The Advantages of Bayesian Decision Analysis in Small Populations

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Frequentists vs Bayesians

"Statistics has not, traditionally, been an exciting word. It's most common prefix is the word *dry*."

The Economist, February 11th, 2017. Obituary of Hans Rosling

Three Main Reasons to Prefer Bayesian Approach in Clinical Research

Permits simple, intuitive and relevant statements of statistical inference regarding the parameters of interest directly
(Bayes Lite)

Provides a transparent framework for combining new information with current knowledge
(Bayes)

Facilitates decision theory (value of information methods) for optimal decision-making and research design
(Full-on Bayes)

Children with High risk, Stage 3 Neuroblastoma

ABMT - myeloablative chemotherapy, total-body irradiation and transplantation of purged autologous bone marrow

CC - intensive non-myeloablative continuation chemotherapy

5 years of recruitment: 72 eligible patients, 43 consented and enrolled

Park JR et. al. *Pediatr Blood Cancer* 2009; **52**:44–50

1-sided Fisher exact 0.13	Survival				Total
	No		Yes		
	n	row %	n	row %	N
Treatment Arm					
ABMT	7	35.0	13	65.0	20
CC	13	56.5	10	43.5	23

Bayesian Decision Theory

In the face of uncertainty, decision theory permits optimal decision making, answering the following questions:

Should a new intervention be adopted for future patients?

Is more research needed?

If so, how big should the study be?

Bayesian Decision Theory
Guiding Principles

A new intervention should be adopted if *no* more research is needed

More research is needed if the *value of the information* from the research is greater than its *cost*

The size of the study should maximize the difference between the *value* and the *cost*

Incremental Net Benefit (Utility)

Incremental net benefit of a new intervention defined as:

$b(\lambda) \equiv \lambda\Delta_e - \Delta_c$

Δ_e is the increase in mean effectiveness

λ is the threshold value placed on a unit of effectiveness

Δ_c is the increase in mean cost

Children with High risk, Stage 3 Neuroblastoma

Δ_e is the difference in probability of survival

Mean = 0.196; SD = 0.1402

Δ_c is the increase in mean cost

Mean = 50,000; SD = 50,000 (*i.e.* CV = 1)

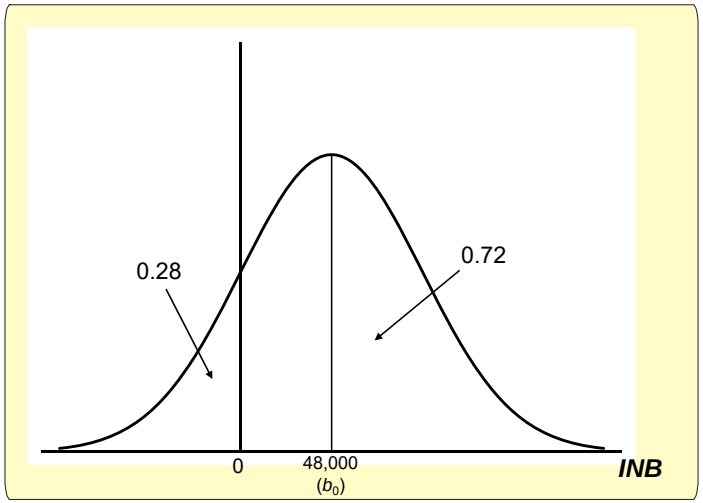
λ = 500,000

ICER = Δ_c/Δ_e = 50,000/0.196 = 255,102

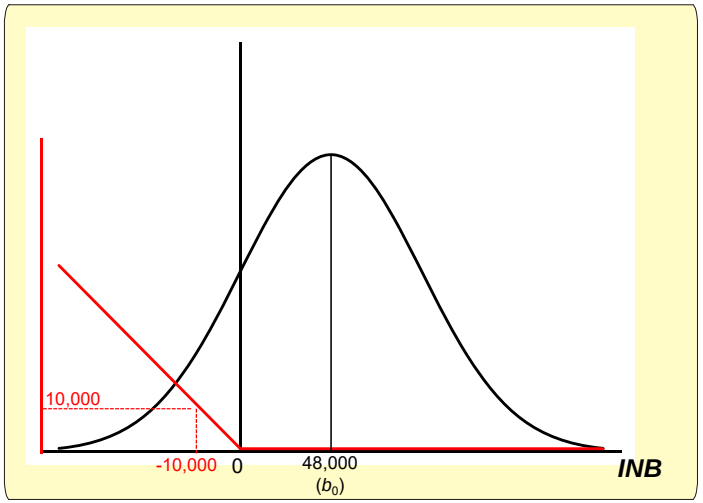
$b(500,000) \sim N(b_0, v_0) = N(48,000, 6,794,410,000)$

Prob. cost effective: Prob[$b(500,000) > 0$] = 0.72

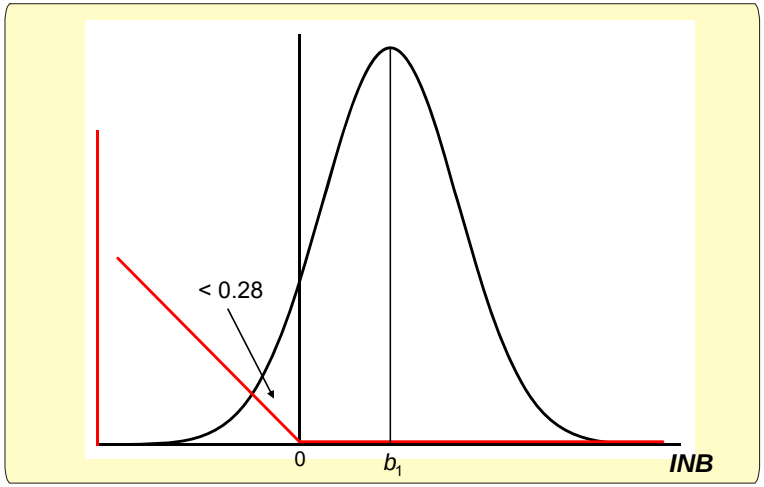
Value of Additional Evidence
Current Distribution of INB



Value of Additional Evidence
Opportunity Loss Function and _Current_ Distribution of INB



Value of Additional Evidence
Opportunity Loss and "_Future_" Distribution of INB



Reduction in patient Expected Opportunity Loss (EOL) = $\mathcal{K}(b_0, v_0, n, \sigma_+^2)$

Value of Additional Evidence
Reduction in Population Expected Opportunity Loss

Expected Value of new trial = the reduction in population EOL

$$EV(n) = k(h-t) \times \mathcal{K}(b_0, v_0, n, \sigma_+^2)$$

k = incidence

h = time horizon

t = duration of trial

$k \Uparrow$ Value of New Trial $\Uparrow$

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

Expected Total Cost

$ETC(n) = C_f + 2nC_v + (kt - n)b_0$

where

C_f = fixed financial cost

C_v = variable financial cost per patient

$(kt - n)$ is the number of patients who are denied intervention (*i.e.* receive standard) because of the trial, each of whom incur an expected opportunity cost of b_0

$k \Uparrow$ Cost of New Trial $\Uparrow$

Expected Net Gain

$ENG(n) = EV(n) - ETC(n)$

Let n^* maximize $ENG(n)$

If $ENG(n^*) < 0$ then current evidence is sufficient and optimal decision is to adopt the intervention

If $ENG(n^*) > 0$ then current evidence is insufficient and optimal decision is to do a trial with $2n^*$ patients

Children with High risk, Stage 3 Neuroblastoma

h = 20 years

k = 20 per year

accrual = $0.7k$ = 14 per year

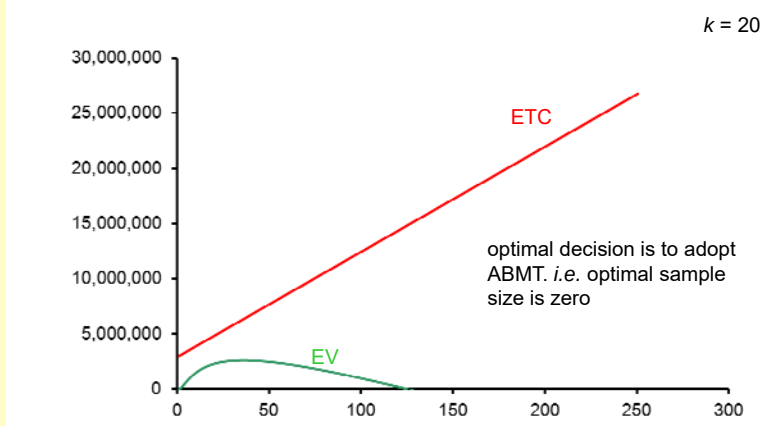
follow-up = 2 years

$t = (2n/14) + 2$

C_f = 1,000,000

C_v = 3000

Children with High risk, Stage 3 Neuroblastoma



Children with High risk, Stage 3 Neuroblastoma

Standard Approach

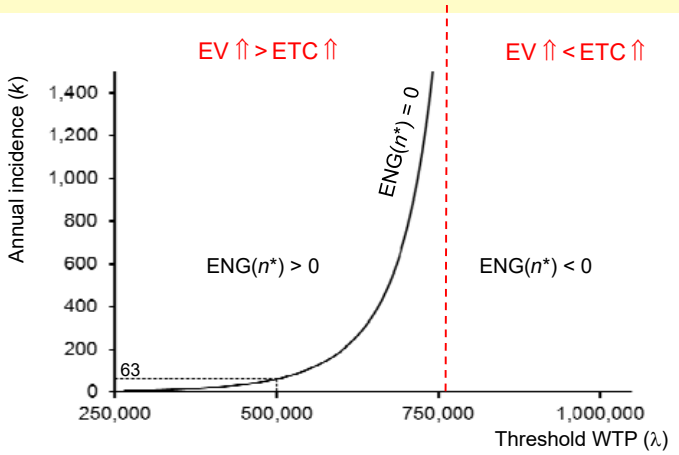
Type I error probability = 0.05, one-sided

Power = 0.8

SCID = 0.1, based on an NNT of 10 $(\text{NNT} \times \Delta_c \leq \lambda)$

n/arm = 305

Children with High risk, Stage 3 Neuroblastoma



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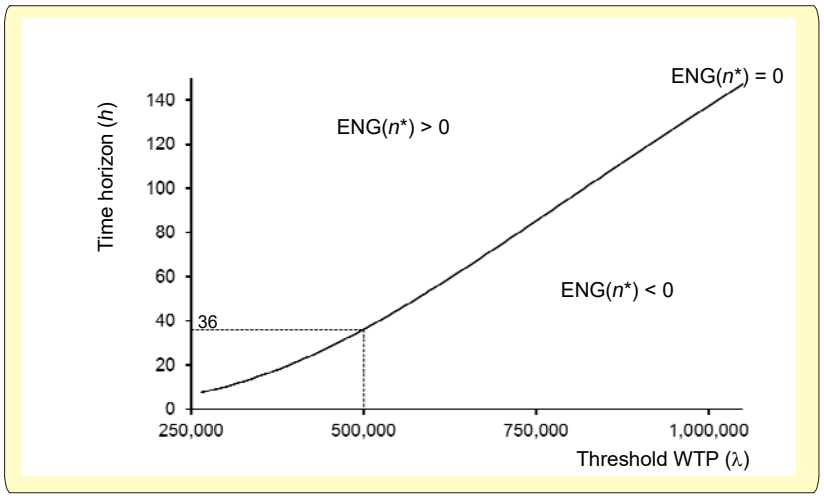

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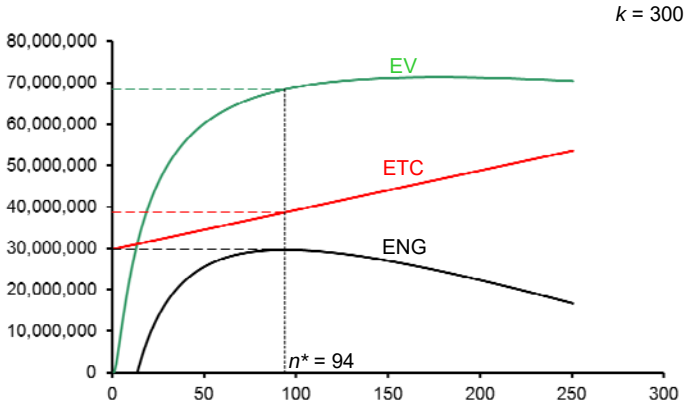

Summary

Bayesian Decision Analysis has advantages in assessing the evidence in support of new health care interventions

Takes into account:

- current evidence
- threshold value for health outcomes
- trial costs (financial and opportunity)
- accrual rate
- duration of follow-up
- time horizon
- incidence (requiring less evidence for rare health conditions)

Allow for comparison of “return for investment” between proposed trials

For rare health conditions, trials are smaller (and cheaper), may lead to less expensive interventions

References—Bayesian Advantages

Spiegelhalter DJ, Abrams KR, Myles JP. (2004) *Bayesian Approaches to Clinical Trials and Health-Care Evaluation*. Wiley, Chichester.

Willan AR. (2013) Bayesian methods provide important advantages for the design, analysis and interpretation of clinical studies. In: Berger VW, Zhang X. (Eds.) *Important Considerations for Clinical Trial Methodologies*. Future Medicine, London. (eISBN 978-1-909453-31-9)

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