

Introduction to Value of Information analysis (in Health Technology Assessment)

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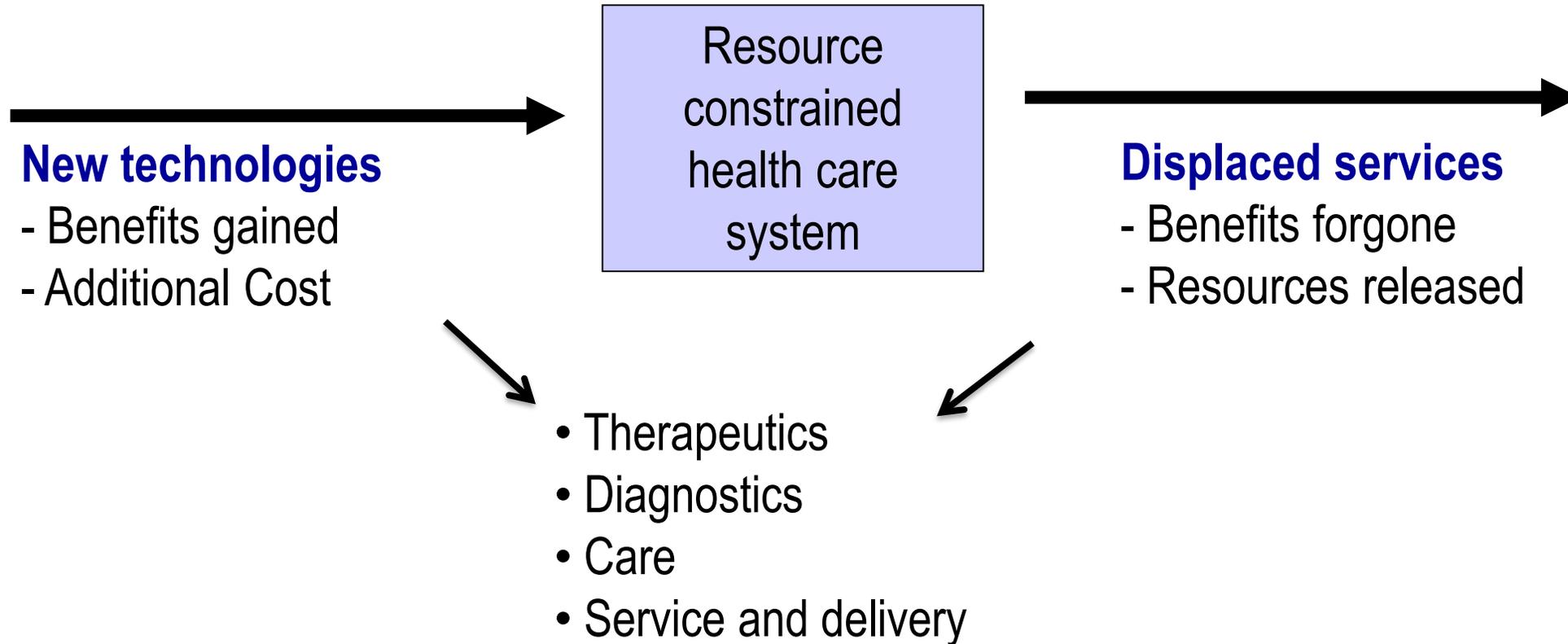
Overview

- Characterising uncertainty in Health Technology Assessment (HTA)
 - Economic challenge for health care decisions
 - What is uncertain?
 - Would more evidence improve health?
- Bayesian methods of Value of Information analysis to address decision uncertainty
 - Expected Value of Perfect Information (EVPI)
 - Expected Value of Perfect Parameter Information (EVPPI)
 - Expected Value of Sample Information (EVSII)
 - Expected Net Benefit of Sampling (ENBS)
- Other considerations for value of research

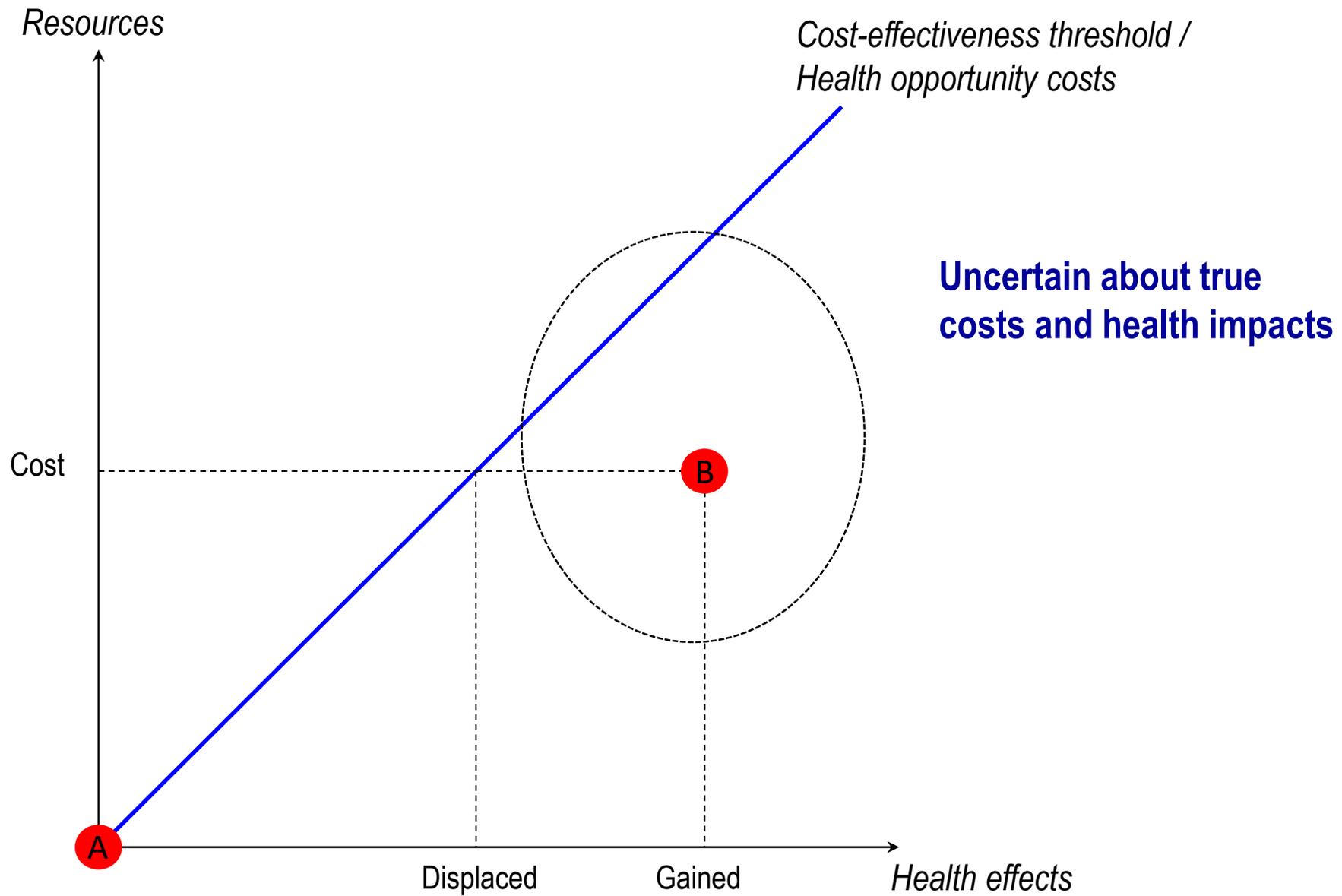
Making choices based on economic criteria

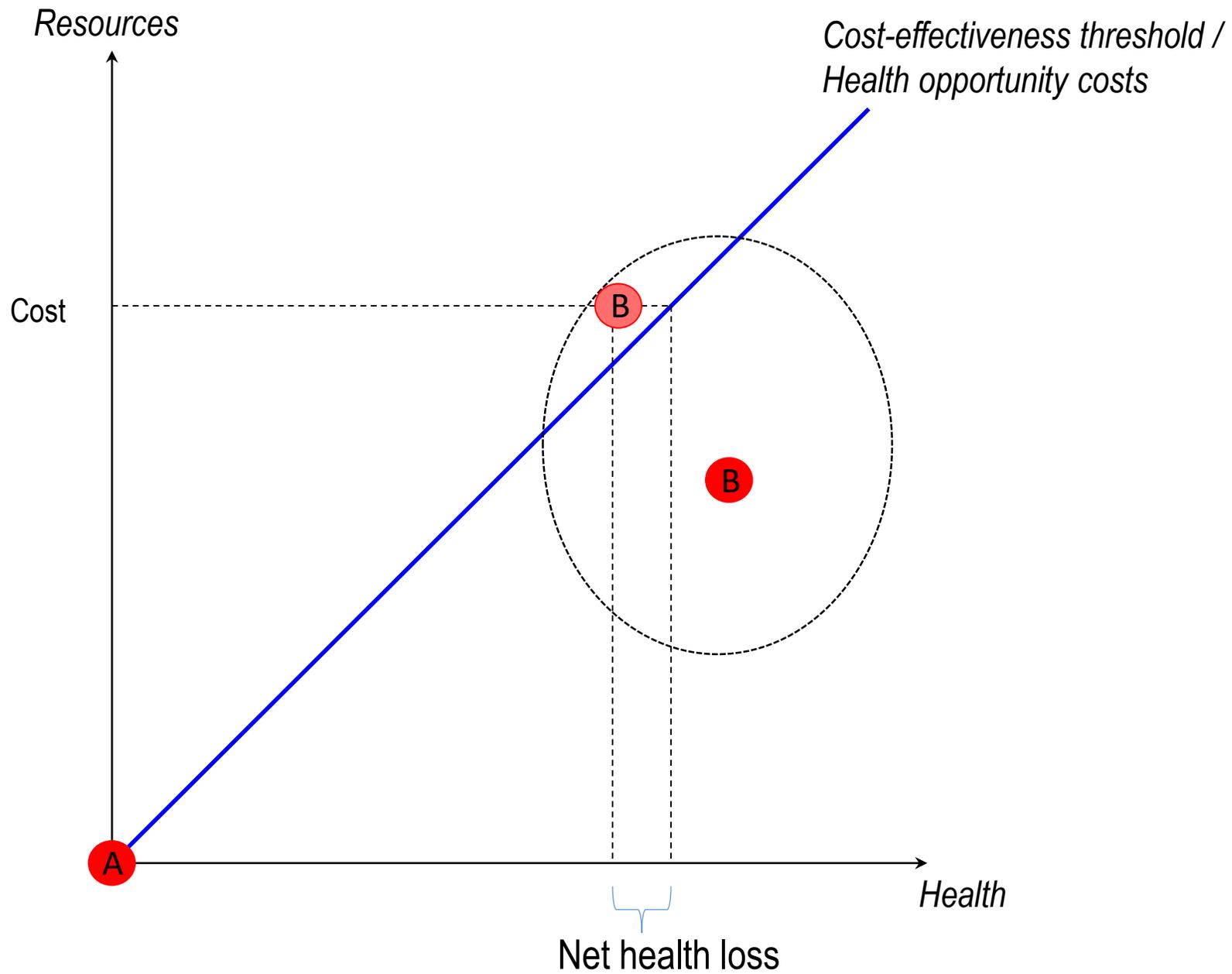
- All collectively funded health care systems (whether predominantly tax-based, social insurance or mixed) need to **make choices about the allocation of resources**
- The underlying problem is one of **limited resources, unlimited 'wants'**
 - Not everything that offers a benefit can feasibly be funded
 - Choices need to be made between alternative uses of resources
- Decision maker's objective is to ensure that a particular programme represents an efficient use of healthcare resources
 - Choose programmes which **maximise total health benefits**
subject to the budget constraint (resource constraints)

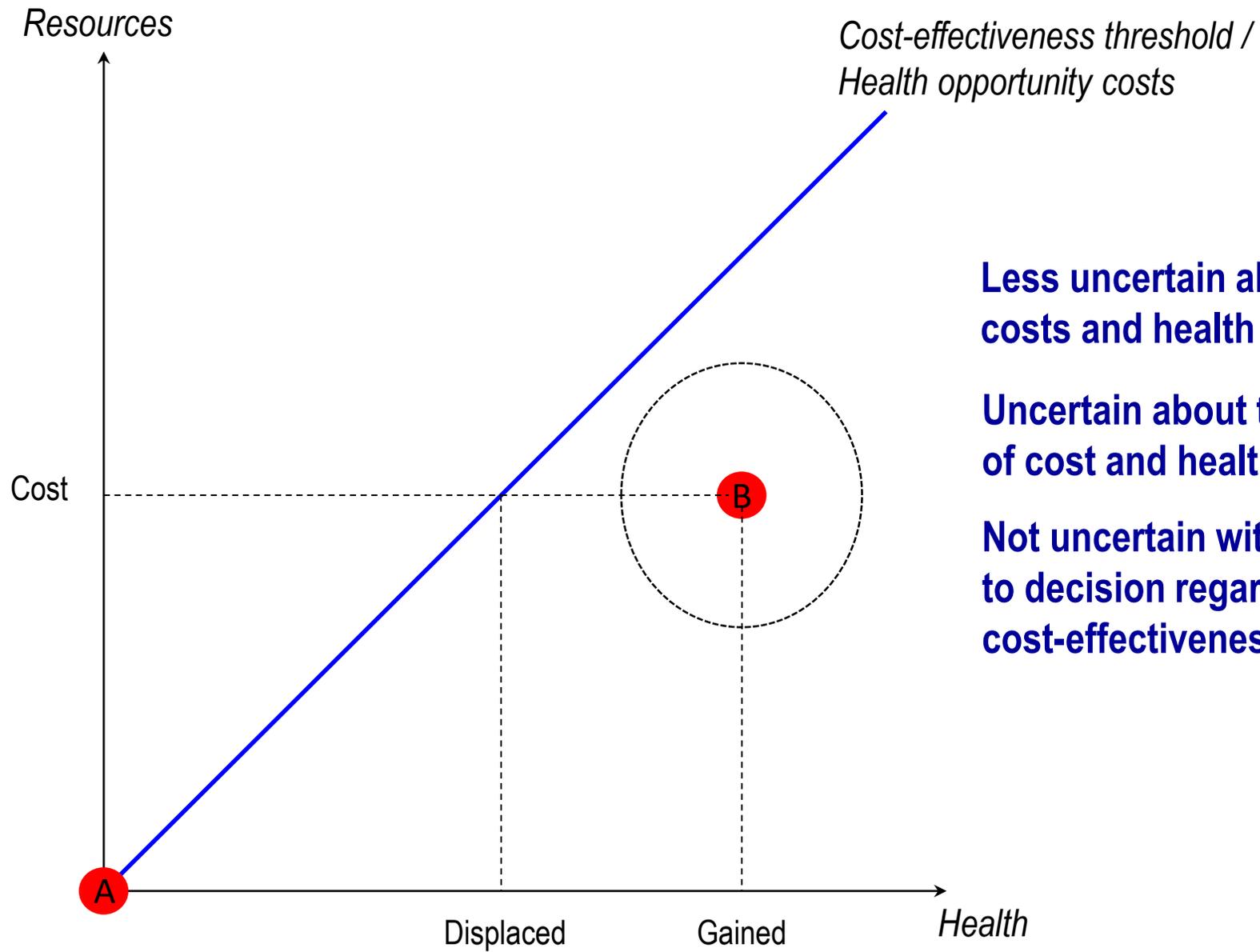
The challenge of health care decisions



Is the benefit gain from the new treatment greater than the benefit foregone through displacement?







Less uncertain about true costs and health impacts

Uncertain about true value of cost and health impact

Not uncertain with respect to decision regarding cost-effectiveness

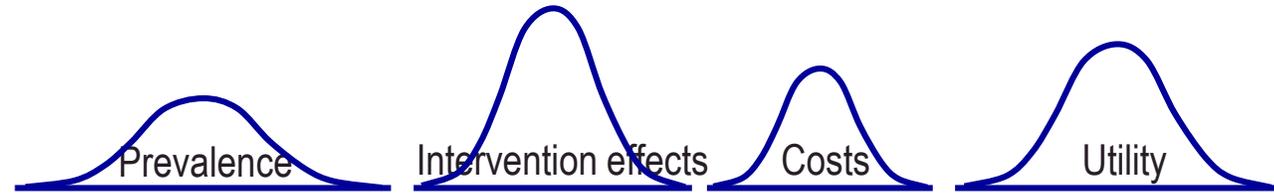
What is uncertain?

- Different possible values or outcomes for parameters
- Lack of knowledge or certainty about parameter values
- Different outcomes in different populations / subgroups
- Structural uncertainty in the model
- Uncertainty
 - Unknown 'population' quantities where data only provides imprecise estimates
 - Additional evidence can reduce this uncertainty
- Variability (also known as stochastic uncertainty)
 - Differences in effects between individuals within a target population
 - Reasons for differences cannot be observed / additional evidence cannot reduce this variability
- Heterogeneity
 - Sources of variability that can be observed / characteristics that 'explain' a proportion of the overall variability between individuals
 - Generate outcomes per subgroup population

Probabilistic sensitivity analysis (PSA)

Step 1: Assigning distributions

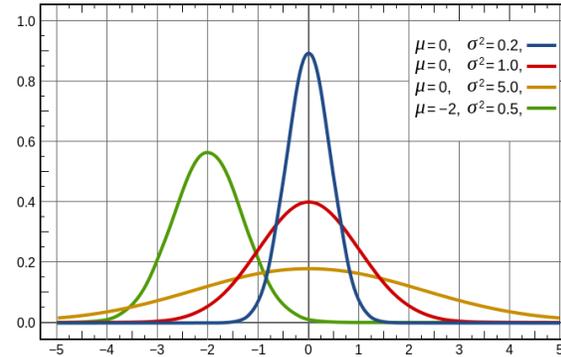
-Assign probability distribution to input parameters to represent uncertainty



Assigning distributions to input parameters

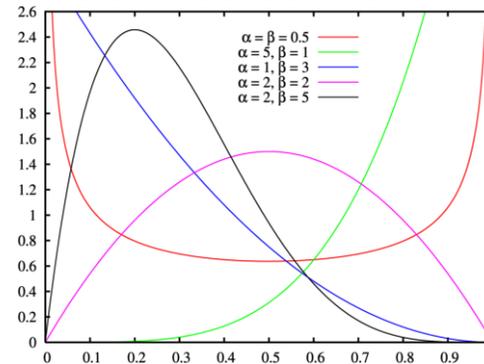
➤ Match what is known about the model input with the characteristics of the distribution

- Normal
- Log-normal
- Gamma
- Beta
- Uniform
- Exponential
- Weibull etc.

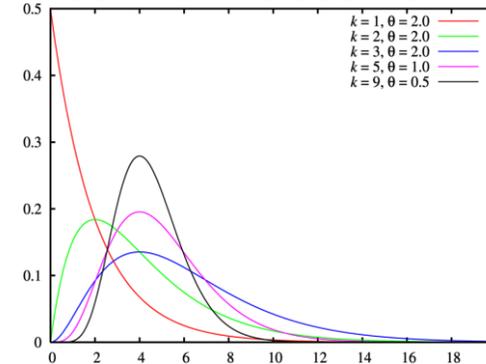


Normal – values unbounded

Beta – between 0 and 1



Gamma – values > 0

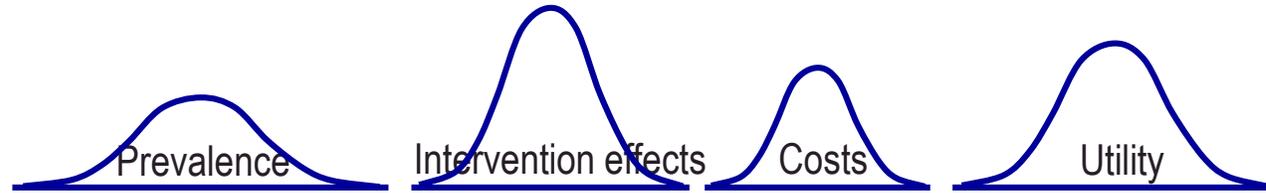


- Nature of the data e.g. probability parameters are bounded between 0 and 1
- Method of parameter estimation or data generation
- Can correlate model inputs e.g. multivariate distribution

Probabilistic sensitivity analysis (PSA)

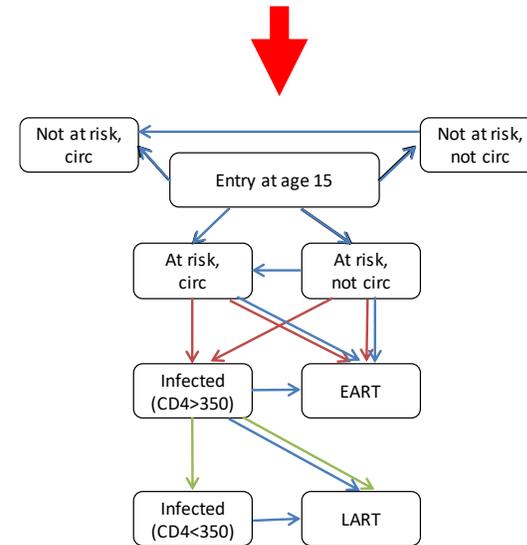
Step 1: Assigning distributions

-Assign probability distribution to input parameters to represent uncertainty



Step 2: Propagating uncertainty

-Randomly select value from each input distribution
-Model evaluated many times (e.g. >1000)

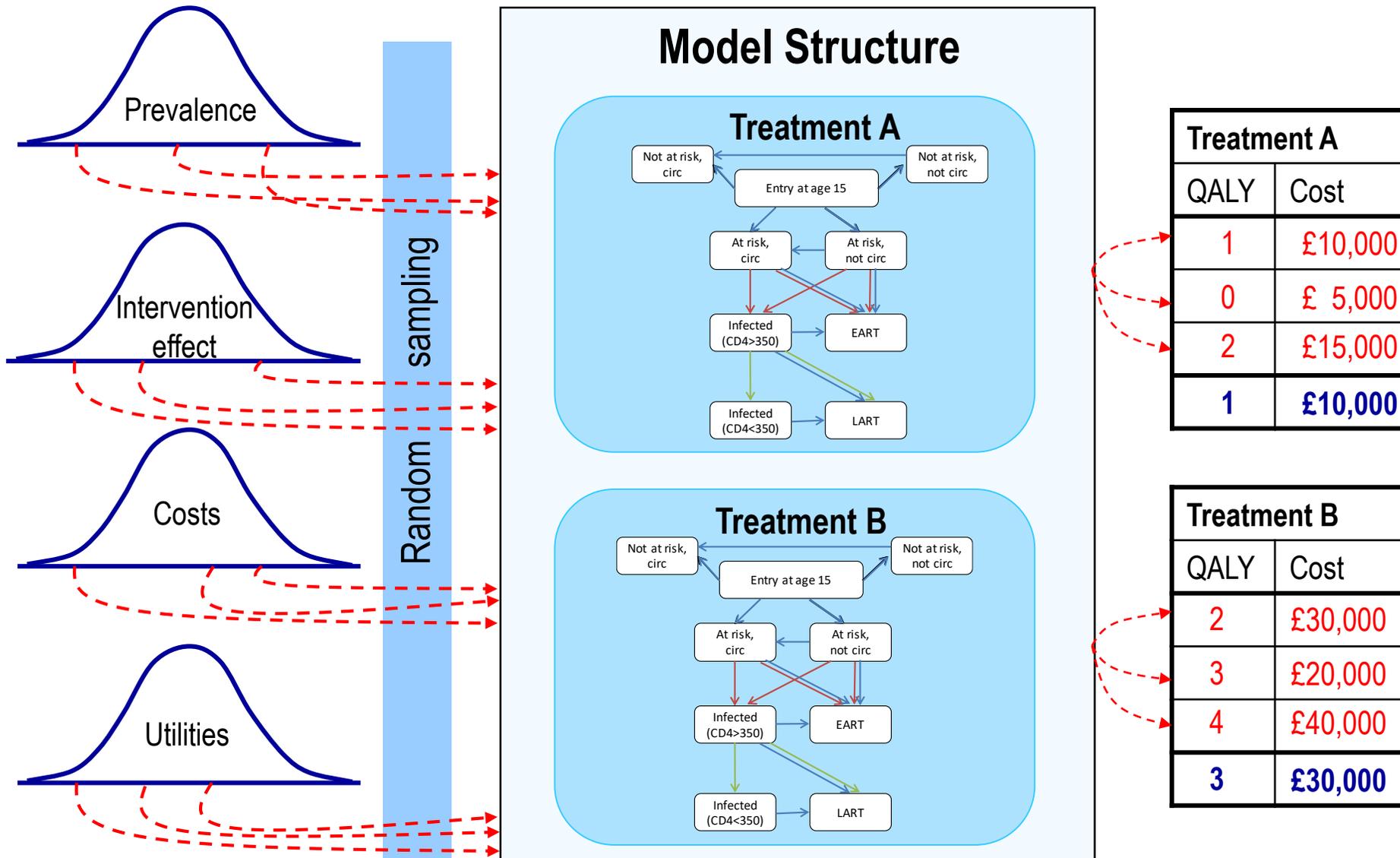


Step 3: Reporting results

-Distribution of outcomes for each strategy
-Probability that a strategy is optimal



Predicting costs and effects with uncertainty



Is the treatment cost-effective?

Treatment A	
QALY	Cost
1	£10,000
0	£ 5,000
2	£15,000
1	£10,000

Treatment B	
QALY	Cost
2	£30,000
3	£20,000
4	£40,000
3	£30,000

$$\text{ICER} = \frac{\text{Additional cost}}{\text{QALYs gained}} = \frac{£20,000}{2 \text{ QALYs}} = £10,000 \text{ per QALY}$$

Is the ICER less than the cost-effectiveness threshold?

£10,000 per QALY < £20,000 per QALY

→ Treatment B is cost-effective

Is the net health benefit (NHB) positive?

NHE = QALYs gained – (additional costs/threshold)

$$= 2 - (£20,000/£20,000)$$

$$= 1 \text{ QALY} > 0$$

→ Treatment B is cost-effective

How uncertain is a decision?

Realisations of uncertainty that could occur	Net health benefits (QALYs)	
	Treatment A $j = 0$	Treatment B $j = 1$
θ_1	9	12
θ_2	12	10
θ_3	14	17
θ_4	11	10
θ_5	14	16
$E_{\theta} NB(j, \theta)$	12	13

What's the best we can do now?

Choose B and expect 13 QALYs

How uncertain is a decision?

Realisations of uncertainty that could occur	Net health benefits (QALYs)		
	Treatment A $j = 0$	Treatment B $j = 1$	Best treatment choice
θ_1	9	12	B
θ_2	12	10	A
θ_3	14	17	B
θ_4	11	10	A
θ_5	14	16	B
$E_{\theta} NB(j, \theta)$	12	13	

What's the best we can do now?

Choose B and expect 13 QALYs

But we are not always right:

Chance that B is the best = $3/5 = 0.6$

Chance that A is the best = $2/5 = 0.4$

If we choose B the probability of error = 0.4

Would more evidence improve health?

- Information is valuable because it reduces the expected consequences of decision uncertainty
- Decisions based on more precise information → greater health gains
- Value of information (VOI) analysis combines the probability of an incorrect decision with the consequential loss function
- Compare the consequences of uncertainty to the cost of obtaining additional evidence to determine if the research is worthwhile

If consequences of uncertainty < cost of research → sufficient condition for establishing that research is not of value

If consequences of uncertainty > cost of research → additional research may be of value

Value of information (VOI) analysis

- Is additional evidence required to support the use of the health technology?
 - How uncertain are the expected benefits?
 - Does this uncertainty matter (will it change the adoption decision)?
 - How much does it matter (consequences of getting it wrong)?
- What type of evidence would be most valuable?
- Which research designs would be worthwhile?
- When to approve the technology?
 - Early approval? Can the evidence be provided with approval?

Expected value of perfect information (EVPI)

Realisations of uncertainty that could occur	Net health benefits (QALYs)			Best outcome for each realisation, $\max \text{NB}(j, \theta)$
	Treatment A $j = 0$	Treatment B $j = 1$	Best treatment choice	
θ_1	9	12	B	12
θ_2	12	10	A	12
θ_3	14	17	B	17
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$E_{\theta} \text{NB}(j, \theta)$	12	13		13.6

What's the best we can do now?

Choose B, expect 13 QALYs

Could we do better?

With perfect information, expect 13.6 QALYs

Expected value of perfect information (EVPI)

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θ_5	14	16	B	16
$E_\theta \text{NB}(j, \theta)$	12	13		13.6

What's the best we can do now?

Could we do better?

Choose B, expect 13 QALYs

With perfect information, expect 13.6 QALYs

EVPI = Perfect information – current information

$$= E_\theta \max_j \text{NB}(j, \theta) - \max_j E_\theta \text{NB}(j, \theta)$$

$$= 13.6 - 13 = 0.6 \text{ QALYs per patient}$$

EVPI: Maximum value of additional evidence to resolve uncertainties

EVPI at population level

- EVPI at a population level

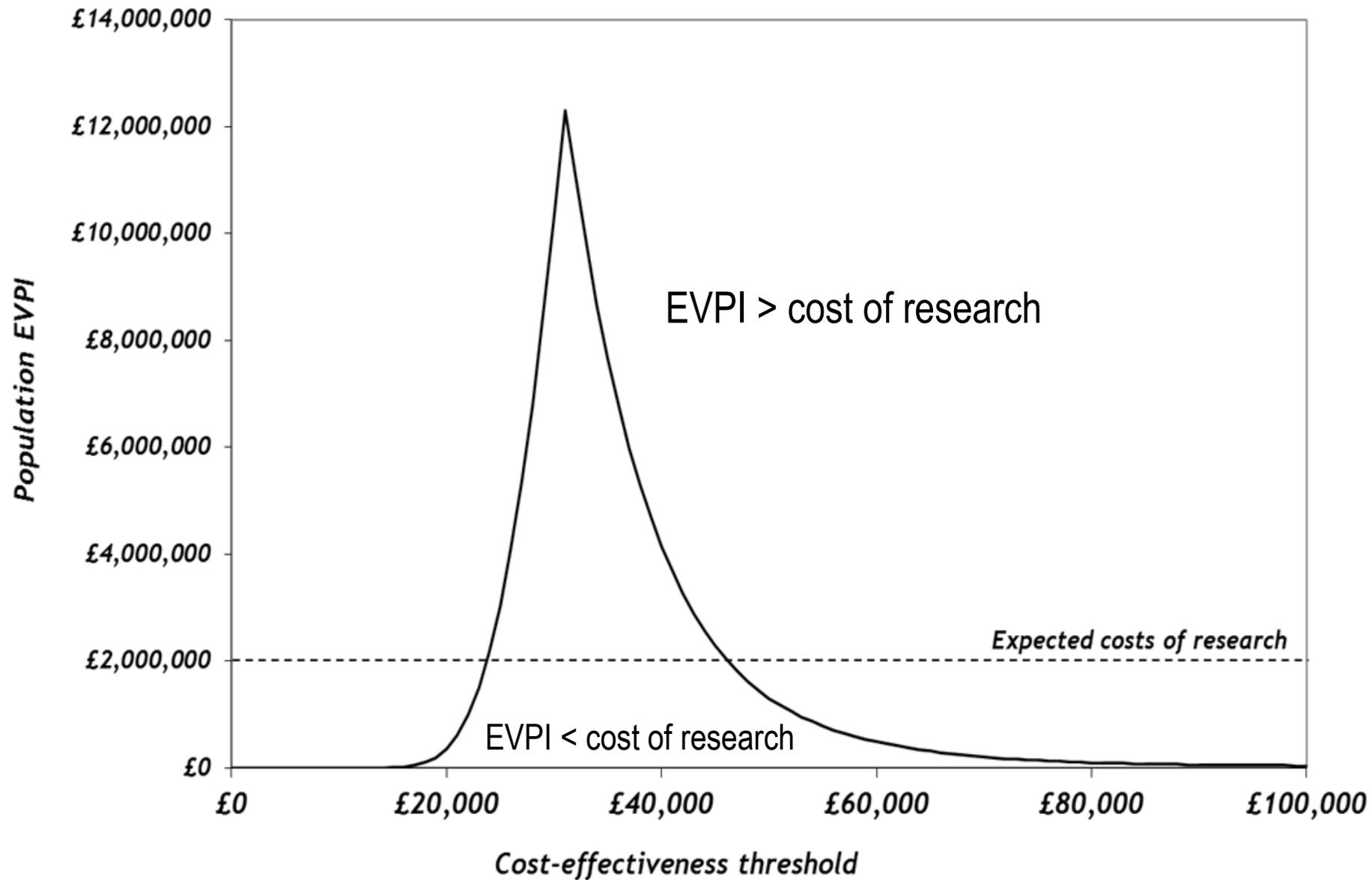
- Multiply the 'per patient EVPI' by the number of times this information is used to inform treatment choice (size of the beneficiary population)
- Depends on size of prevalent and incident population, P_t , I_t
- Depends on time horizon over which information is valuable, T

$$\text{Population EVPI} = \text{EVPI} \cdot \sum_{t=1}^T \frac{I_t}{(1+d)^t} \quad \text{d, discount rate}$$

- Provides an expected upper bound on the value of research

- Population EVPI > cost of research
- If EVPI is lower than the expected costs of conducting further research then it is not cost-effective to conduct further research, i.e. EVPI provides a necessary condition for conducting research

EVPI at population level, an example



What type of evidence is required?

Expected value of perfect information for parameters (EVPPI)

- EVPPI considers the value of particular elements of the decision problem in order to direct and focus research towards those areas where the elimination of uncertainty has the most value
- The consequences of uncertainty that is attributable to:
 - Single parameters or groups of parameters e.g. costs, effectiveness
 - Shows sensitivity of model results to inputs and consequences of error

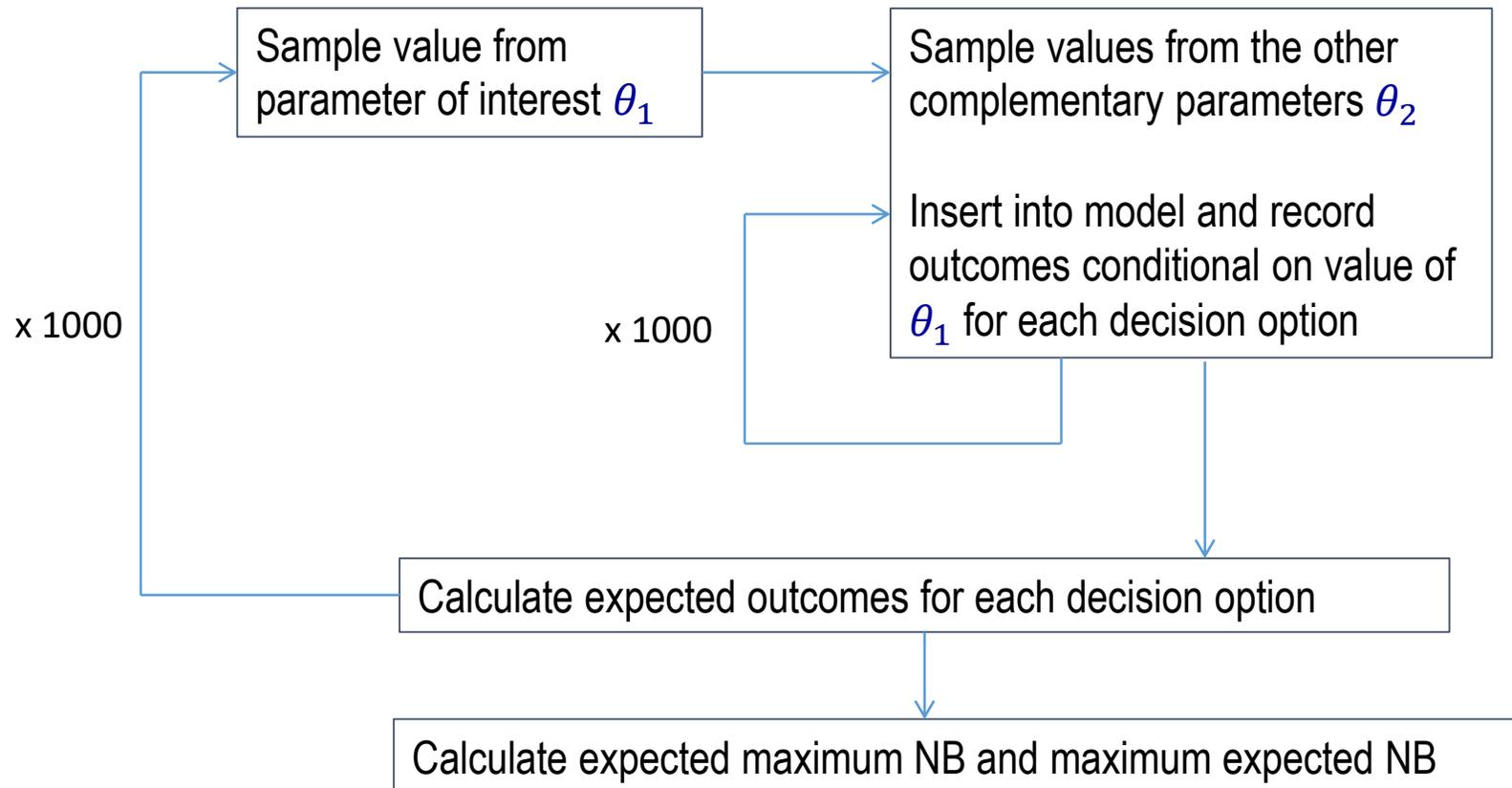
$$\theta \begin{cases} \theta_1 = \text{parameter of interest} \\ \theta_2 = \text{other uncertainties (complementary parameters)} \end{cases}$$

- For each parameter or group there will be a different potential value of research and appropriate research design

Computing EVPPI

$$EVPPI_{\theta_1} = E_{\theta_1} \max_j E_{\theta_2|\theta_1} NB(j, \theta_1, \theta_2) - \max_j E_{\theta} NB(j, \theta)$$

θ $\left\{ \begin{array}{l} \theta_1 = \text{parameter of interest} \\ \theta_2 = \text{other uncertainties (complementary parameters)} \end{array} \right.$

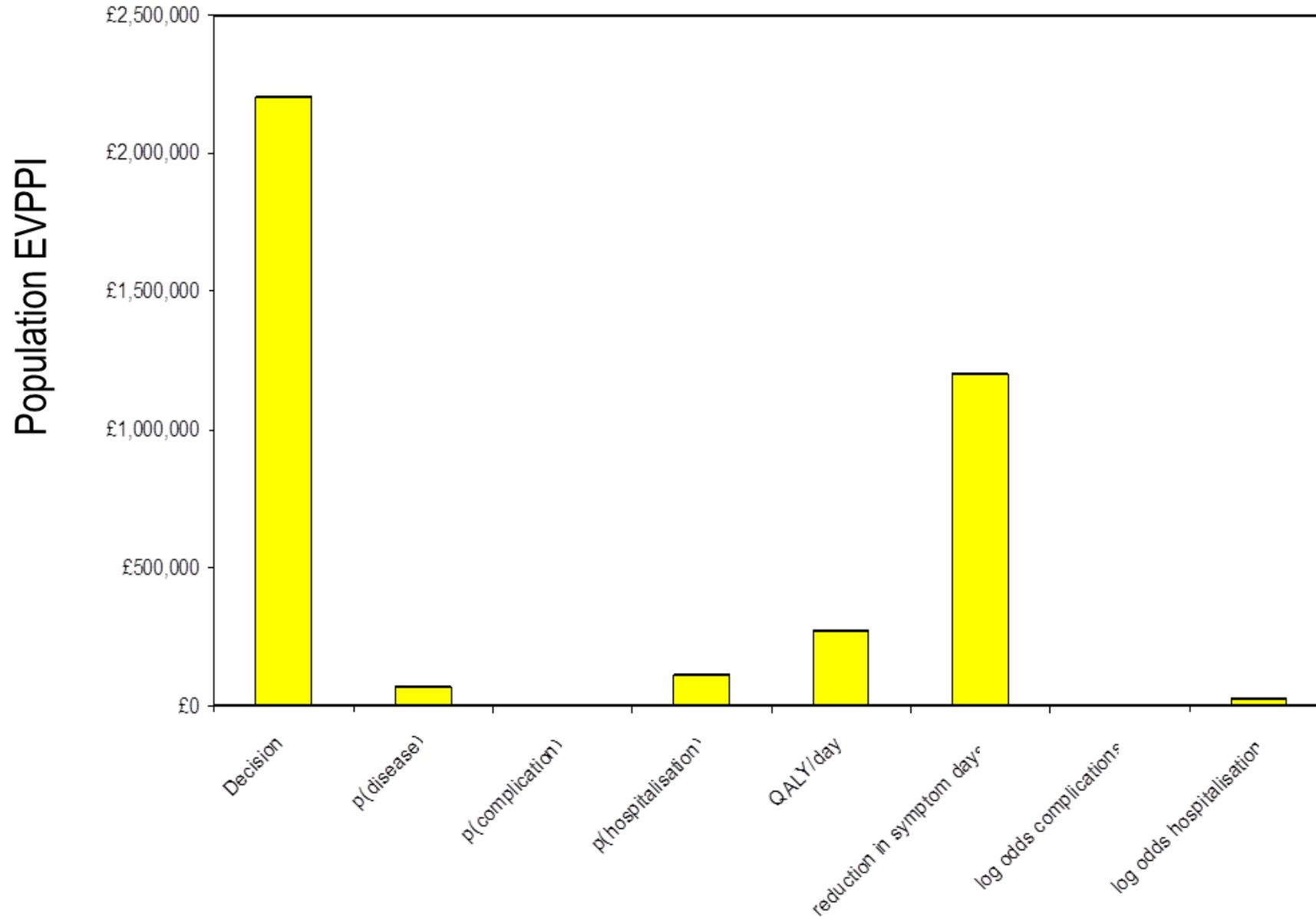


EVPPPI

- Two-level sampling algorithm (unless model is linear)
 - Sample parameter of interest (outer loop)
 - Analyse model probabilistically (inner loop)
- Analysis time
 - How many simulations? Which parameters/groups of parameters to include?
- Sum of EVPPPI \neq EVPI
- Knowing θ_1 alters value of θ_2
- Can calculate EVPPPI as group to embed correlation between parameters
- More flexible regression-based methods available to reduce to single-loop sampling (efficient EVPPPI computation)

Ref: ISPOR Task Force report. Value of Information Analytical Methods: Report 2 of the ISPOR Value of Information Analysis Emerging Good Practices Task Force. Rothery et al (2020)

EVPPI at population level, an example



What type of research design?

Expected value of sample information (EVSI)

- In practice unlikely to obtain perfect information
 - Additional research will reduce, rather than eliminate uncertainty
- Research design may include sample size, allocation of patients between arms of clinical trial, length of follow-up, endpoints to include
- EVSI provides the value of a decision based on having additional sample information. It predicts possible sample results that would be obtained from a study with a sample size of n
- To establish if the study is an efficient use of resources, the societal value of the study is compared to the costs of gathering the sample information
- Sufficient condition for further research
 - Expected net benefit of sampling (ENBS) = $EVSI - \text{cost of research}$
 - If $ENBS > 0$ for a particular sample design then further research is worthwhile

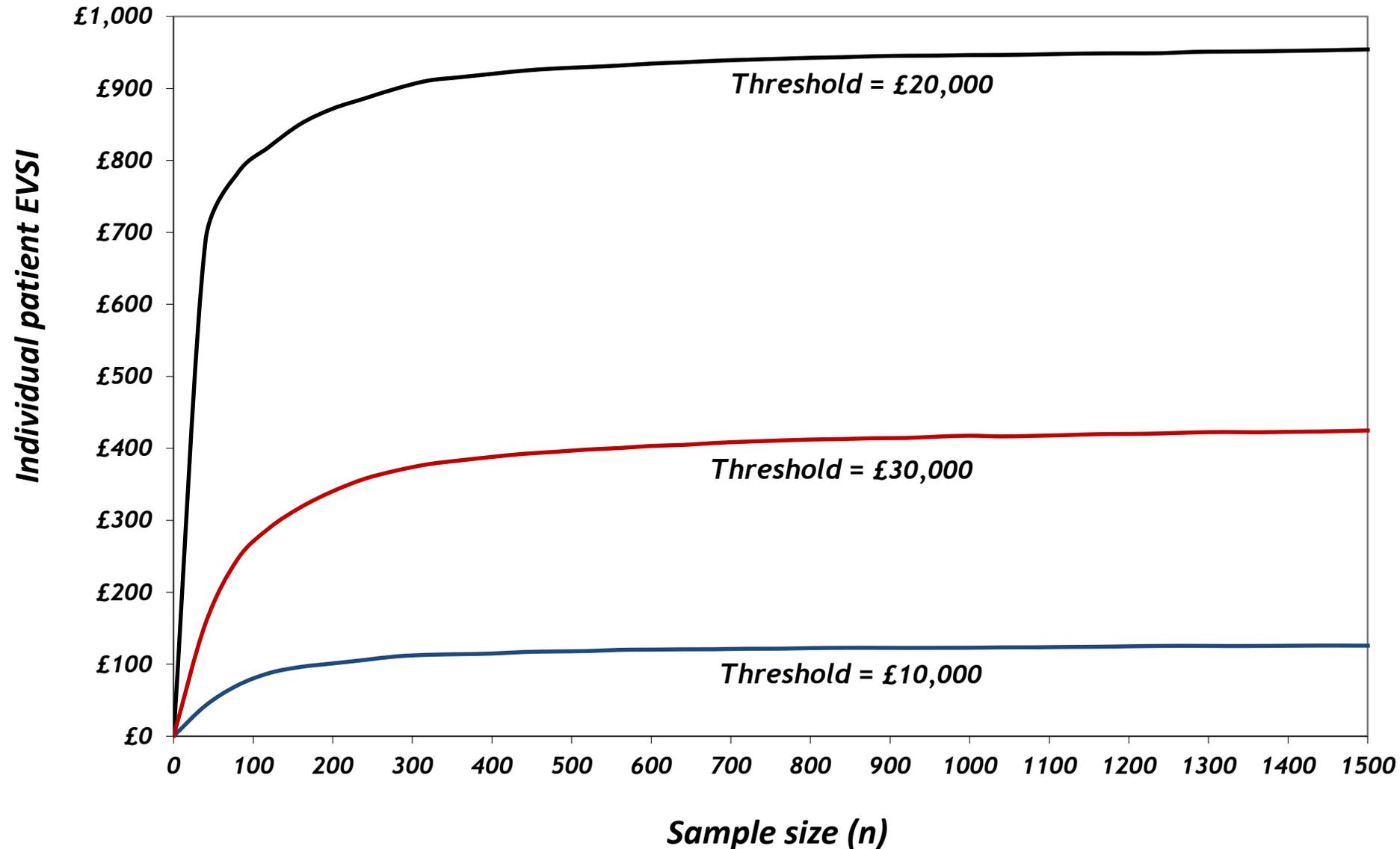
Expected value of sample information (EVSI)

1. Define proposed new data collection exercise (sample size, length of FU etc). Determine the likelihood for new data under this design
2. Sample from the prior distributions of parameter(s) that is informed by new data
e.g. $\theta \sim \text{Beta}(\alpha = 3.64, \beta = 47.14)$
3. Predict possible sample results for new study of size n conditional on prior data (likelihood function), $D|\theta$
e.g. $D \sim \text{Binomial}(\theta, n)$
4. Combine the prior and predicted sample distributions to form predicted posterior results for each sample
e.g. $X' \sim \text{Beta}((\alpha+n\theta), (\beta+n-n\theta))$
5. Calculate NB for each predicted posterior and choose the treatment with the highest NB
6. Since the actual results of each sample are not known in advance, average the maximum expected NB over the distribution of possible sample results: $E_{\theta} E_{D|\theta} \max_j E_{\theta|D} NB(j, \theta)$

EVSI = NB with sample information – NB with current information

$$EVSI = E_{\theta} E_{D|\theta} \max_j E_{\theta|D} NB(j, \theta) - \max_j E_{\theta} NB(j, \theta)$$

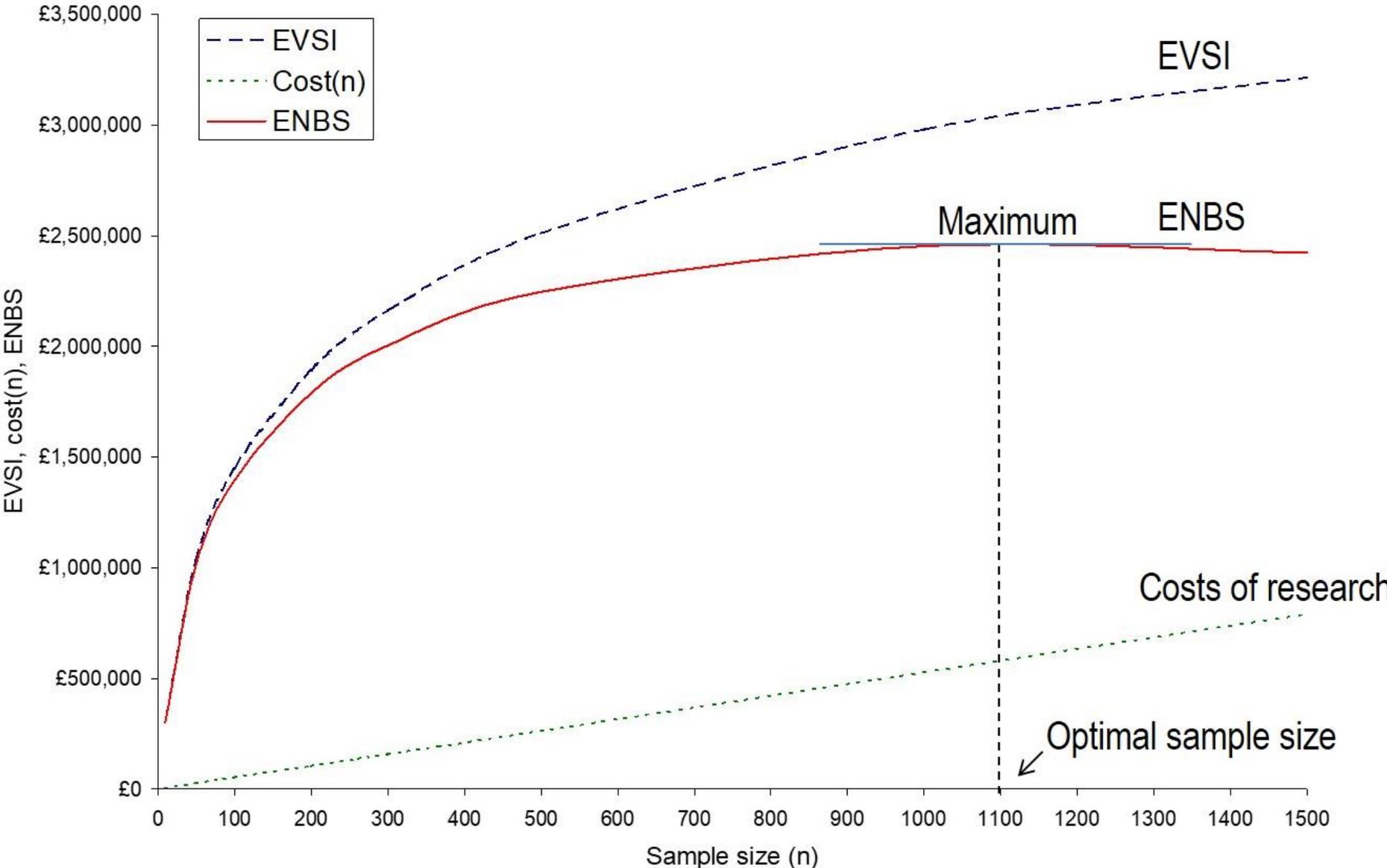
EVSI, an example (...as function of cost-effectiveness threshold)



Is research an efficient use of resources?

- ENBS = Population EVSI - cost of research
- Cost of research as function of study design and sample size
 - Costs of running study and opportunity costs to patients
 - Patients enrolled in study no longer part of population to benefit from additional information (acute condition)
- Use ENBS to prioritise research and in place of traditional power calculations
 - ENBS > 0 for a particular sample design then further research is worthwhile
 - Choose between alternative research designs, e.g. appropriate length of follow-up, sample size, where the **ENBS reaches a maximum**
- Need to also consider the time to research reports and the likelihood that research is completed

Expected net benefit of sample information (ENBS), an example



Summary: setting research priorities using VOI

➤ EVPI and EVPPI

- Maximum return to research
- Comparing the EVPI to the opportunity costs of research
- Comparing EVPI across technologies
- Comparing EVPPI to focus research design

➤ EVSI and ENBS

- Identify technically efficient research designs
- Allocations between clinical areas
- Allocation between research and service provision

Other considerations for value of research

- Feasibility of research
 - Type of research design (observational versus experimental)
- Likelihood of research
 - Research itself may be an uncertain prospect (fail to complete)
- Time to research reports
 - Value of research declines the longer it takes to report
- Irrecoverable costs associated with investment
 - Sunk costs with implementing 'wrong' decision option
 - Opportunity cost of delay until research reports
- Value of implementation
 - Alternative methods to change practice
- Sequence of research decisions
- Future uncertain events
- Budgetary policies in place