Summary

- Expected Value of Sample Information
- Expected Net Benefit of Sampling
  - Trial costs
- Challenges/Discussion

References

Welton NJ et al 2014. *Expected Value of Sample Information for Cluster Randomised Trials with Binary Outcomes*: Medical Decision Making, **34**:352-365

EVSI for Study Design

- EVSI measures the value of **reducing** uncertainty by running a study of a given design

- Can compare the benefits and costs of a study with given design
  - To see if a proposed study likely to be a good use of resources
  - To find the optimal study design

EVSI Can Help Assess

- Do we really need another study?
- What type of study (or studies)? RCT (# arms?)?
- What should the new study measure?
  - Efficacy? Which interventions? Which outcomes?
  - Economic data?
- Length of follow-up? Follow-up existing trials?
- What patient group should the new study include?
- What sample size should be used?
- etc...

EVSI: Basic Idea

- A new study with given design (eg sample size) will provide new data, $D = d$
  - Reducing uncertainty in a subset of model parameters
- Update inputs (eg meta-analysis) to CEA model
- Update the cost-effectiveness model
  - If the optimal decision changes **gain** in NB from using new optimal treatment
  - If optimal decision unchanged, **no gain** in NB

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- Average this gain in INB over future possible datasets D to obtain EVSI
  - Based on a prediction from existing evidence
- Expected Value of Partial Perfect Information (EVPPI) is an upper bound for EVSI for given subset of parameters

Posterior given data d

$$\text{EVSI} = \text{E}_{\boldsymbol{\theta},d|\boldsymbol{\theta}}\left[\max_t\left\{\underbrace{\text{E}_{\boldsymbol{\theta}|d}\left[\text{NB}_t(\boldsymbol{\theta})\right]}_{\substack{\text{Value of decision based on}\\ \textbf{sample}\text{ information}\\ \text{(for a given study design)}}} - \underbrace{\text{NB}_{t^*}(\boldsymbol{\theta})}_{\substack{\text{Value of decision based on}\\ \textbf{current}\text{ information}}}\right\}\right]$$

Prior predictive distribution (pre-posterior)

- Expected Net Benefit of Sampling:

  ENBS = Pop. EVSI - Cost of Trial

- Population EVSI:

  Pop. EVSI = EVSI $\times$ prevalence $\times$ time horizon

- Cost of Trial:

  Cost = Fixed + Intervention + Opportunity

Depend on sample size

Trial Costs

- Fixed Costs
  - Staff time: managers, coordinator, administrator, statistician, data-base support
- Costs per practise
  - Recruitment, training, site visits
  - Data collection
- Opportunity Costs
  - Net Benefit differences between randomised arm and (current) optimal arm
  - Value of research to those involved in the trial.

$$C(n) = \left[c_f + \sum_{t=1}^{T} (c_t n_t)\right] + EVSI(n) \sum_{t=1}^{T} n_t + \sum_{t=1}^{T} \{n_t E_\vartheta [NB_{t*}(\vartheta) - NB_t(\vartheta)]\}$$

Optimal Trial Design

- Only studies where expected benefits outweigh study costs are a good use of resources
- Choose the design with greatest Expected Net Benefit of Sampling (ENBS):
  - No value of a study design with ENBS < 0
  - There is value in a study where ENBS > 0... even if it not the maximum ENBS

Case Study 1: Interventions for Attendance at Breast Screening[1]

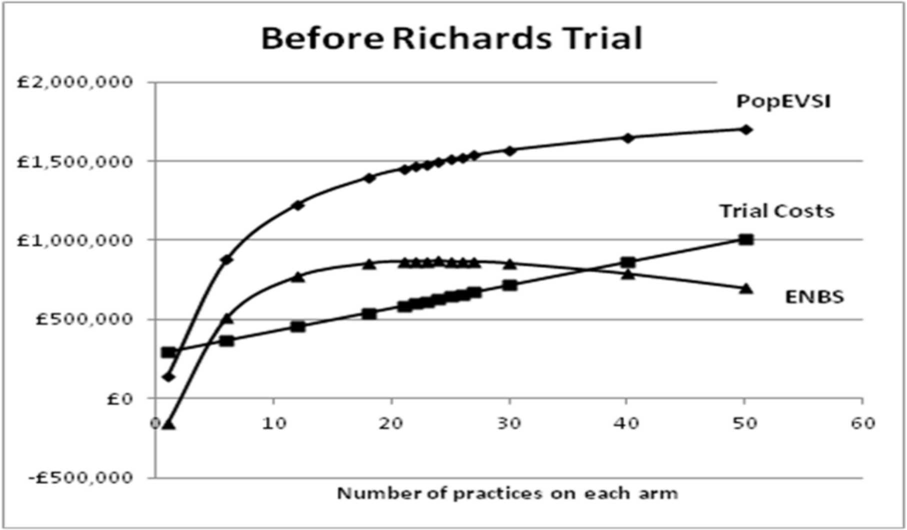
- Richards et al (2002)
  - Cluster randomised 2×2 factorial trial
  - 24 practices randomised
  - None, Flag, Letter, Both

- EVSI analysis
  - BEFORE: Based on evidence base before the trial
    - Monte Carlo (MC) simulation
  - AFTER: Based on pre-trial evidence base updated by the trial
    - Markov Chain Monte Carlo (MCMC) simulation

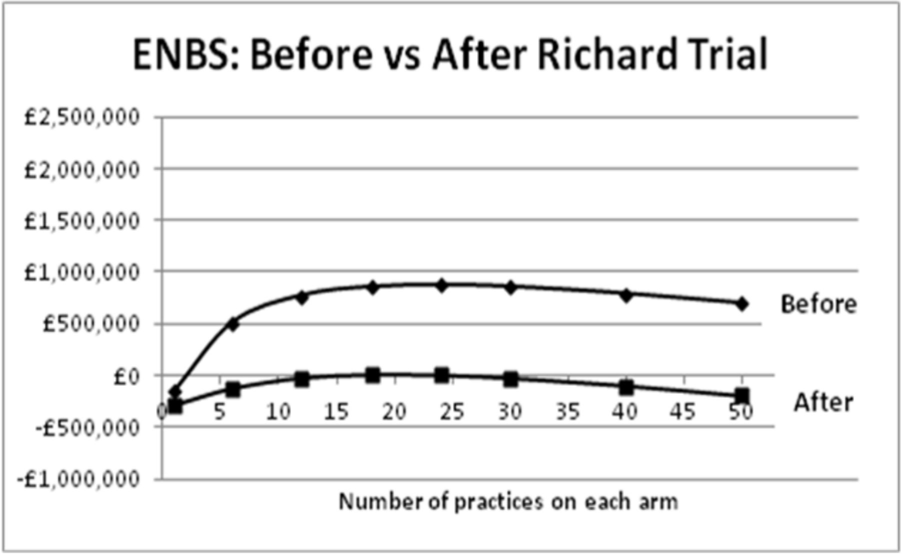
[1] Richards et al 2001. Cluster randomised controlled trial comparing the effectiveness and cost-effectiveness of two primary care interventions aimed at improving attendance for breast screening. Journal of Medical Screening. **8**:91-98

- Decision tree model
- Evidence on efficacy before Richards et al based on systematic review of similar types of intervention
- Other model inputs from routine data sources (Toms 2004) and cohort study (Wolstenholme 1998)
- Prevalence: 300,000 per year eligible for 1st invitation to screening
  - 30,000 in low-uptake practices as sensitivity analysis
- Time horizon = 10 years, 3.5% discount rate
- Willingness to pay per QALY = £20,000

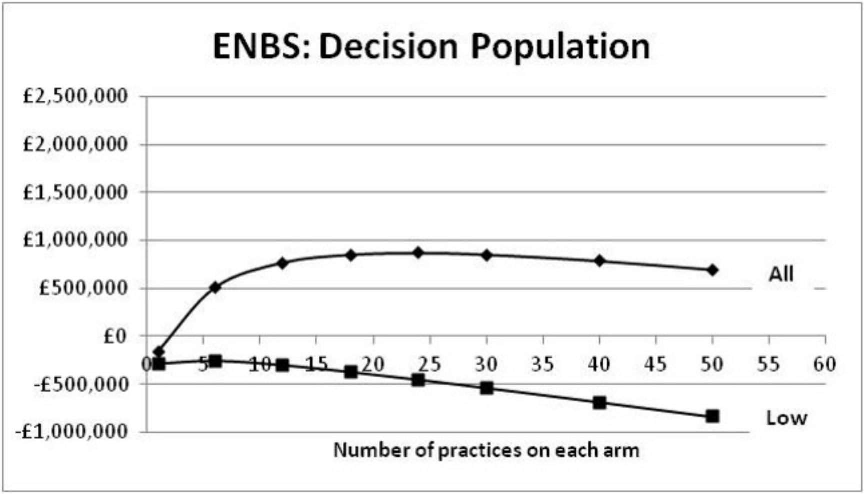
Before Richards Trial (WTP=£20,000)



Before & after...



BEFORE, WTP = £20K, decision population



- Lower decision uncertainty for low-uptake practices

Implications for Research Design

- There was value in carrying out the Richards trial based on prior evidence
  - Sample size could have been larger
- No further value in running a new trial subsequent to the Richards et al trial
- Only considered new study measuring relative intervention effects
  - ... and only one aspect of study design (sample size)
  - Richards et al also collected intervention cost data

EVSI Computation: Nested Simulation

$$\text{EVSI} = \mathsf{E}_{\boldsymbol{\theta},d|\boldsymbol{\theta}} \left[\max_t \left\{ \mathsf{E}_{\boldsymbol{\theta}|d} \left[\mathsf{NB}_t(\boldsymbol{\theta}) \right] - \mathsf{NB}_{t^*}(\boldsymbol{\theta}) \right\} \right]$$

- Simulate data from prior predictive distribution (pre-posterior) “outer” simulation
- Given data, form the posterior expected NB_t
  - Typically requires “inner” simulation, which may need to be Markov Chain Monte Carlo simulation
  - Average over “inner’ simulation to find posterior ENB
- Find maximum posterior expected net benefit
- Average over “outer” simulation
- This can be very time-consuming!
- Optimising over different study designs is even more expensive.

Efficient Computation Methods for EVSI

- There are four general purpose methods to compute EVSI:
  - Importance Sampling Method (Menzies, 2016)
  - Gaussian Approximation Method (Jalal and Alarid-Escudero, 2018 & Jalal et al., 2015)
  - Moment Matching Method (Heath et al., 2018)
  - Regression-Based Method (Strong et al., 2015)
- We will discuss Moment Matching and the Regression-Based method in this course.
- Each method requires different expertise and has different advantages.

Required Inputs and Expertise to Compute EVSI

Requirements	Methods			
	RB	IS	GA	MM
Inputs				
Decision-Analytic Model				x
Probabilistic sensitivity analysis	x	x	x	x
Simulations of the expected net benefit conditional on ϕ (required to compute EVPPI)		x		x
Expertise & Skills				
Regression methods	x		x	
Specification of likelihoods		x		
Requirement of summary statistic	x		$*$	
Bayesian updating			$*$	x

Strengths and Limitations of Each Method

Requirements	Methods			
	RB	IS	GA	MM
Can estimate EVSI with a large number of outcomes		x		x
Inaccurate with sample sample sizes or prior sample sizes			x	x
Computational challenges with large proposed studies		x		
Requires a low-dimensional summary statistics	x			
Requires accurate EVPPI estimation		x		x
Uses non-parametric regression	x		x	
Quantifies uncertainty in EVSI estimation	x		x	x
Estimates EVSI across sample size			x	x