-\alpha)\%$ confidence interval for ICER is no greater than θ

For a particular sample size and given $\lambda_L, \lambda_H, \alpha$ and between patient variation in effectiveness and costs



Gardiner JC *et al. Health Economics* 2000; **9**: 227-234.

Willan AR, O'Brien BJ *Health Economics* 1999; **8**: 203-211.

Problems with ICERs and INB as an Alternative

Not properly ordered, *e.g.* $\text{ICER} = \frac{-1000}{0.1} = \frac{1000}{-0.1} = -10{,}000$

Confidence intervals can include undefined values (observed difference in effectiveness is not statistically significant)

Confidence intervals may not exist (observation is "too close" to origin)

Incremental net benefit (INB) defined as $b \equiv \Delta_e\lambda - \Delta_c$

Treatment is cost-effective iff $b > 0$

Adopt T iff $b_0 > 0$, where b_0 is the current estimate of b
(Bayesian: b_0 is the mean of the prior distribution for b)

Question: Is the evidence sufficient for adopting T

Value of Information (VOI) Methods (AKA Bayesian Decision Theory)

Prior distribution for INB has mean $b_0 > 0$ and variance $v_0 > 0$

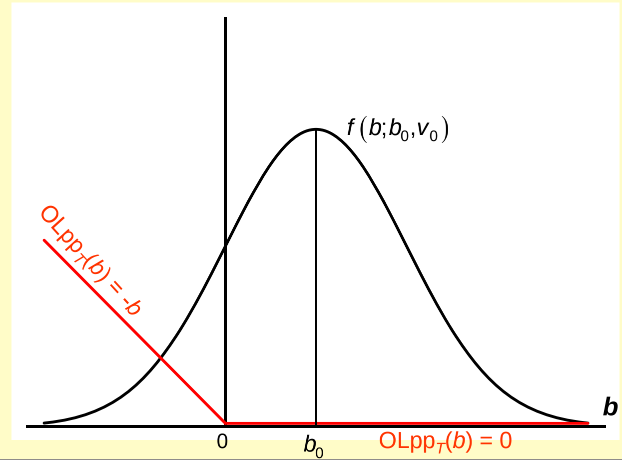
Based on current evidence, VOI methods can identify

- The expected value of an additional clinical trial (function of *n*/arm)
- The expected cost of the trial, opportunity and financial (function of *n*/arm)

If expected value < expected cost for all sample sizes
then current evidence is sufficient to adopt *T*

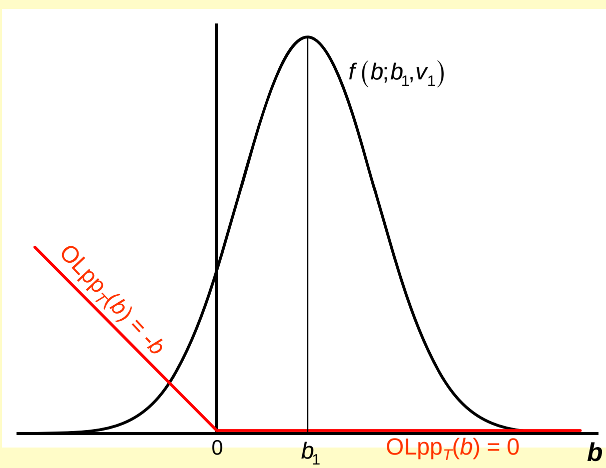
If expected value > expected cost for any sample size
- state of equipoise exists
- conduct study with *n*/arm that maximizes value *minus* cost

Opportunity Loss for Adopting *T* (per patient) ($OLpp_T$)



$$E_0 OLpp_T = \int_{-\infty}^{0} -b\, f(b; b_0, v_0)\, db \equiv \mathcal{D}(b_0, v_0)$$

Post Expected Opportunity Loss (per patient)



$E_1 OLpp_T = E_{trial\ data} \mathcal{D}(b_1, v_1)$ (a function of n, b_0, v_0 and σ_+^2)

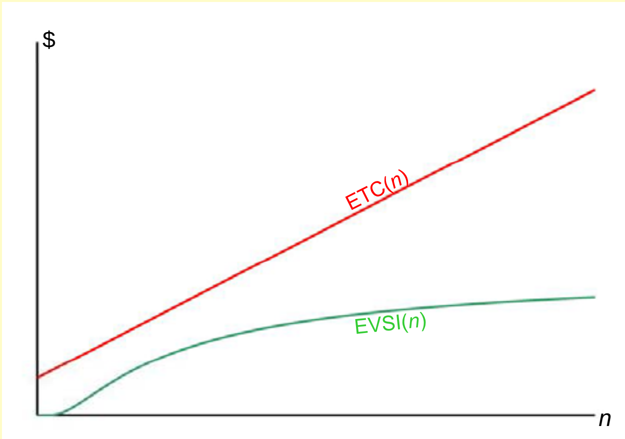
Expected Value, Cost and Net Gain

Value: $EVSI(n) = B(n)\left\{\mathcal{D}(b_0, v_0) - E_{trial\ data}\mathcal{D}(b_1, v_1)\right\}$,
where $B(n)$ = the number of patients that can benefit

Cost: ETC(*n*) = financial costs(*n*) + expected opportunity costs(*n*),
where expected opportunity cost(*n*) = $D(n) b_0$,
and $D(n)$ is the number of patients who receive *S* because of the trial

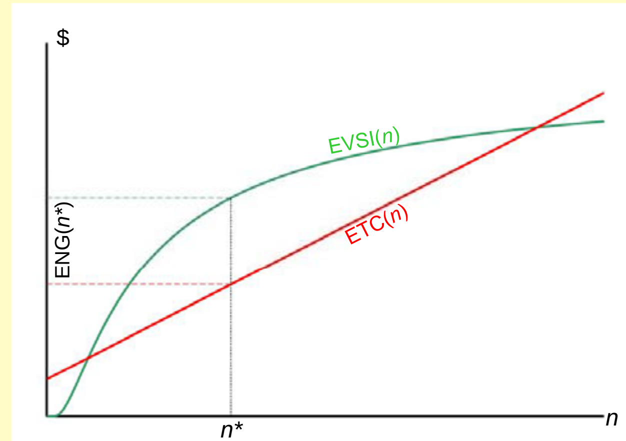
Net Gain: ENG(*n*) = EVSI(*n*) - ETC(*n*)

Expected Value, Cost and Net Gain



Current evidence sufficient for decision making

Expected Value, Cost and Net Gain



State of equipoise exists since current evidence is insufficient

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.

Chiba N *et al. BMJ* 2002; **324**: 1012-1016.

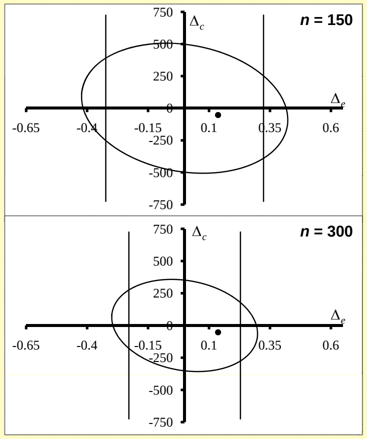
Chiba N *et al. Alim. Pharm. Therap*. 2004; **19**: 349-358.

Willan AR. *European J. of Gastro. and Hepat.* 2004; **16**: 543-549.

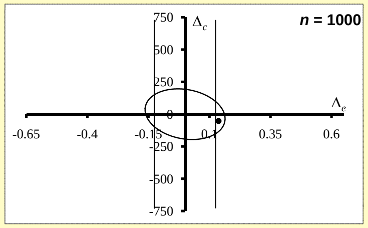
CADET-Hp Trial

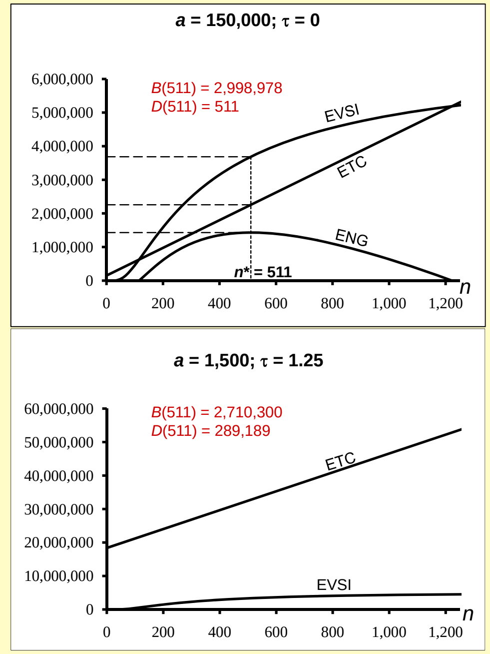
	Treatment (n_T = 142)	*Standard* (n_S = 146)	
Mean Effectiveness	0.5070	0.3699	difference = $\hat{\Delta}_e$ = 0.1371
Mean Cost	476.97	529.98	difference = $\hat{\Delta}_c$ = -53.01
$V(\hat{\Delta}_e) = 0.003356$		$V(\hat{\Delta}_c) = 4792$	$C(\hat{\Delta}_e, \hat{\Delta}_c) = -0.7129$
ICER = -387		90% confidence limits = -1708, 612	

CADET-Hp Trial



$\lambda_L = 500; \quad \lambda_U = 1500$





λ = \$500

$\therefore b_0 = 306.51; \quad v_0 = 6343.90$

Incidence = 150,000 / year

Time horizon = 20 years

a = accrual rate/year

τ = follow-up duration

References

- Willan AR. *PharmacoEconomics* 2011; **29**: 513-524.
- Willan AR, O'Brien BJ. *Health Economics* 1999; **8**: 203-211.
- Gardiner et al. *Health Economics* 2000; **9**: 227-234.
- Claxton K, Posnett J. *Health Economics* 1996; **5**: 513-524.
- Claxton K. *Journal of Health Economics* 1999; **18**: 341-364.
- Ades AE, Lu G, Claxton K. *Medical Decision Making* 2004; **24**: 207-227.
- Willan AR, Pinto EM. *Statistics in Medicine* 2005; **24**: 1791-1806.
- Eckermann S, Willan AR. *Health Economics* 2007; **16**: 195-209.
- Willan AR. *Clinical Trials* 2007; **4**: 279-285.
- Willan AR. *Clinical Trials* 2008; **5**: 587-594.
- Willan AR, Kowgier ME. *Clinical Trials* 2008; **5**: 289-300.
- Eckermann S, Willan AR. V*alue 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
- Willan AR, Eckermann S (2011) Expected value of information and pricing new health care interventions. *Pharmacoeconomics* (accepted).
- Willan AR, Eckermann S (20??) Accounting for between-study variation in value of information methodology. *Health Economics* (under review).

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