Value of Information Analysis in the Prioritisation and Design of RCTs

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Using Existing Data to Inform Clinical Trial Design

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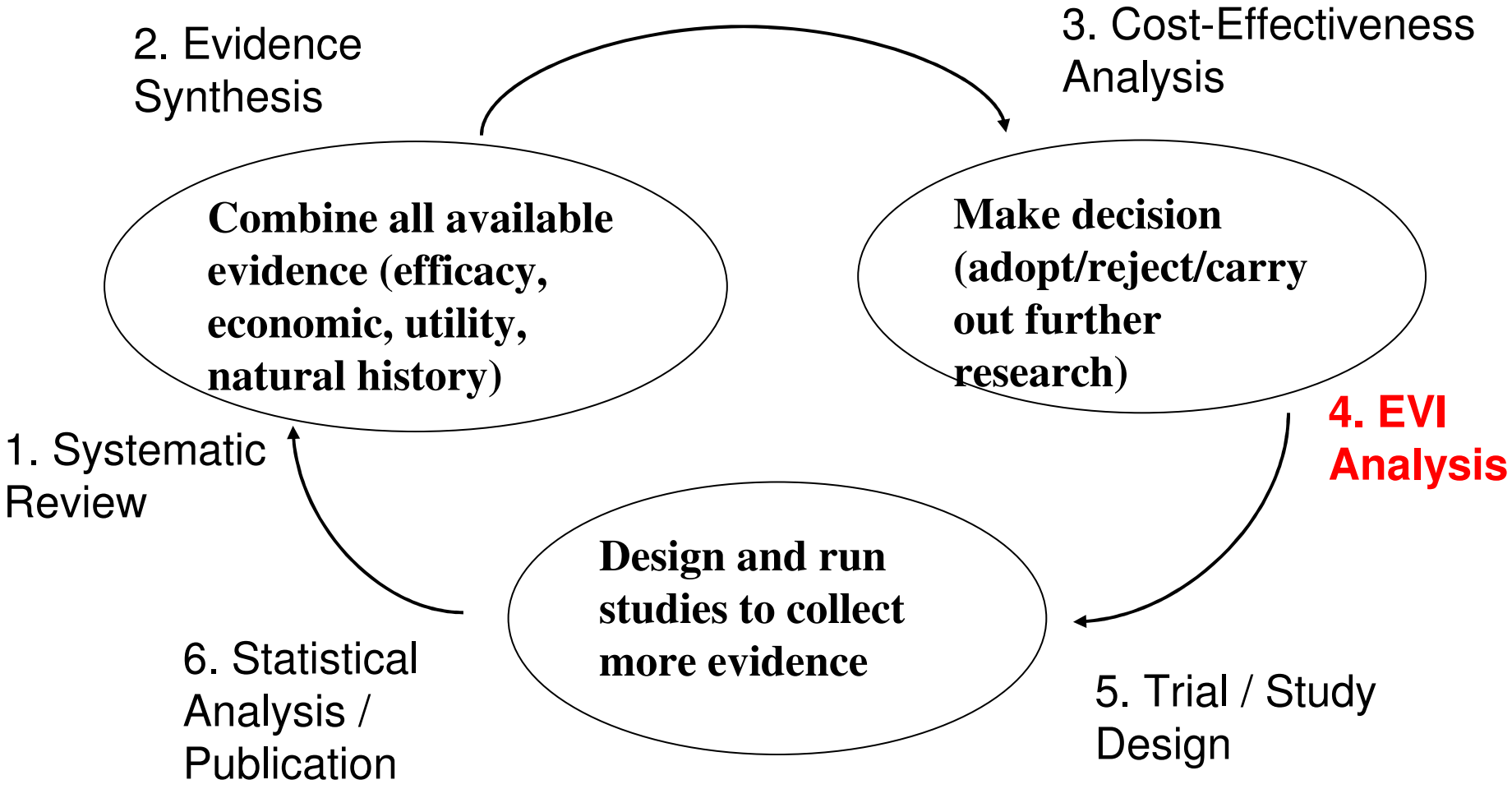
Dept. Community Based Medicine

Outline

- Introduce Expected Value of Information methods
  - Identify key parameters driving decision uncertainty
  - Guide research funders prioritising research efforts
  - Guide trial design
- Illustrate methods using two examples
- Discuss barriers to and potential for the routine use of EVI methods

Evidence Based Decision-Making



- **Process Inherently Bayesian**

Decision-Making Context

- Eg: “Which screening/treatment strategies for group B streptococcus in pregnant women are cost-effective in the UK?”

- Maximise Expected Net Benefit, E(NB)
  - NB = Incremental Benefit – Incremental Cost
  - Depends on treatment, efficacy, economic, utility, natural history parameters

Based on Current Evidence

- Choose treatment k* with greatest Expected NB
  - i.e. average over all joint uncertainties in model inputs

- Value of a decision based on current information:

$$E\left[NB(k^*, \theta, \eta, \upsilon, \psi)\right]$$

- Optimal treatment k* is only best on average
  - …there is a chance that it's wrong
  - EVI measures the value lost as a result of a wrong decision

EVI: Key Idea

- Given a study design (eg sample size)
  - we collect data, D
  - reduce parameter uncertainty
  - hence reduce decision uncertainty
  - If the optimal decision changes, there is a gain in NB from using the new optimal treatment, rather than k*
- Choose design to maximise this gain in E(NB)
  - RCT (how many arms?)/Cohort
  - Sample size
  - Follow-up time

Expected Value of Sample Information

$$EVSI = \underset{D|\theta,\nu,\eta,\psi}{E}\left[\underbrace{\max_k \left\{\underset{\theta,\nu,\eta,\psi|D}{E}\left[NB(k,\theta,\nu,\eta,\psi)\right]\right\}}_{\text{Value of decision based on sample information (for a given study design)}} - \underbrace{NB(k^*,\theta,\nu,\eta,\psi)}_{\text{Value of decision based on current information}}\right]$$

Prior predictive distribution

Posterior given data D

- EVPI: provides an upper bound … easy!

Optimal Trial Design

- Population EVSI:

  Pop. EVSI = EVSI*prevalence*time horizon

- Cost of Trial:

  Cost = Fixed + Intervention + Opportunity

  Depend on sample size

- Expected Net Benefit of Sampling:

  ENBS = Pop. EVSI – Cost of Trial

Two Examples

1. Breast Cancer Screening
   - Cluster randomised trial

2. Early Onset Group B Streptococcus (EOGBS)

1. Breast Cancer Screening (Richards et al 2001)

- Cluster randomised factorial 2x2 design trial
  - 6 practices on each arm

- Interventions to increase probability of uptake of breast cancer screening
  1. No intervention (*none*)
  2. GP signed letter + leaflet (*letter*)
  3. Paper reminder in GP notes + leaflet (*flag*)
  4. Both interventions (*both*)

Objectives

- How EVI methods could have been used to design the trial (sample size):
  - Based on a summary of literature available before the trial
- Apply the methods again after trial
  - Incorporating trial evidence

Statistical Model

- Binomial outcomes: attendance at screening
- Logistic regression model for uptake probabilities π:

$$\text{log-odds}(\pi_j) = \mu_j^{RCT} + \beta_{letter} + \beta_{flag} + \beta_{int}$$

Baseline log-odds for practice j

Main Effects

Interaction

- Random effects model for baseline log-odds by practice:

$$\mu_j^{RCT} \sim N(\beta_{none}, \sigma^2)$$

Evidence BEFORE Trial

- Prior to 2000
  - Substantial body of research available (mainly non-UK)
  - Meta-analyses* of patient and practitioner targeted interventions (active control)

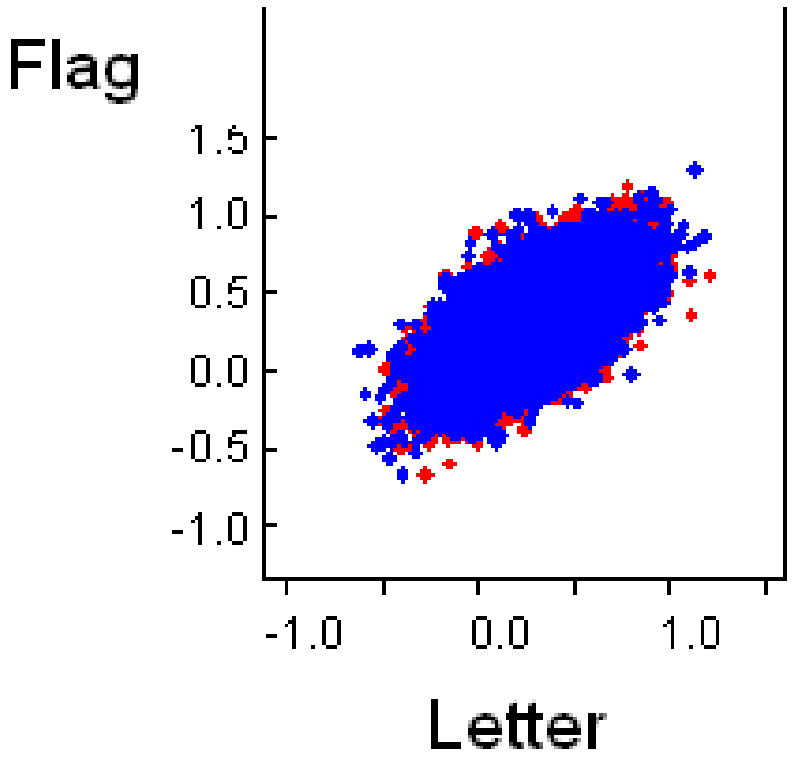
- Main effects from distribution of intervention effects
  - Normal(.3,.232)

- Very little evidence on which to base correlations and interaction effects

*Mandelblatt & Yabroff (1999); Yabroff & Mandelblatt (1999)

Flag & Letter Positively Correlated

- Women differ in persuadability
- If a woman responds to one intervention, likely to respond to another



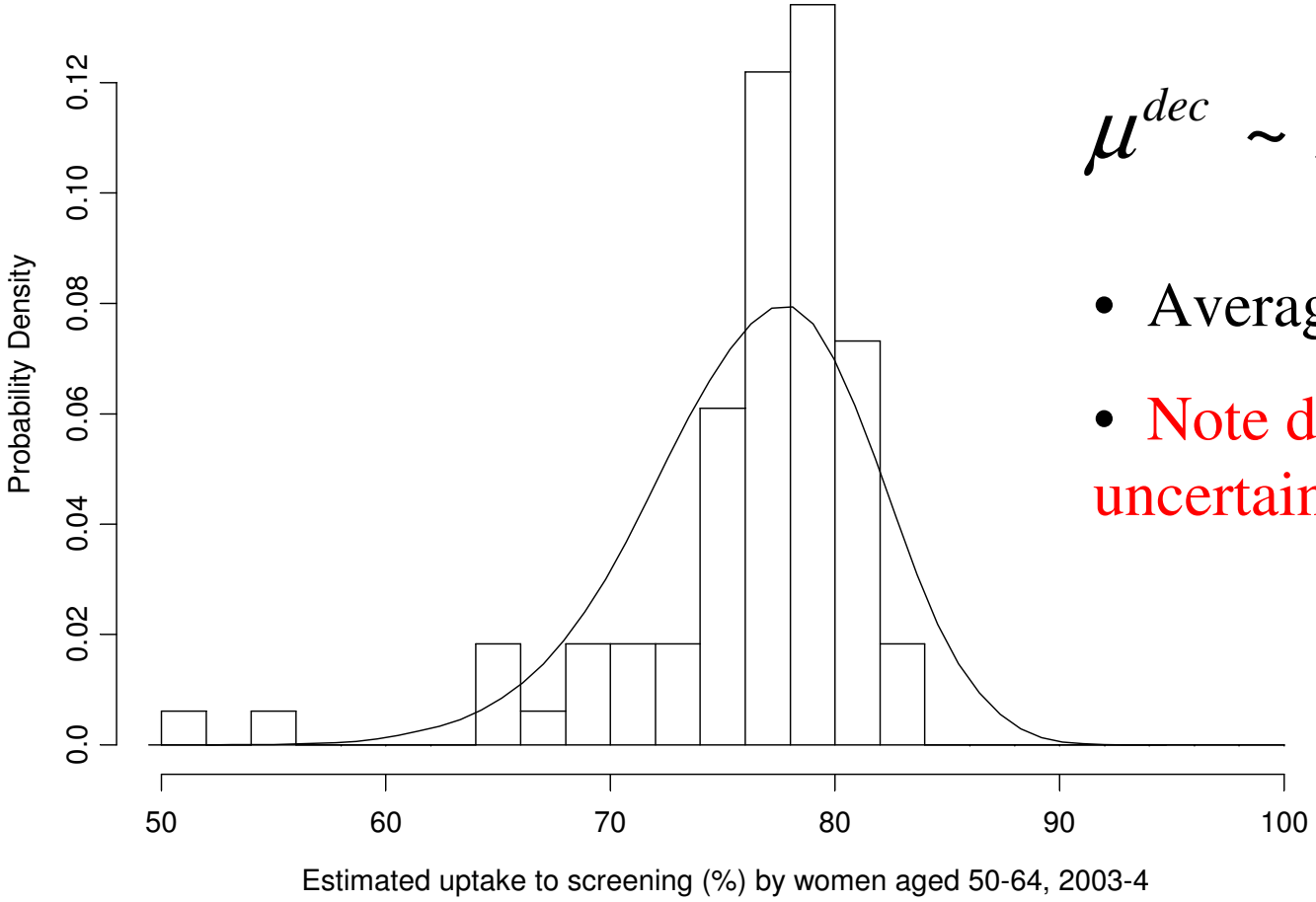
Negative Interaction

- Women differ in persuadability
  - After one intervention has been given, we're left with women who are less persuadable
  - Effect of Both less than the sum of Letter and Flag effects

- Simulation based on these beliefs gives prior:

$$\begin{pmatrix} \beta_{letter} \\ \beta_{flag} \\ \beta_{int} \end{pmatrix} \sim N\left(\begin{pmatrix} .3 \\ .3 \\ -.11 \end{pmatrix}, \begin{pmatrix} .23^2 & .65\times.23^2 & -.71\times.23\times.13 \\ .65\times.23^2 & .23^2 & -.71\times.23\times.13 \\ -.71\times.23\times.13 & -.71\times.23\times.13 & .13^2 \end{pmatrix} \right)$$

Baseline Uptake in CEA



$$\mu^{dec} \sim N(1.2, 0.076)$$

- Average over this in CEA
- Note distinction between uncertainty and variation

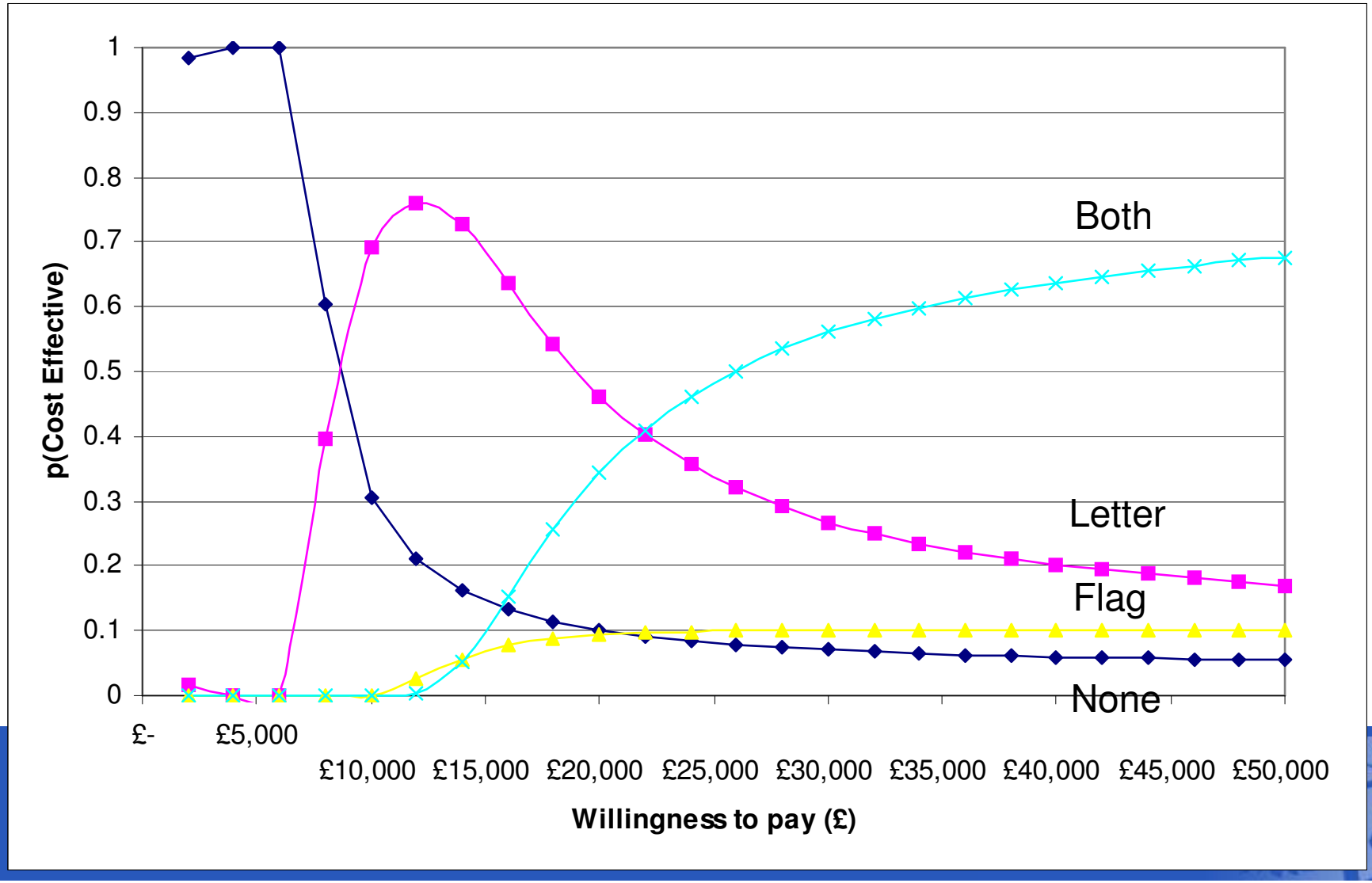
CEA (£30,000 per QALY)

$$INB(k) = \underset{\mu^{dec}}{E}\left[\pi_k^{dec} \left(\underbrace{p_R p_{C|R} G * £30,000}_{\text{Incremental Benefit}} - \underbrace{(screen + recall + treat)}_{\text{Incremental Cost}} \right) - \text{cost}_k \right]$$

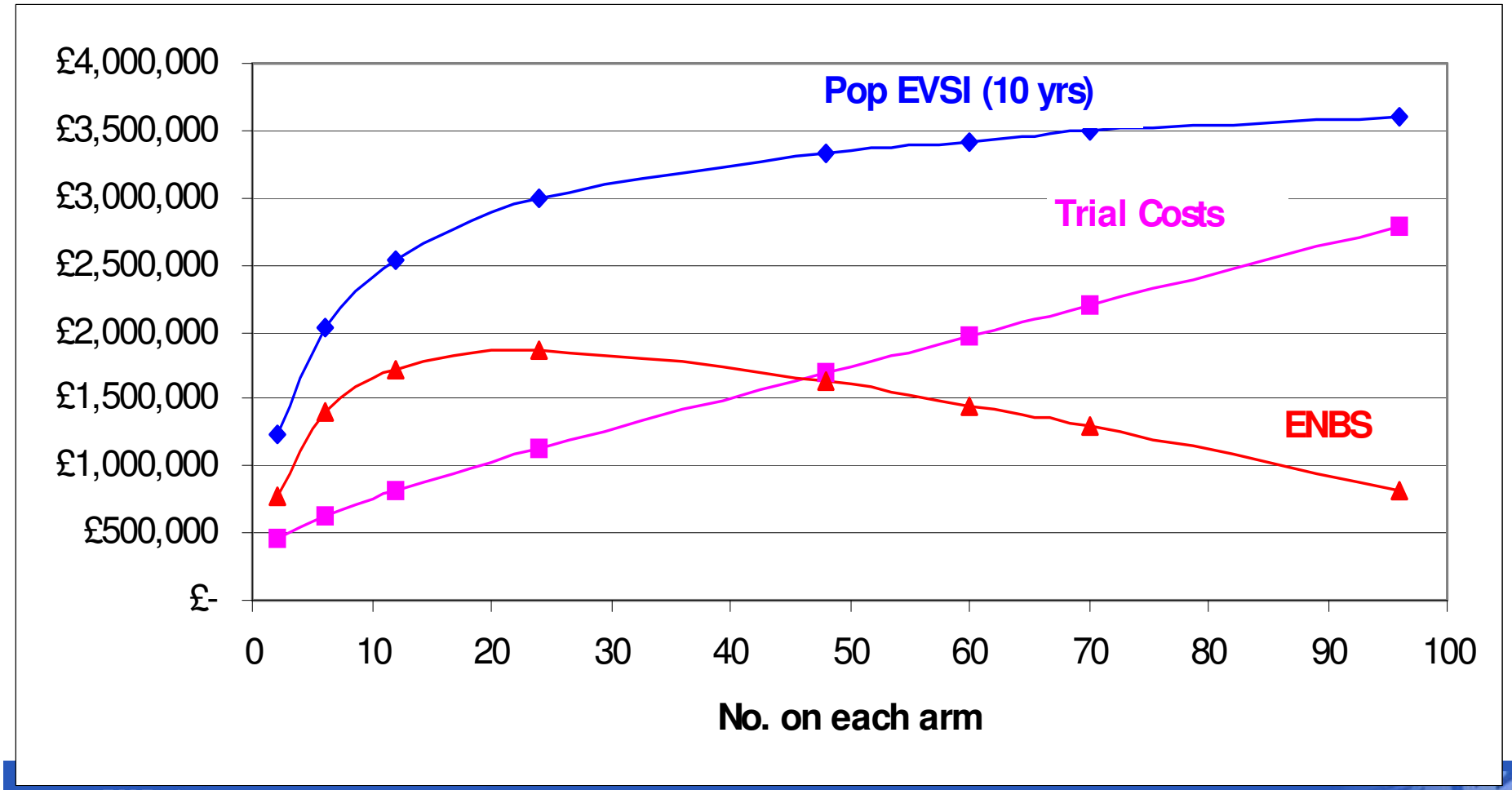
- We average over the baselines relevant to decision population to get INB for intervention k:

- Uptake probabilities use baseline relevant for decision population, μ^{dec}

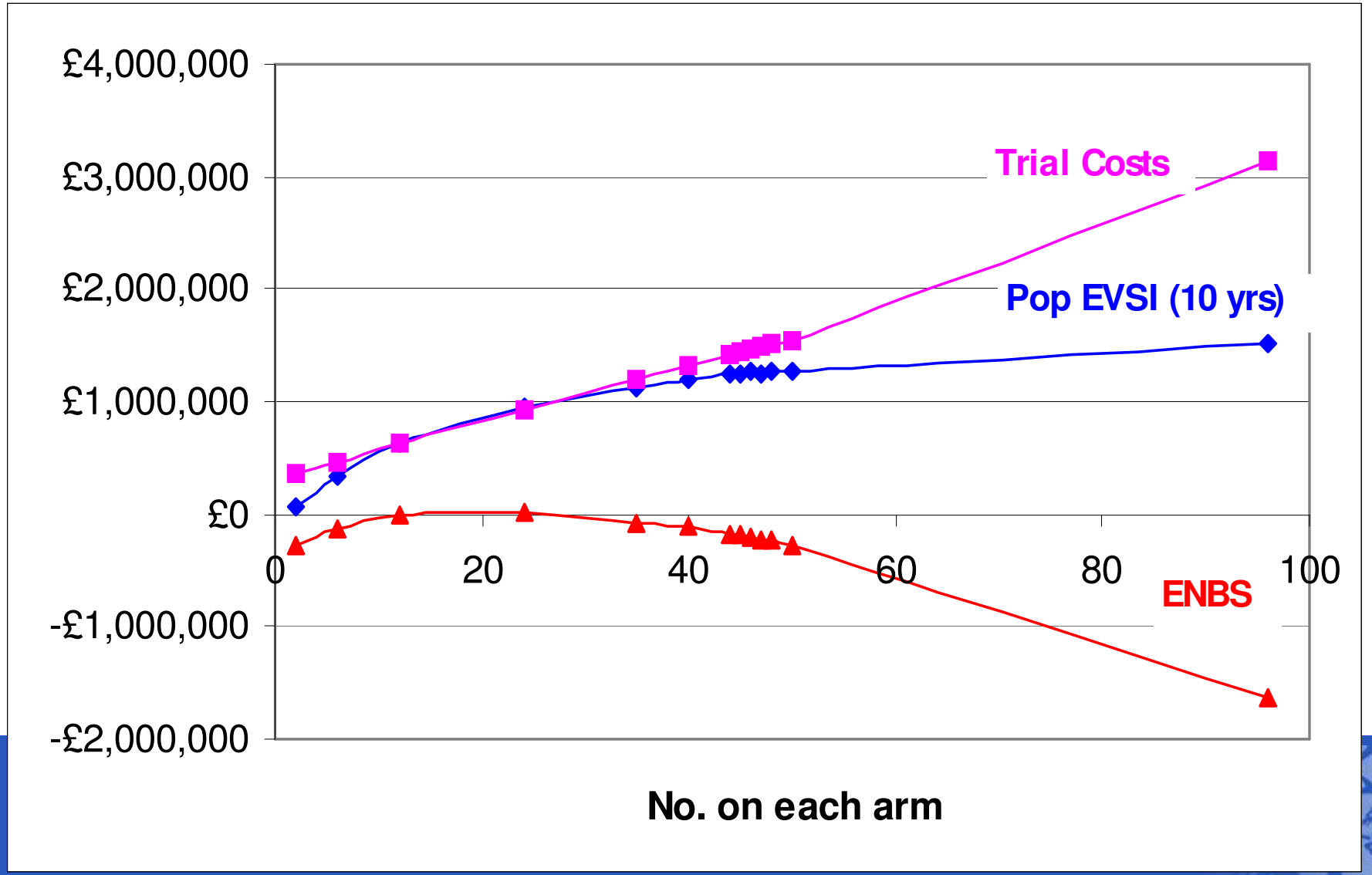
Based on Evidence BEFORE Trial



Based on evidence before trial … value in further research



EVSI: Balanced Designs based on evidence after trial



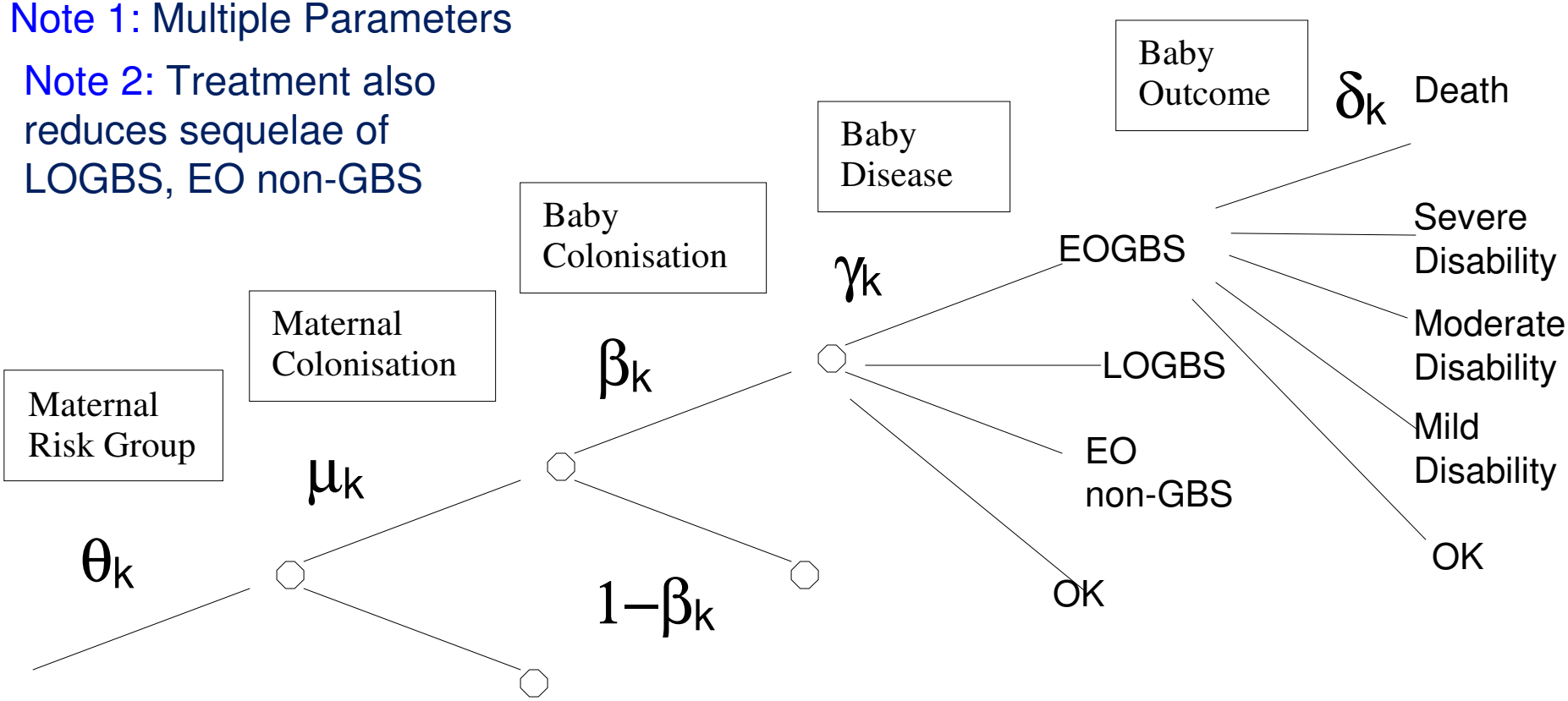
2. Early Onset Group B Streptococcus (EOGBS)

- Neonatal infection acquired at delivery from a maternal GBS infection
- 4.5/10,000 births in the UK
- High risk of meningitis
- 15% mortality rate, high risk of disability
- Colbourn et al (BMJ 2007)

EOGBS: Natural History

Note 1: Multiple Parameters

Note 2: Treatment also reduces sequelae of LOGBS, EO non-GBS



UK Current Best Practise

Women in pre-term labour	Women in term labour
Planned Caesarean	Planned Caesarean
Previous GBS baby	**Previous GBS baby**
Positive swab for GBS	**Positive swab for GBS**
Fever >38^0 in labour	**Fever >38^0 in labour**
ROM > 2hrs pre-labour	ROM > 18hrs
ROM < 2hrs pre-labour or after onset of labour	No risk factors

Policy Question

- Other countries screen for GBS
- What screening/treatment strategies are cost-effective in the UK?
- What are the key parameters for further research?
  - £12m HTA Cluster RCT proposed to compare culture screening vs current best practise

Strategies (341!)

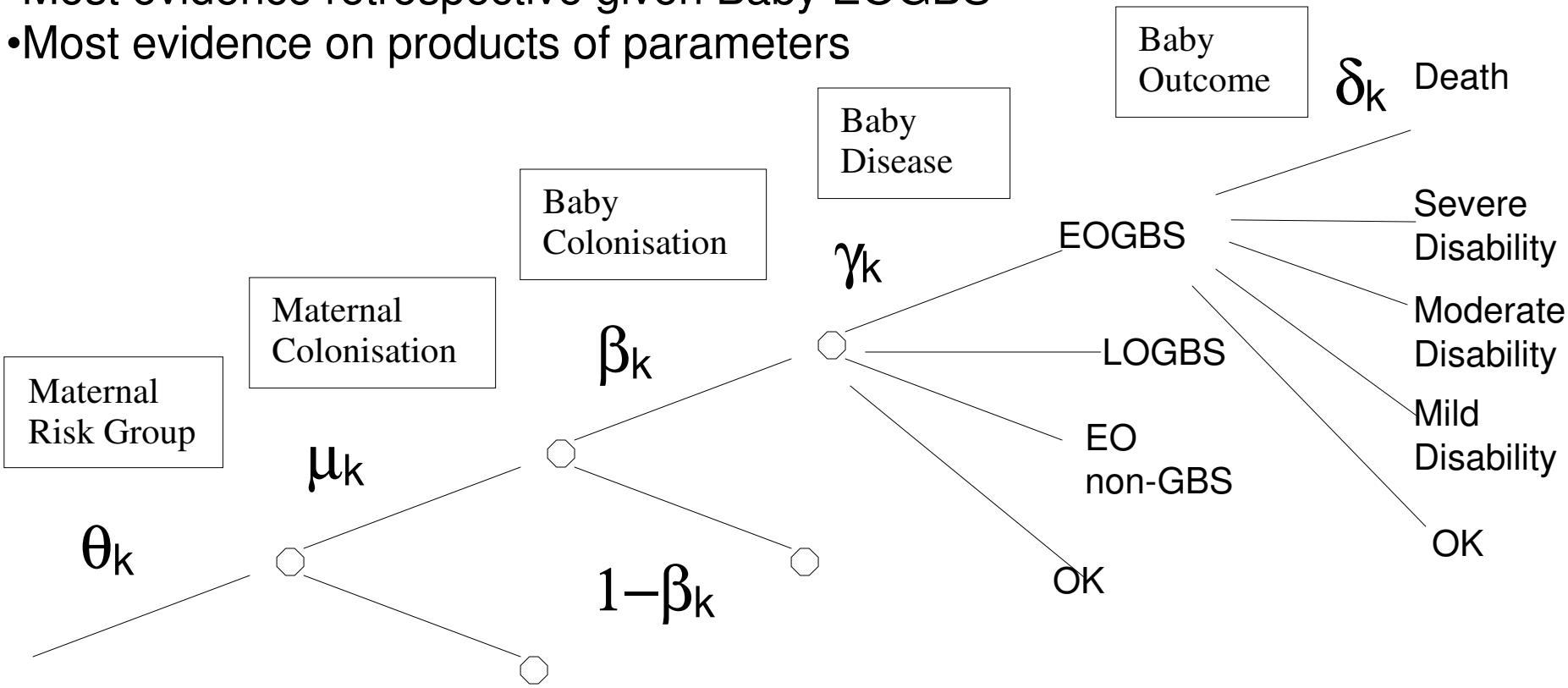
- Do nothing
- Test swabs 35-37w, treat +ve women with IV or oral antibiotics
- Test swabs by PCR in labour and treat +ve women with IV or oral antibiotics
- Oral or IV antibiotics without testing
- Vaccination at 28w, with or without screening and treatment as above

Systematic Review

- 32 systematic reviews were conducted to identify:
  - Published studies
  - Primary data sets
  - Expert opinion
- Identify all relevant available evidence

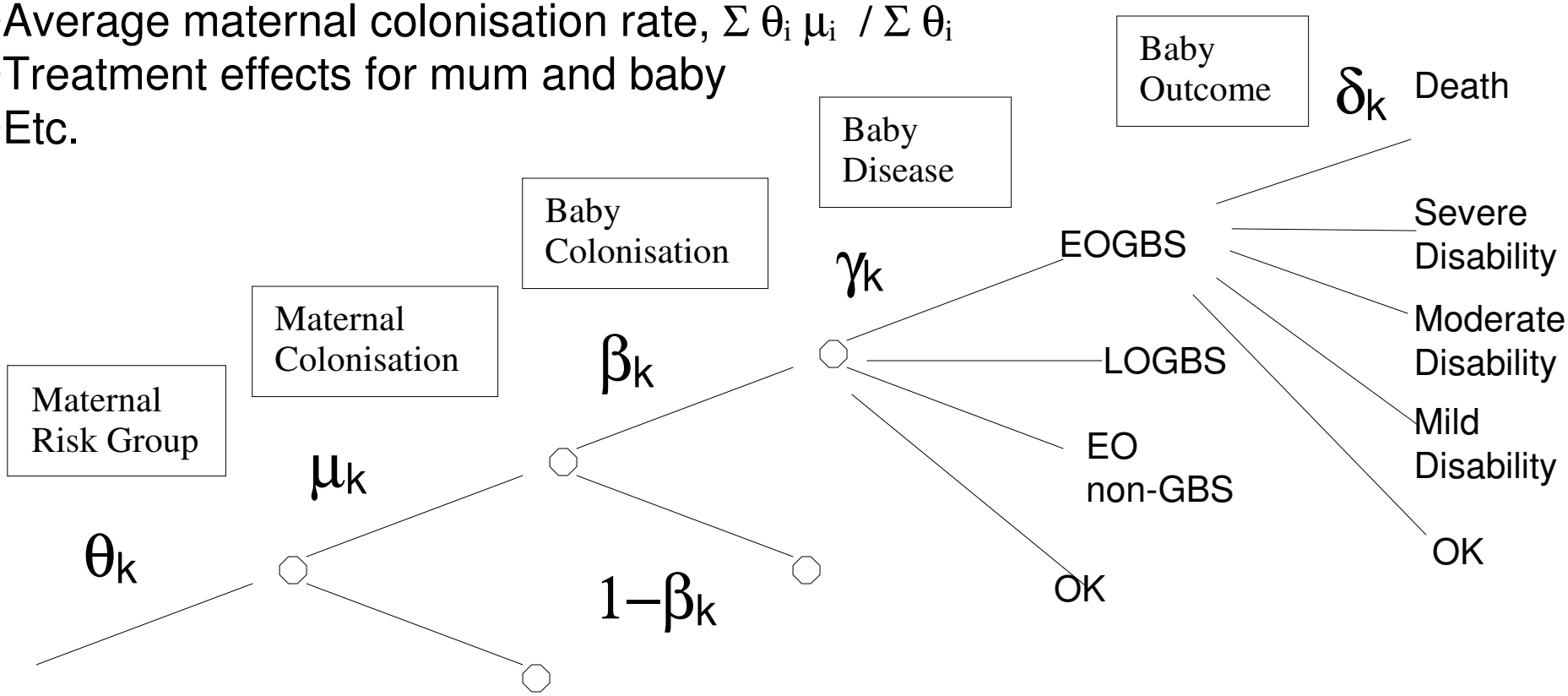
EOGBS: Available Evidence

- Ideally would want prospective evidence
- Most evidence retrospective given Baby EOGBS
- Most evidence on products of parameters



EOGBS: Available Evidence

- Overall pop. rate of EOGBS, $\Sigma\ \theta_i\ \mu_i\ \beta_i\ \gamma_i$
- Proportion of EOGBS in risk group k, $\theta_k\ \mu_k\ \beta_k\ \gamma_k / \Sigma\ \theta_i\ \mu_i\ \beta_i\ \gamma_i$
- Average maternal colonisation rate, $\Sigma\ \theta_i\ \mu_i\ /\ \Sigma\ \theta_i$
- Treatment effects for mum and baby
- Etc.



Multi-parameter Evidence Synthesis

- Jointly estimate multiple basic parameters from multiple evidence sources which may be on complex functions of parameters
- E.g. If evidence on *a*, and evidence on *a/b*, we can estimate both *a* and *b*
- Bayesian MCMC a flexible and easy method to do this

Results: Current Best Practise NOT Cost-Effective

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Results: Key Areas for Future Research

- Value of Information identified as priority trials to evaluate:
  - Vaccine efficacy
  - IV vs oral antibiotics for mothers in pre-term labour
  - Testing vs no intervention in low-risk women delivering at term

Policy Implications

- National Screening Committee
  - Proposed £12m trial no longer planned
    - Would randomise women to interventions that are not cost-effective
    - Would not be able to identify different maternal risk groups
    - This study HTA Grant £120,000 (PI Ruth Gilbert)
  - Screening for GBS carriage in pregnancy is not recommended
  - Exploring issues on development of a vaccine

Barriers to EVI Methods?

- Needs a well-defined decision problem & synthesis of currently available evidence
  - … importance … what study adds
- EVSI can be hard / computationally intensive to calculate
- EVPI straightforward to calculate
  - a quick, easy tool to show potential value
- Ethics/Equipoise?

Potential for EVI Methods

- Focuses research efforts on key parameters driving decision uncertainty
- In contrast to standard power calculations, that only focus on detecting statistical significance
- Can help: “enhance an evidence-base to informing decisions on cost-effectiveness of technologies in the NHS” – Cooksey review

Multi-Parameter Evidence Synthesis page:

- Slides, papers, programs:

http://www.bristol.ac.uk/cobm/research/mpes