Data, Models, and Research: The Role of VoI Methods in Arthritis

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Biologic Therapies in Inflammatory Joint Diseases: Models for Decision Making

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School of Social and Community Medicine

Outline

- Introduce Value of Information (VOI) methods
  - Identify key parameters driving decision uncertainty
  - Guide research funders prioritising research efforts
  - Guide trial design

- Highlight the inputs required for VOI calculations

- Discuss potential role of VOI methods in Arthritis Research

Why Do We Need Further Research?

- To help make better treatment decisions
- To reduce uncertainty in key parameters that help us make treatment decisions
- Efficacy, costs, resource use, utility, natural history parameters

Is Further Research Required?

- Yes, if:

  1. There is uncertainty in parameters that input into the decision model (e.g. used by NICE)

  AND

  2. The optimal decision is sensitive to values of those parameters

If So, Which Study Design(s)?

- Depends on which key parameters drive decision uncertainty
- RCT for efficacy parameters
  - Which treatment(s) / how many trial arms?
  - Sample size?
  - Follow-up time?
- Cohort study for natural history parameters
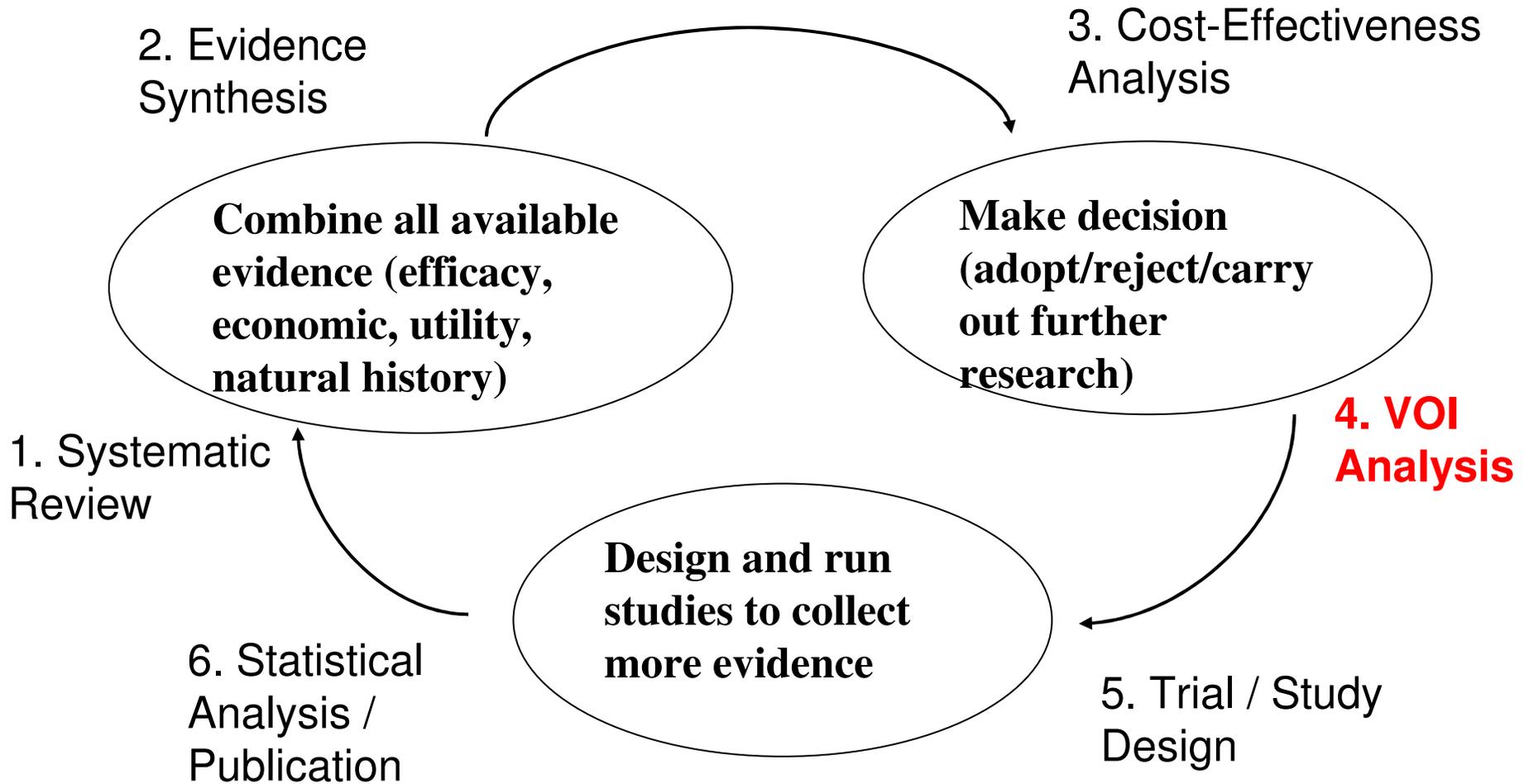 - Sample size?

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Value of Information (VOI)

- Measures the value of further research in terms of expected net gains in health benefits
  - Eliminating uncertainty in all parameters
    - Expected Value of Perfect Information, EVPI
  - Eliminating uncertainty in some parameters
    - EV of Partial Perfect Information, EVPPI
  - Reducing uncertainty in some parameters
    - EV of Sample Information, EVSI

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Decision-Making Context

2. Evidence Synthesis

3. Cost-Effectiveness Analysis

Combine all available evidence (efficacy, economic, utility, natural history)

Make decision (adopt/reject/carry out further research)

1. Systematic Review

4. VOI Analysis

Design and run studies to collect more evidence

6. Statistical Analysis / Publication

5. Trial / Study Design

Inputs Required for VOI

- Same inputs as required for a cost-effectiveness analysis:
  - Well-defined decision question
  - Model for incremental benefits and costs
  - Input data for model
  - Population prevalence and time-horizon
- Additionally need:
  - Costs of proposed new study

Decision Question

- For example:
  - "Which is the most cost-effective biologic therapy for rheumatoid arthritis patients that have failed on methotrexate?"

  - "What is the optimal treatment sequence of biologics for rheumatoid arthritis patients that have failed on methotrexate?"

Optimal Decision

- Maximise Expected Net Benefit, E(NB)
  - NB = Incremental Benefit – Incremental Cost
  - Depends on:
    - Treatment efficacy (from MTC analysis of RCT's)
    - Economic cost / resource use (from RCT's or other sources?)
    - Utility (from RCT's or other sources?)
    - Natural history (from registry data?)
    - Cost-effectiveness model

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Based on Current Evidence

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

- Can write down the net health benefits of a decision based on current information

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

EVSI: Key Idea

- Given a study design (eg sample size)
  - We collect data
  - Reduces parameter uncertainty
  - If the optimal decision changes, there is a gain in NB from using the new optimal treatment, rather than k*
  - Average over possible new data we could collect
  - Giving the expected net gain in health benefits from such a new study
- Choose design that maximises
  - Net gain in health benefits – cost of study

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Expected Value of Sample Information

$$EVSI = \underset{D|\theta,\nu,\eta,\psi}{E} \left[\underset{k}{\max} \left\{ \underset{\theta,\nu,\eta,\psi|D}{E} \left[NB(k,\theta,\nu,\eta,\psi) \right] \right\} - \underbrace{NB(k^{*},\theta,\nu,\eta,\psi)}_{\substack{\text{Value of decision based on} \\ \textbf{current} \text{ information}}} \right]$$

$$\underbrace{}_{\substack{\text{Value of decision based on} \\ \textbf{sample} \text{ information} \\ \text{(for a given study design)}}}$$

Prior predictive distribution

Posterior given data D

- EVPI: provides an upper bound ... easy!

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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

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Illustration of Decision Uncertainty
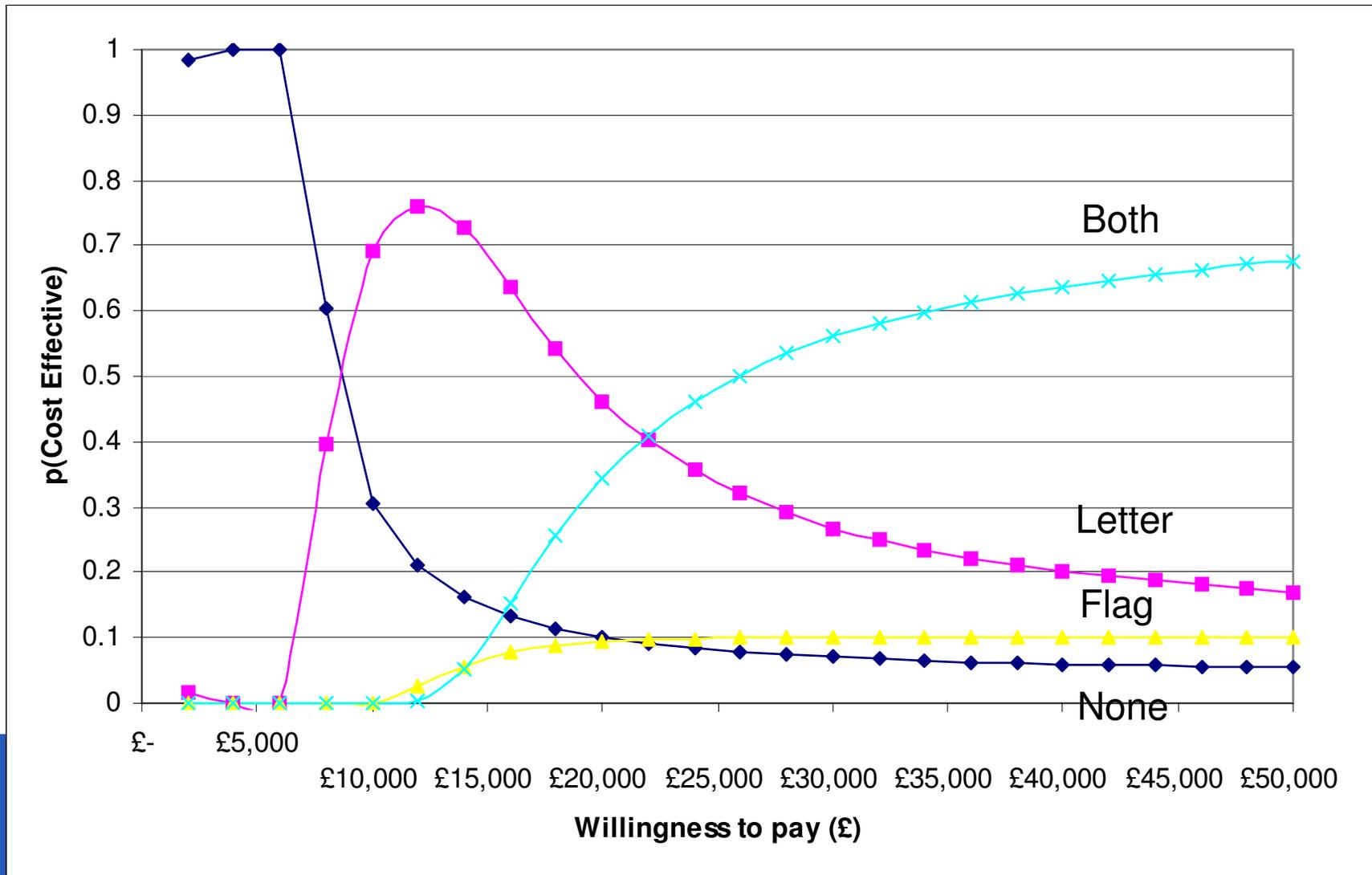
Illustration of Optimal Trial Design (I)

Illustration of Optimal Trial Design (II)

£4,000,000
£3,000,000 — **Trial Costs**
£2,000,000 — **Pop EVSI (10 yrs)**
£1,000,000
£0
-£1,000,000 — **ENBS**
-£2,000,000

0 20 40 60 80 100

No. on each arm
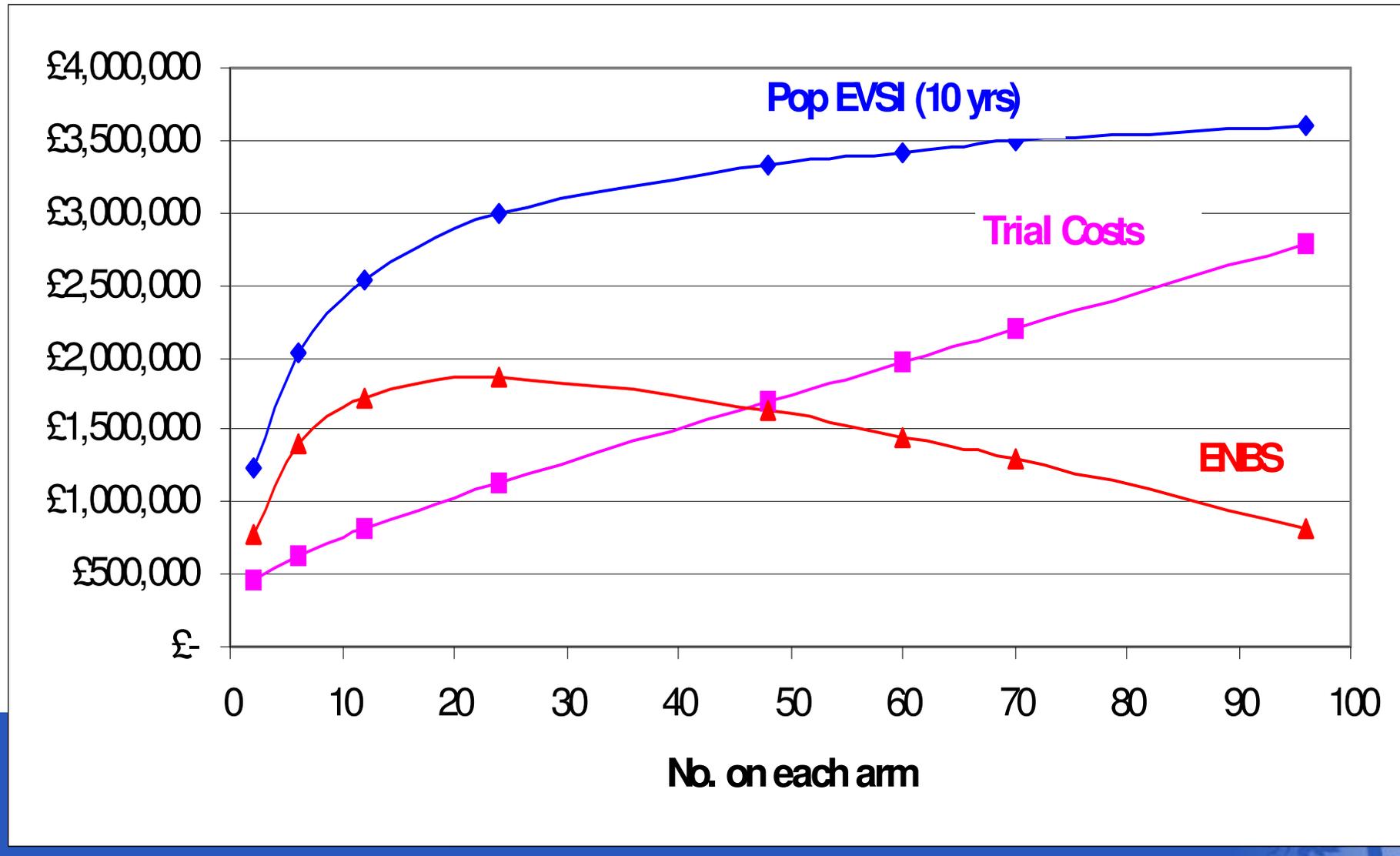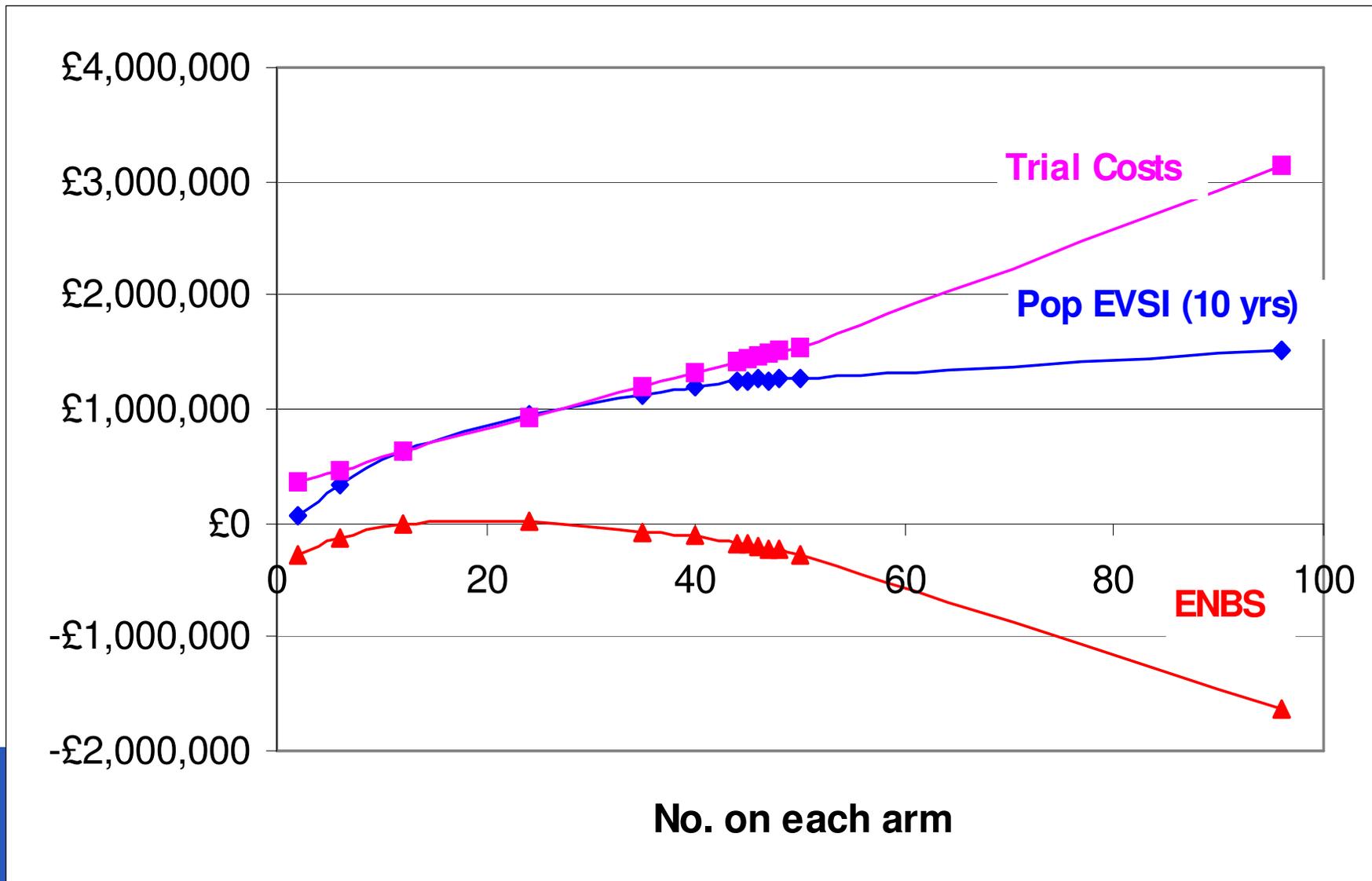
Multiple Competing Health Technologies

- Evidence base has a Mixed Treatment Comparison (MTC) structure

- Trial design options
  - How many trial arms?
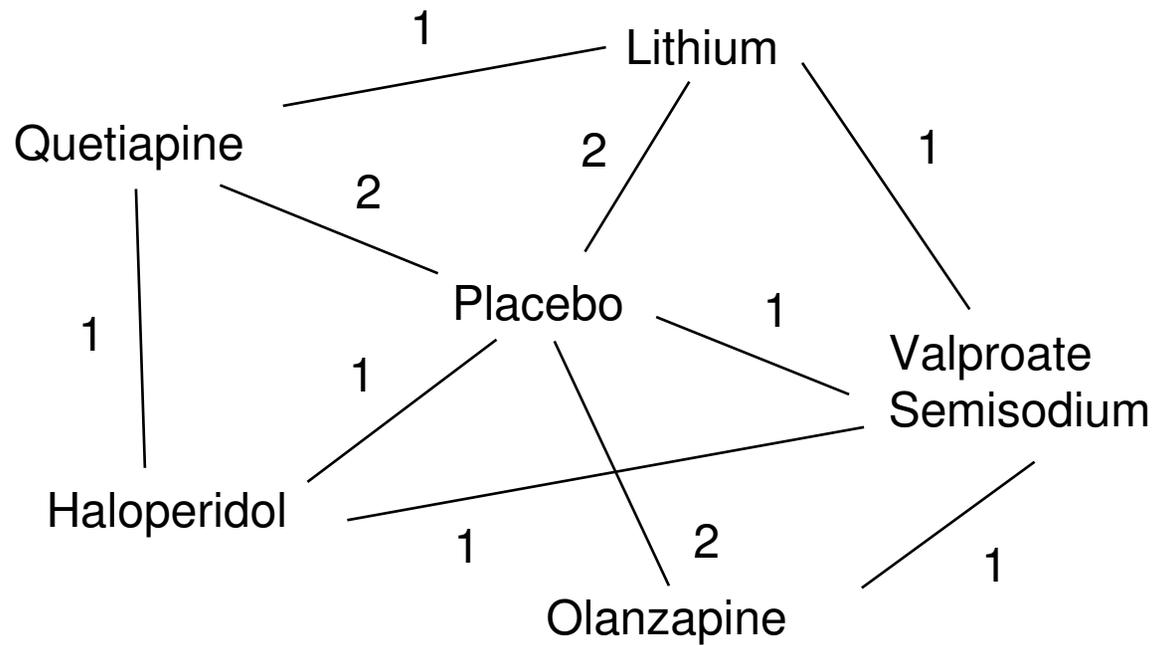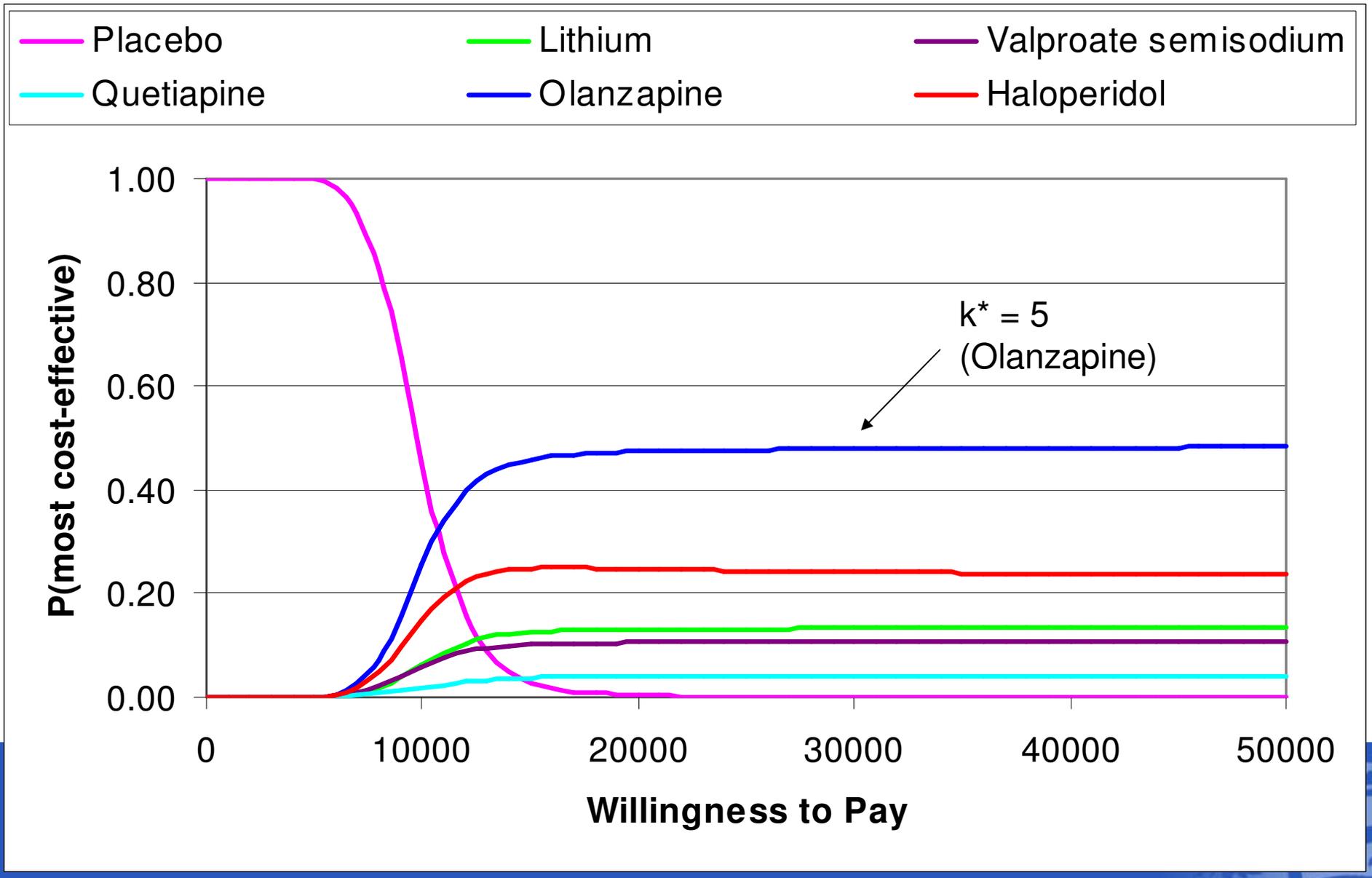 - Which treatments to include?
  - Sample size (?for each arm)?

Example: Bipolar Disorders

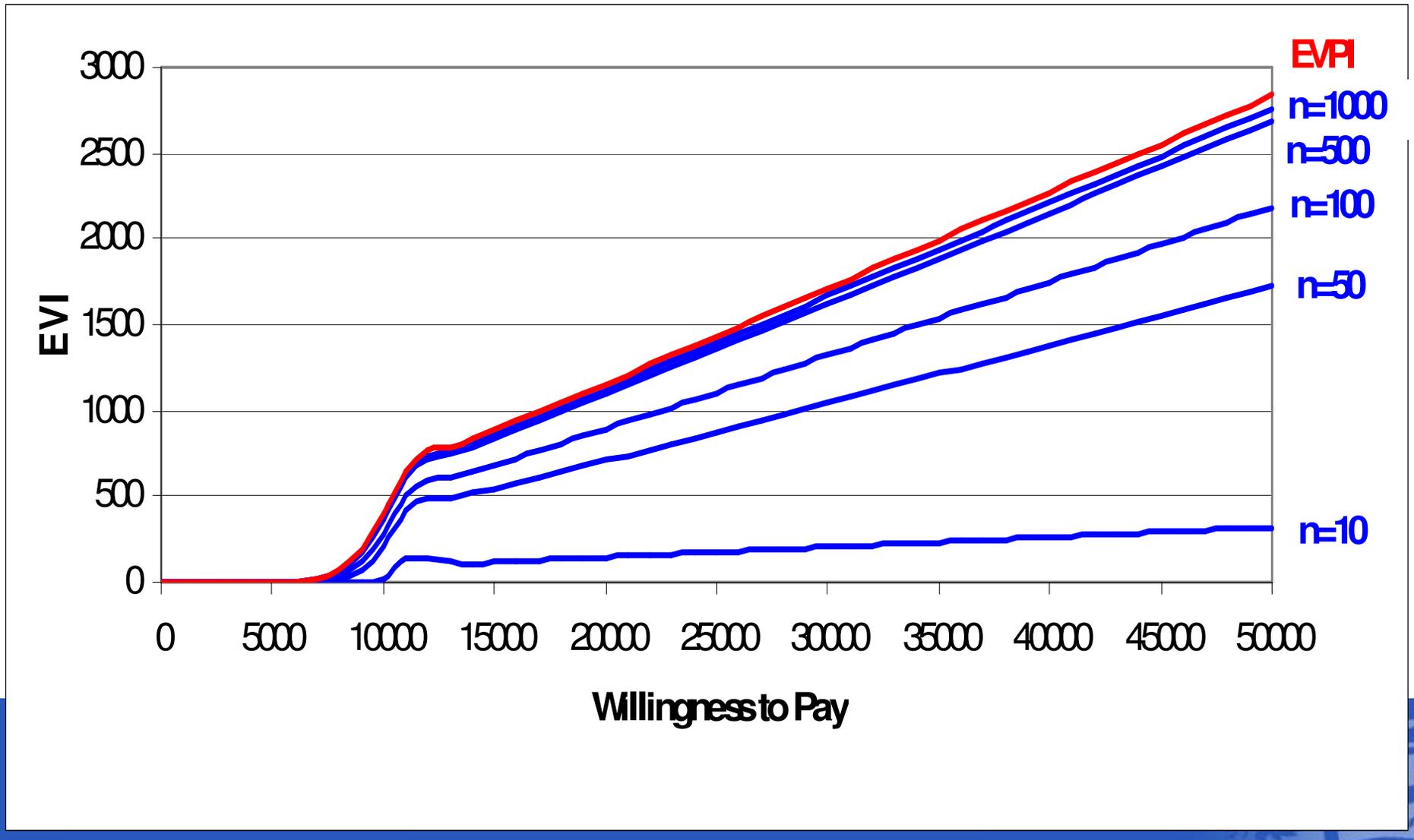| RCT	Placebo	Lithium	Valproate Semisodium	Quetiapine	Olanzapine	Haloperidol
1	16/62				30/70	
2	19/56				30/54	
3	18/72	17/35	32/67			
4			52/123		68/125	
5	35/100			43/101		55/98
6	27/97	51/98		57/107		
7			10/21			5/15

Bridle et al (2004) HTA report

⚡MTC Evidence Network
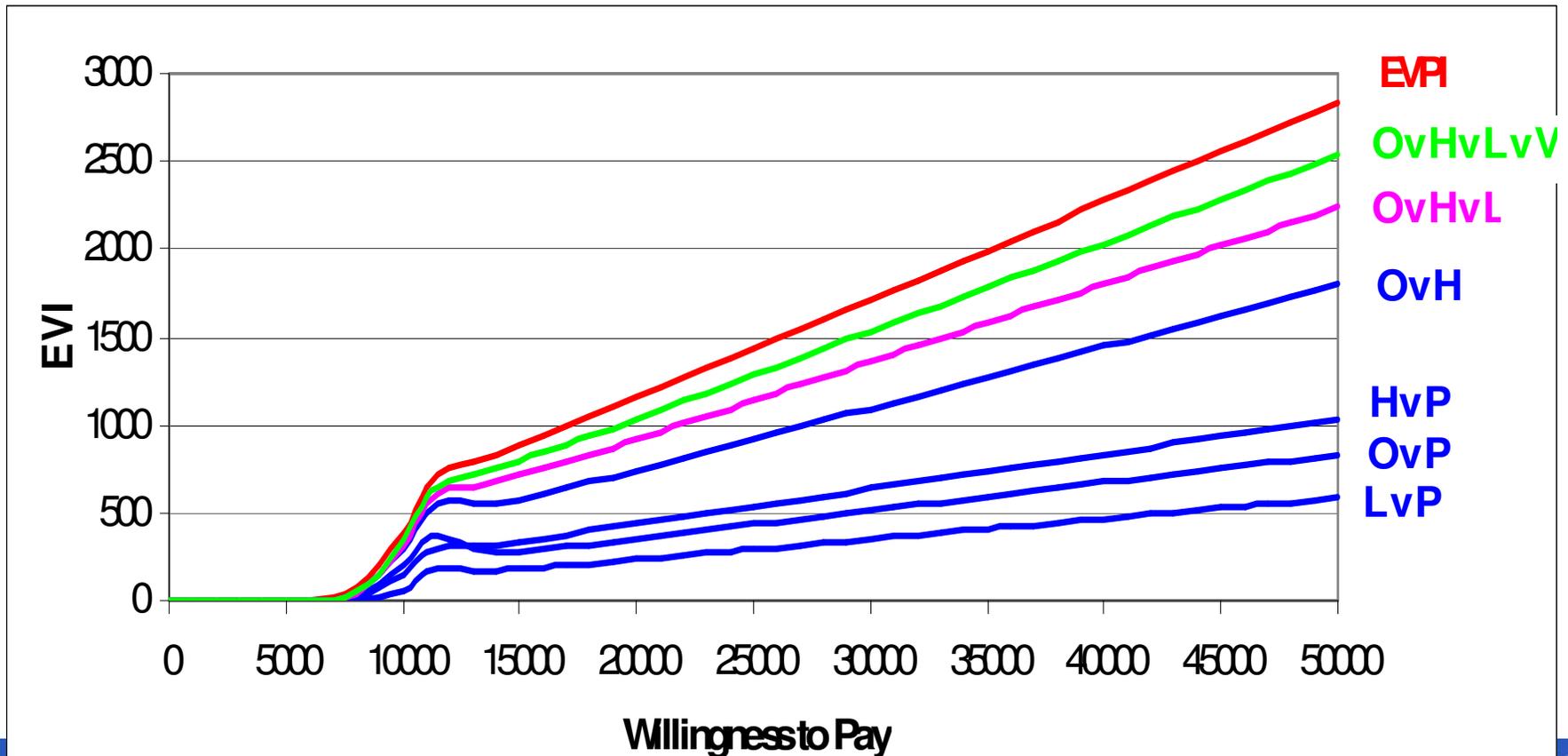
Based on Current Information

EVSI: Balanced 6-arm trials

EVSI: How Many Arms?

- N=1500 in total … split equally between arms

Comments

- EVSI can be hard / computationally intensive to calculate

  - EVPI a quick, easy tool to show potential value

- 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

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Potential for VOI Methods in Arthritis Research (I)

- Evidence suggests biologics are very powerful and effective therapies
  - indirect comparisons possible
- Is there a research need for head-to-head trials?
  - Head-to-head trials are very costly
  - Will the benefits of running head-to-head trials outweigh the costs?
  - If so, which therapies should be included?

Inputs Required for VOI Methods in Arthritis Research (I)

- Decision Question
  - Which is the most cost-effective biologic therapy for patients that have failed on methotrexate?
  - What is the optimal sequence in which to give biologic therapies in patients that have failed on methotrexate?
  - Others …

Inputs Required for VOI Methods in Arthritis Research (II)

- Same inputs as for cost-effectiveness analysis
  - Previous models have varied in input data, model structure, and assumptions made
  - Need a consensus on these for resulting decision and research recommendations to be accepted by the research community

Inputs Required for VOI Methods in Arthritis Research (III)

- Population prevalence
  - From registry data?
- Time-horizon for the technology
  - ?
- Trial costs
  - From previous trials / grant proposals

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Steps Required for a VOI Analysis in Arthritis Research

1. Agree decision problem(s)
2. Agree model structure, data inputs, and assumptions
3. Perform cost-effectiveness analysis
   - Based on MTC for efficacy
4. VOI calculations
   - If EVPI suggests value in further research, calculate Partial EVPPI's
   - If EVPPI's suggest value in further research, calculate EVSI and ENBS to determine optimal design

Likely Effect of Head-to-head trials of biologics

1. Currently, tendency to approve several treatments, on basis of CE against standard treatment

2. Biologics have similar efficacy, a priori, and on basis of Indirect comparisons

3. Logical to choose the one that is least costly.

4. If so, Direct evidence only worth collecting if it shows one or more biologics are less effective than others.

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Multi-Parameter Evidence Synthesis page:

- Slides, papers, programs:

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