

# Mixing Econometrics and Epidemiology: the perfect job for Health Economics?

Gianluca Baio

Department of Epidemiology and Public Health — University College London (UK)

Collaborative Meeting on “Mixing Econometrics and Epidemiology in the context of estimating treatment effects”

Imperial College London  
9 March, 2009

# Outline of presentation

- ① **What is health economic evaluation?**
- ② Statistical decision process
- ③ Frameworks for health economics & data analysis
  - Licensing
  - Reimbursement
  - Post-marketing surveillance
- ④ Conclusions

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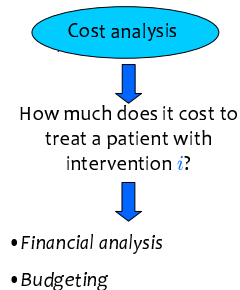
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- 1 What is health economic evaluation?
- 2 Statistical decision process
- 3 **Frameworks for health economics & data analysis**
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# What is Health Economics?



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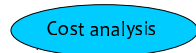
Cardiovascular system (C)	Expenditure <sup>1</sup>	%*	DDD <sup>2</sup>	%*
Bosentan	37.0	47.9	0.3	0.2
Cardiac stimulants	8.8	11.4	3.5	2.1
Statins	5.5	7.2	15.9	9.9
Calcium Antagonists (diidro.)	4.5	5.8	20.1	12.4
Nitrates	3.7	4.8	21.0	13.0
Diuretics	2.2	2.8	18.8	11.6
Ace Inhibitors	2.1	2.8	24.0	14.8
Beta Blockers	1.7	2.2	17.2	10.7
Alfa Blockers	1.0	1.3	3.2	2.0
Angiotensin II Antagonists	0.9	1.1	3.5	2.2
...				

<sup>1</sup> Millions €

<sup>2</sup> Millions days of therapy

\*Percentages are calculated over the total of the ATC category

Source: Osmed (2007)

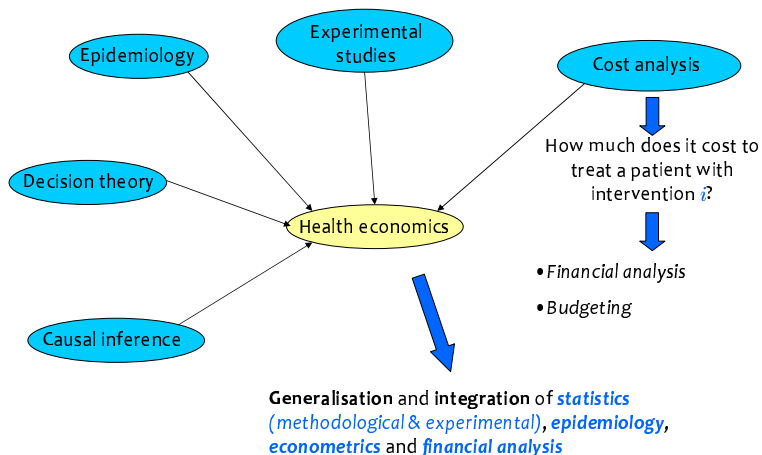


How much does it cost to  
treat a patient with  
intervention *i*?



- Financial analysis
- Budgeting

# What is Health Economics?



# Health economic evaluations

- **Objective:** Combine costs & benefits of a given intervention into a rational scheme for allocating resources
  - Recently, models have been built upon more advanced statistical foundations
  - This problem can be formalised within a statistical decision-theoretic (DT) approach. Rational decision-making is effected through the comparison of expected utilities

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- Increasingly under a Bayesian framework, especially in the UK
  - David Spiegelhalter (2006). *Bayesian methods, health technology assessment, and performance monitoring*. Report on progress 2001-2006 for MRC Unit's Quinquennial Review
    - Specific focus on Bayesian decision-theoretic development of cost-effectiveness analysis
  - Contributions by several scholars and research groups
    - Karl Claxton (University of York)
    - Tony O'Hagan (University of Sheffield — Centre for Bayesian Statistics in Health Economics)

# General framework

- Consider a set of “units” (patients) that can be regarded as **similar** (exchangeable) before treatment
  - Randomised, stratified, ...
- The interest is in the management of a particular condition for which a set of interventions  $t \in (0, 1, \dots, T)$  is available
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- We need to decide what intervention to apply to a **new** unit  $i'$ , again judged as similar with all the others receiving the same treatment
  - Units might themselves be a population, and treatments might be some population-level policy interventions

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  - The current *uncertainty* about  $\theta$  is formally described by a suitable probability distribution
  - This describes the state of science about the parameters before observing any new data. For instance, we will generally have patient-level data in the form  $\mathcal{D}^t = \{y_i : i = 1, \dots, n_t\}$  and the whole set of background information as  $\mathcal{D} = \bigcup_t \mathcal{D}^t$
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- 2 Conditionally on  $\theta$ , the  $Y_i$ 's are drawn independently from the probability distribution  $p(y | \theta)$ , which describes the individual *variability* of the future (yet unobserved) health economic response

## (Bayesian) Decision-making process

- Consider (for simplicity) two alternative *treatments*  $t = 0, 1$  that can be applied
- The *health economic outcome* is quantified as  $y = (e, c)$ 
  - $e$  suitable measure of effectiveness (*i.e.* QALYs)
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  - *Increment in mean effectiveness*

$$\Delta_e := E[e \mid \theta^1] - E[e \mid \theta^0]$$

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- **NB:** These two quantities are *random variables* upon variations in the parameters  $\theta$

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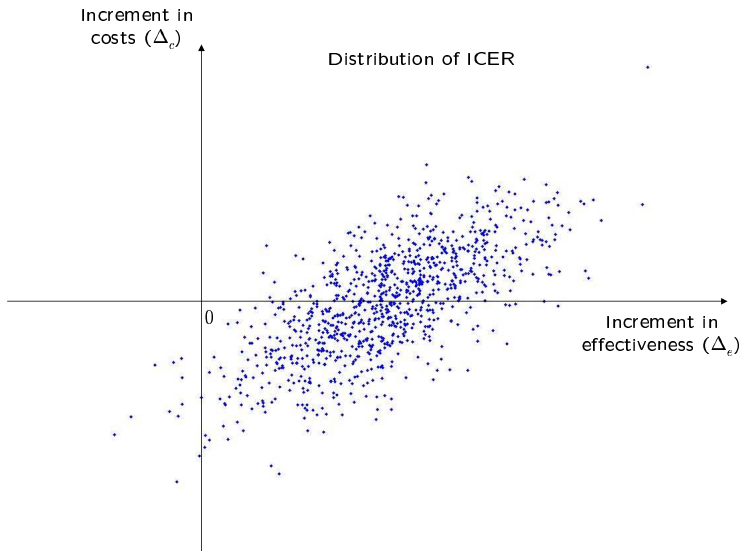
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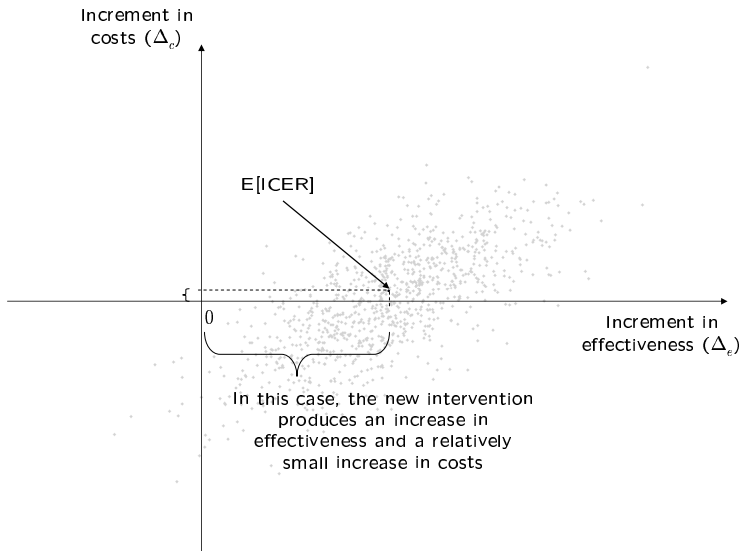
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# HE in a Bayesian framework

Besides the philosophical aspects, there are a few pragmatical aspects that have perhaps driven the establishment of the Bayesian approach in HE, especially in the UK

- Bayesian decision theory provides an **absolute ranking of options**
- Existing information, at least on some aspects of the intervention being tested, are often available in the form of previous data; consequently, prior distributions can be based on “hard evidence” and are less affected by subjective matters
- Bayesian framework particularly effective to handle **sensitivity analysis** (more of this later!)

## Frameworks for HE evaluation

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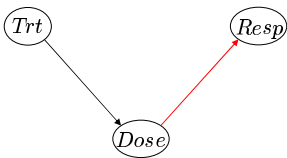
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# Non compliance (Jin & Rubin vs Efron & Feldman)

EF (1991) addressed the problem of partial compliance in a RCT

JR (2008) re-analysed the same data and used Potential Response outcome to estimate causal effect of *Trt* on *Resp* weighing for the effect of *Dose*



*Trt* = Active treatment vs Placebo (randomised)

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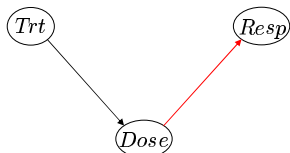


Table 5. Posterior median and 95% interval of representative principal causal effects for different values of  $\rho$

$(D, d)$	(1, 1)	(.68, .89)	(0, 1)	(0, 0)
$\rho = -.2$	49 (39, 59)	24 (18, 30)	-10 (-40, 25)	4 (-6, 14)
$\rho = 0$	50 (39, 59)	24 (17, 30)	-13 (-42, 27)	5 (-6, 16)
$\rho = .2$	50 (39, 59)	23 (16, 29)	-11 (-47, 27)	5 (-7, 18)
$\rho = .4$	50 (40, 59)	23 (16, 29)	-6 (-43, 34)	6 (-7, 20)
$\rho = .6$	51 (39, 62)	22 (15, 30)	-10 (-43, 30)	7 (-8, 23)
$\rho = .8$	52 (38, 63)	22 (11, 33)	-8 (-62, 68)	6 (-11, 28)
$\rho = .9$	51 (37, 66)	22 (6, 36)	-1 (-74, 79)	9 (-25, 41)

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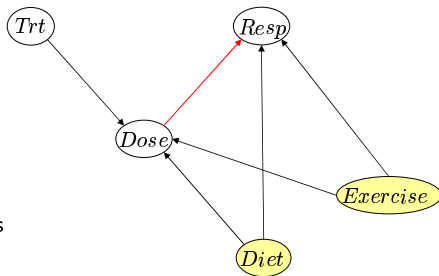
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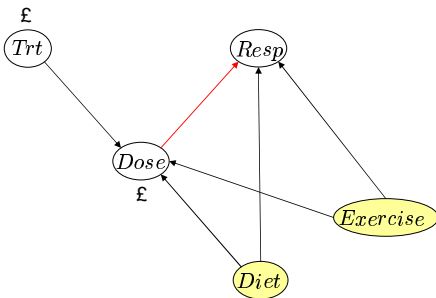
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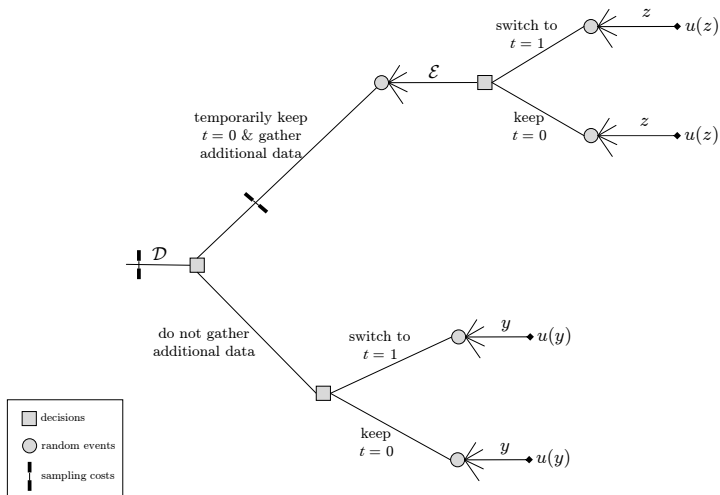
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# A sequential decision problem

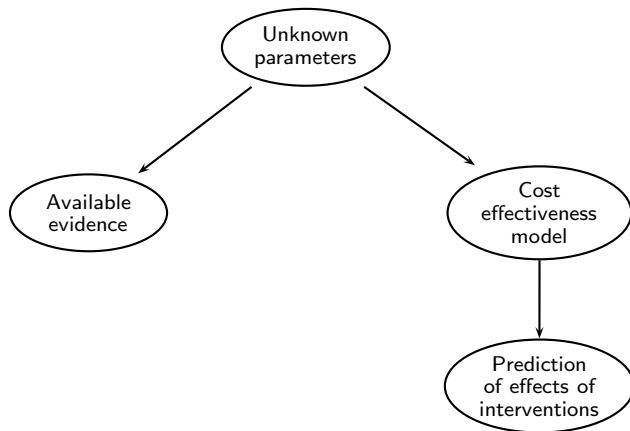


# 1. Evidence integration in HE models

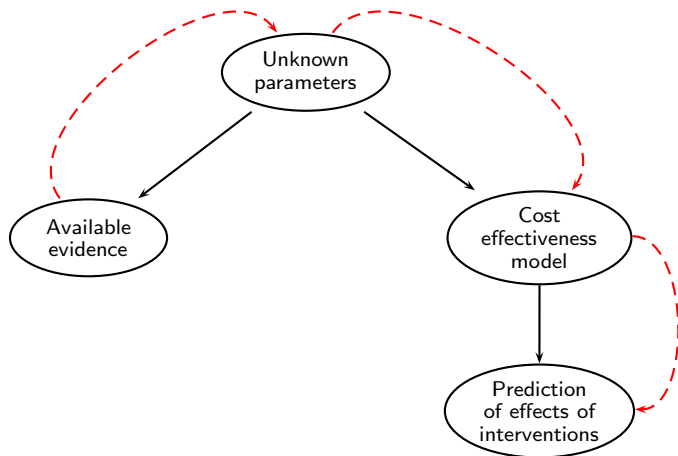
Spiegelhalter & Best (2003) discuss the inclusion of multiple evidence in the HE model

Source	Charnley ( $t = 0$ )		Stanmore ( $t = 1$ )		Estimated Hazard Ratio (95% CI)	
	Number of patients	Revision rate	Number of patients	Revision rate	(HR)	(95% CI)
<i>Fixed effects model</i>						
Registry	28,525	5.9%	865	3.2%	0.55	(0.37–0.77)
RCT	200	3.5%	213	4.0%	1.34	(0.45–3.46)
Case series	208	16.0%	982	7.0%	0.44	(0.28–0.62)
<i>Common effect model</i>						
					0.52	(0.39–0.67)
<b>Quality weights [Registry, RCT, Case series]</b>					<i>Random effects model</i>	
				[1,1,1]	0.54	(0.37–0.78)
				[0.5,1,0.2]	0.61	(0.36–0.98)
				[0.1,1,0.05]	0.82	(0.36–1.67)

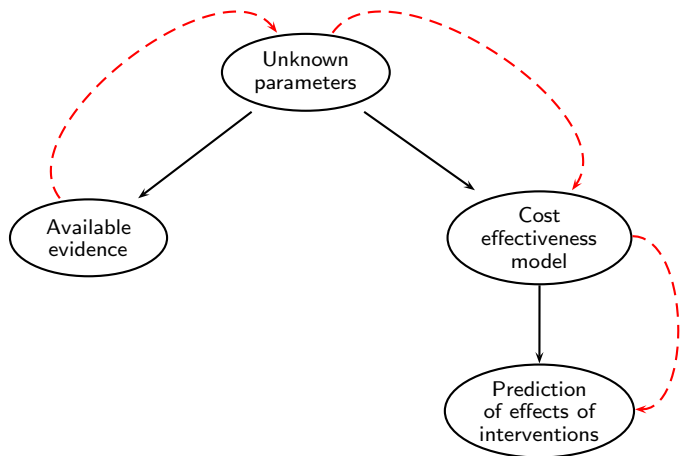
# Integrated two-stage process (Spiegelhalter & Best 2003)



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When evidence is observational, it is necessary to build an overall economic model capable of dealing with potential biases introduced by confounding variables

## 2. Sensitivity Analysis (SA)

Described in the Risk Assessment literature as the study of

*“how uncertainty in some model output ( $y$ ) can be apportioned, qualitatively or quantitatively, to different sources of uncertainty in the model input ( $\theta$ )”*

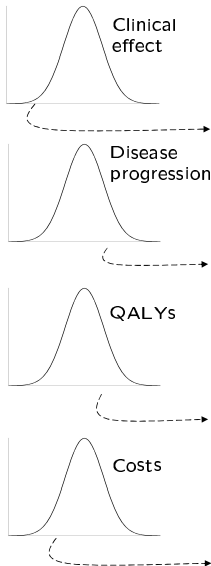
There are many different sources of variation in the random quantities relevant for this problem that can be subject to SA

- Differences in the individual outcomes (*variability*)
- Differences in the expected outcomes that can be explained by identifiable individual characteristics (*heterogeneity*)
- Imperfect knowledge of model parameters (*parameters uncertainty*)

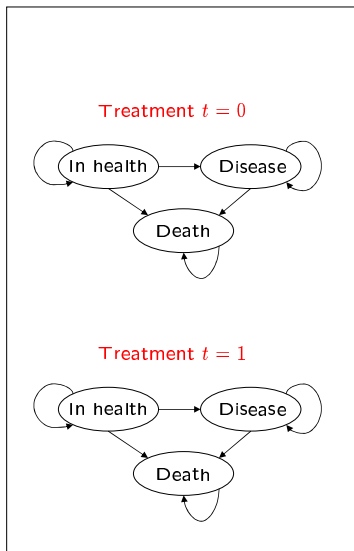
Usually, the most important is **parameters uncertainty** – **Probabilistic Sensitivity Analysis**



## Parameters



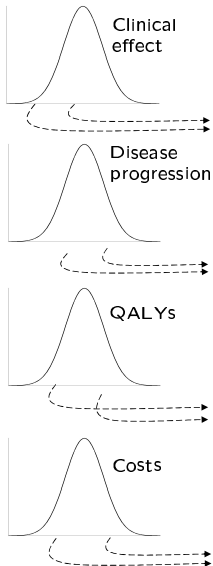
## Model structure



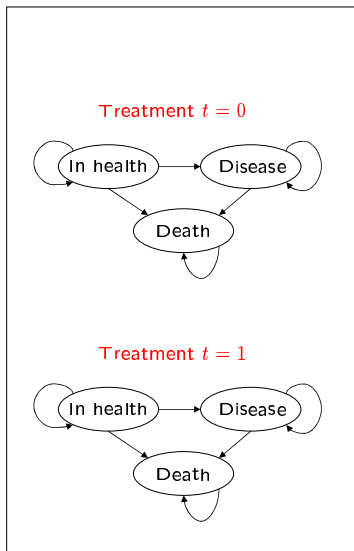
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Treatment $t = 0$	
QALYs	Costs
1	£10,000
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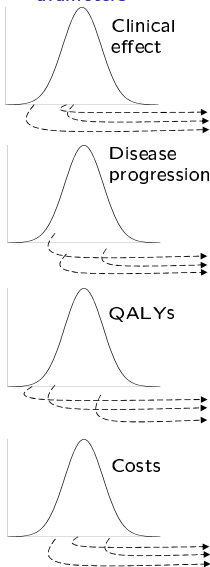
Treatment  $t = 0$ 

QALYs	Costs
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0	£5,000

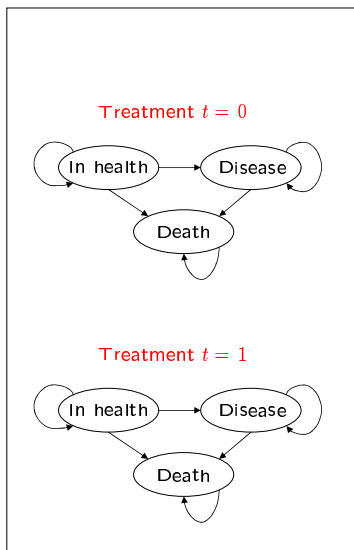
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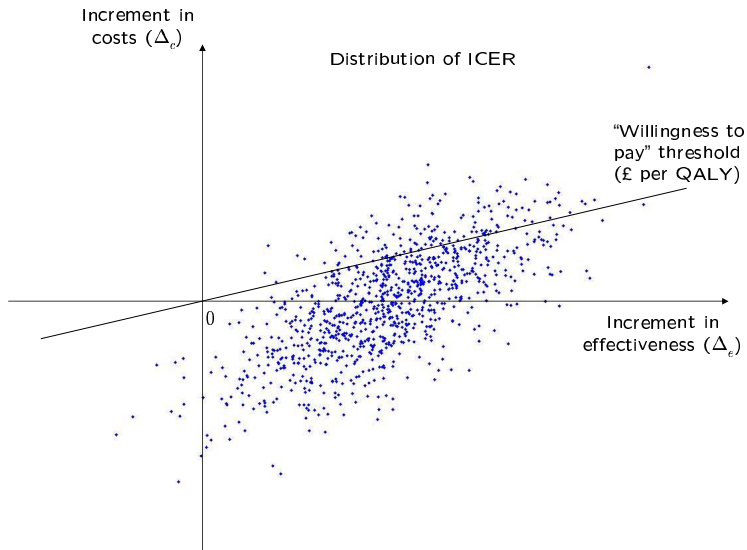
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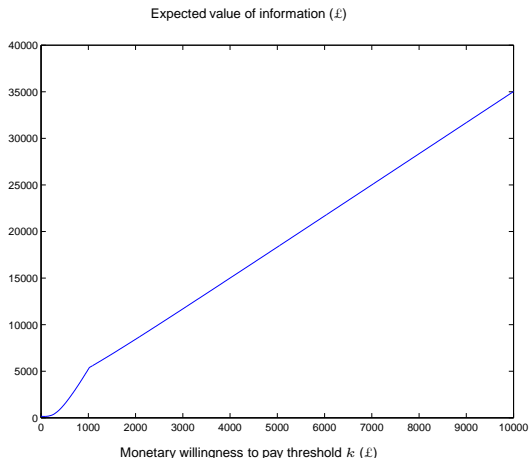
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$$E[\text{ICER}] = \frac{\text{£20,000}}{1\text{QALY}}$$

# More on PSA

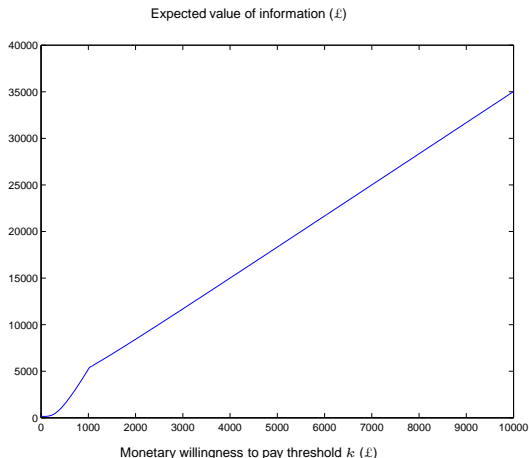


# More on PSA — Expected value of information



- Increasingly important as a summary of PSA in Health Economics
- Describes the maximum amount the decision maker should be willing to pay to *resolve the uncertainty* in the parameters
- By construction, combines
  - a) *how much* we are likely to lose if we take the “wrong” decision
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  - a) *how much* we are likely to lose if we take the “wrong” decision
  - b) *how likely* it is that we take it
- Drives the process of gathering additional evidence
- **NB:** Under the PR framework, the value of information about some parameters is meaningless (as no empirical evidence can ever be produced!)

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# Post marketing research

- Typically clinical studies are conducted for a limited period of time
  - Pharmaceutical companies want to reach final decision on a new compound asap: the overall process takes about 8 years from Phase 1 to Market, and cost is estimated in \$802 million (about other 7 years are necessary to get to Phase 1)
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- Surveillance conducted on several levels
  - Patient Spontaneous Reports (“yellowcards”)
  - Central institutions (FDA, EMeA, European Commission)

# Impact of post-marketing findings on health economic evaluation

- Adverse reactions to drugs, identified in post-marketing may affect the health economic evaluation in many ways:
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  - Quality of life
  - Use of additional resources (hospitalisation, vaccinations, extra treatments)

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  - Use of additional resources (hospitalisation, vaccinations, extra treatments)
- Therefore, any cost-effective treatment (on the basis of current evidence) might turn out into a non-optimal alternative, once these new findings are accounted for
- Some guidelines (eg the Canadian) suggest stratified analysis to account for potential biases in observational data used for pharmaco-vigilance

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- This led in April 2002 to the introduction of warnings on the rofecoxib-based drug labelling concerning the increased risk of CV events
- A few economic studies were performed to assess the cost-effectiveness of rofecoxib
- The results were in general positive
  - “The analysis showed that, with the introduction of rofecoxib, a substantial reduction in the risk of GI complications for patients on conventional NSAIDs therapy is possible at only a modest additional cost to the NHS budget” (Moore et al 2001)
  - “Rofecoxib is economically attractive in high risk and elderly patients” (Maetzel et al 2003)

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  - “The analysis showed that, with the introduction of rofecoxib, a substantial reduction in the risk of GI complications for patients on conventional NSAIDs therapy is possible at only a modest additional cost to the NHS budget” (Moore et al 2001)
  - “Rofecoxib is economically attractive in high risk and elderly patients” (Maetzel et al 2003)
- Sadly, some of the data used to produce effectiveness results were “controversial”, and in fact rofecoxib was more harmful than previously reported, leading the marketer to withdraw it completely

# Other relevant problems

- **Technical issues**

- Adjusting for differences in baseline patient characteristics
- Controlling for centre- or country-effects in multicentre trials (e.g., hierarchical models)
- Extrapolating beyond the end of clinical trials
- Dealing with missing or censored data
- Meta-analysing cost and effectiveness data

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- **“Dissemination” & practical use of HE methods**

- Tension within institutions such as NICE between the level of sophistication of the analyses, and the ability of the members of the Committees to understand them
- Evidence needs to be conveyed in a clear way to the decision-makers so that they can understand use it

# Conclusions

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  - Of course the clinical and the financial aspects are crucial, but to get there, we need more than doctors and economists
- Addressing the issue of (the impact of) uncertainty on the decision process is fundamental
  - Gathering and integrating continuous information
- Different forms of data are often needed to try and reduce this uncertainty
  - Integrating efficacy values from RCTs with “real” costs and effectiveness from observational studies

Thank You!