Μπευζιανης μεθοδων στην οικονομια της υγειας

(thanks/blame mostly to Google Translate)

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Research Seminars
Department of Statistics
Athens University of Economics and Business, Athens

Thursday 3 May 2018

Outline

1. **Health economic evaluation**
   - What is it?
   - How does it work?
2. Statistical modelling
   - Individual-level vs aggregated data
   - The importance of being a Bayesian
3. Some examples — you get to choose...
   - Individual level & partially observed data
   - Survival analysis in HTA
   - Value of information
4. Conclusions

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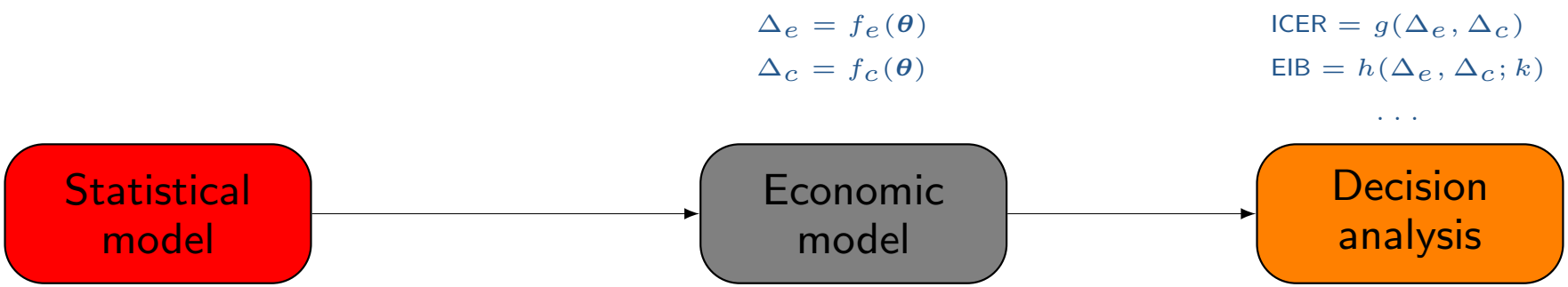

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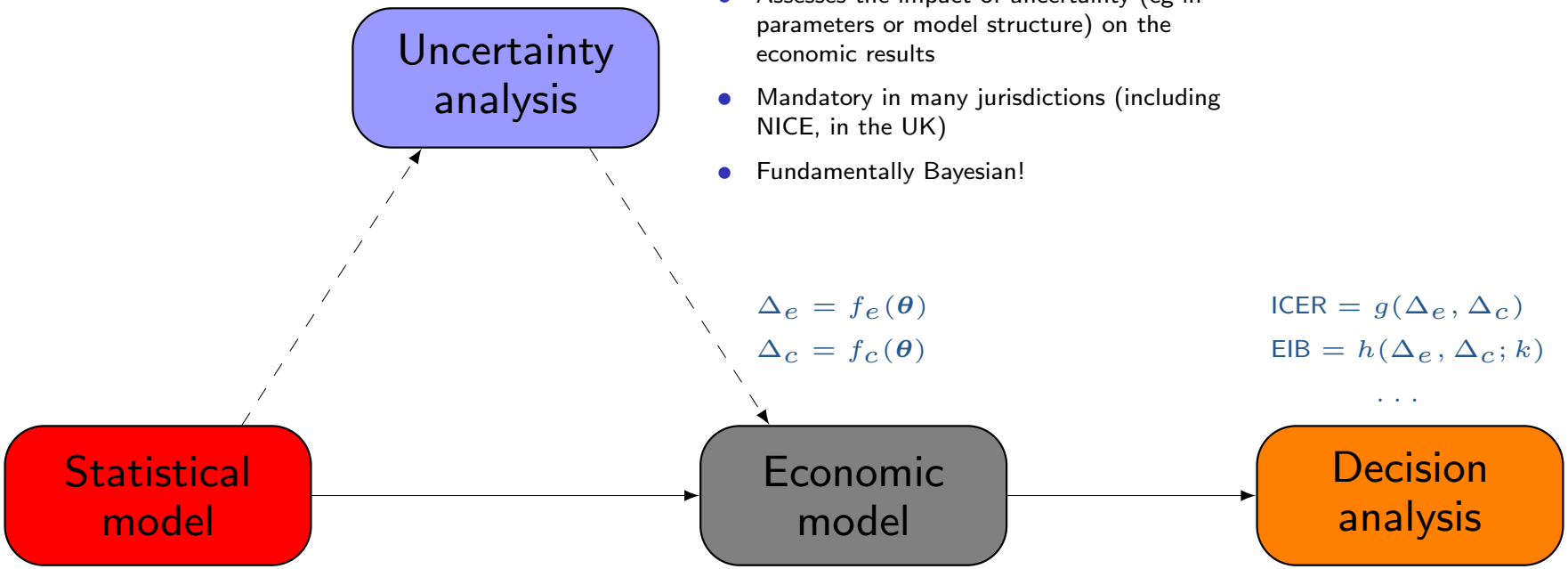

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1. ("Standard") Statistical modelling — **Individual level** data

		Demographics			HRQL data				Resource use data				Clinical outcome			
ID	**Trt**	Sex	Age	...	u_0	u_1	...	u_J	c_0	c_1	...	c_J	y_0	y_1	...	y_J
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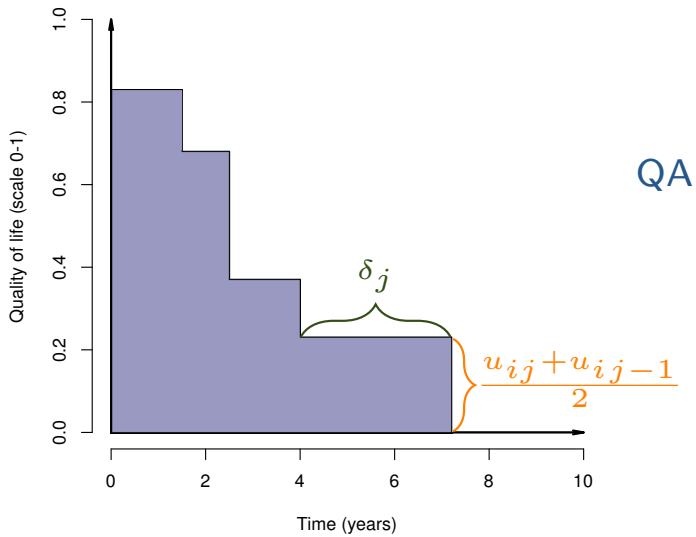

QALY_i = "Area under the curve"

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2. (Often implicitly) assume normality and linearity and model **independently** individual QALYs and total costs by controlling for baseline values

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3. Estimate population average cost and effectiveness differentials and use bootstrap to quantify uncertainty

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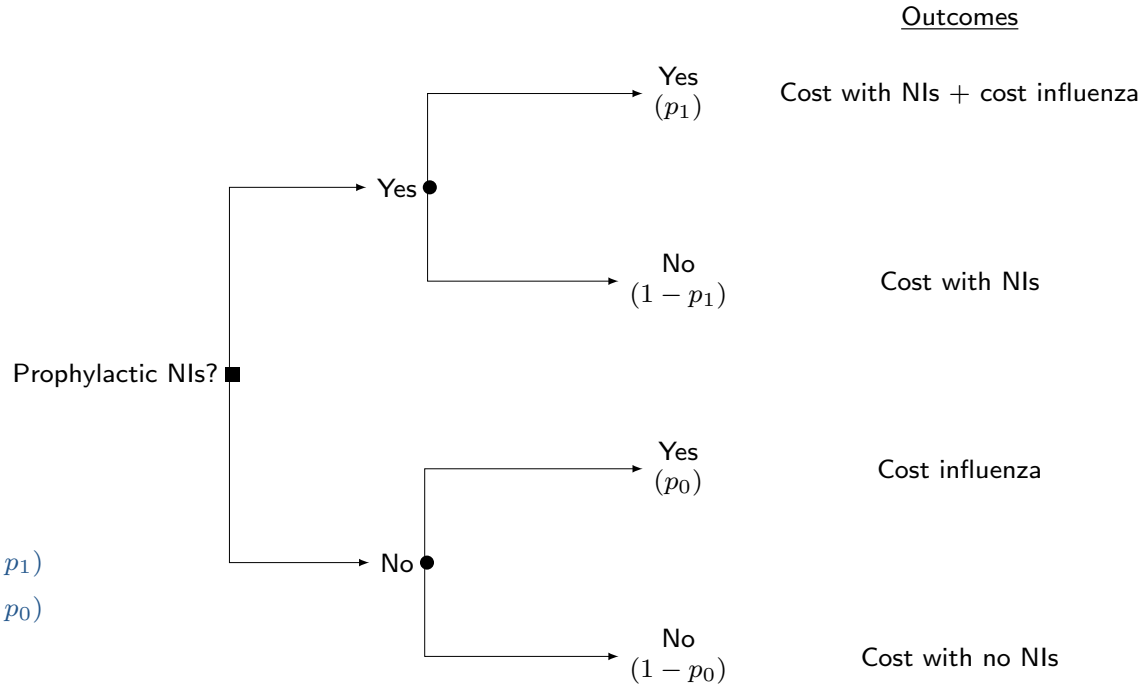

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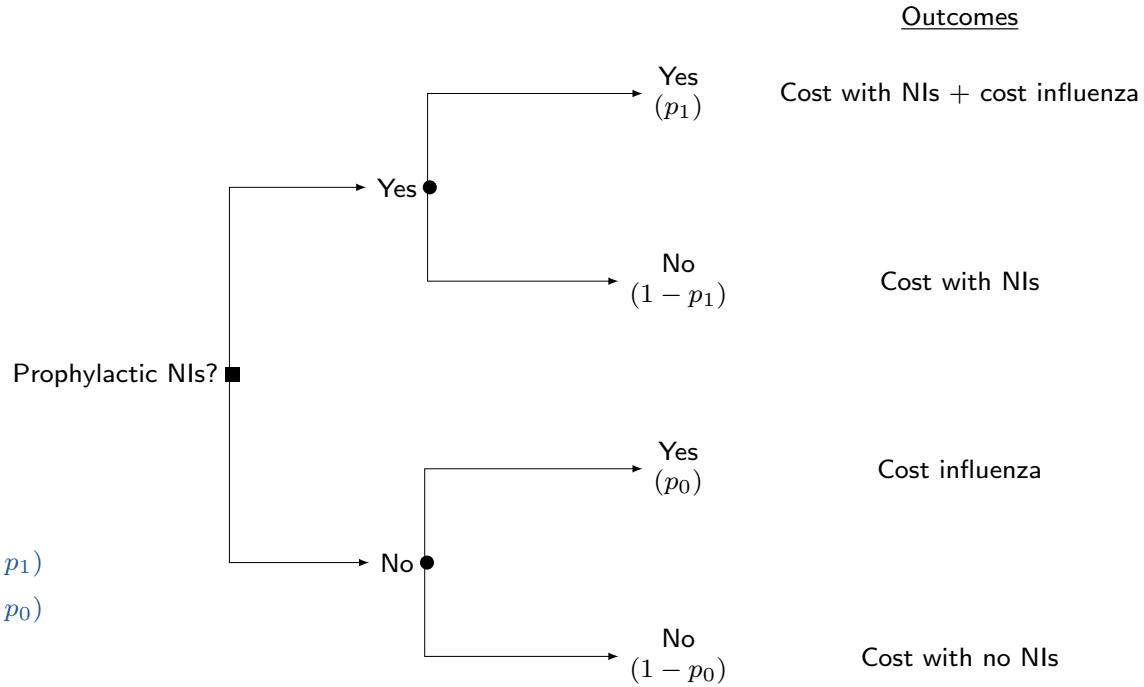

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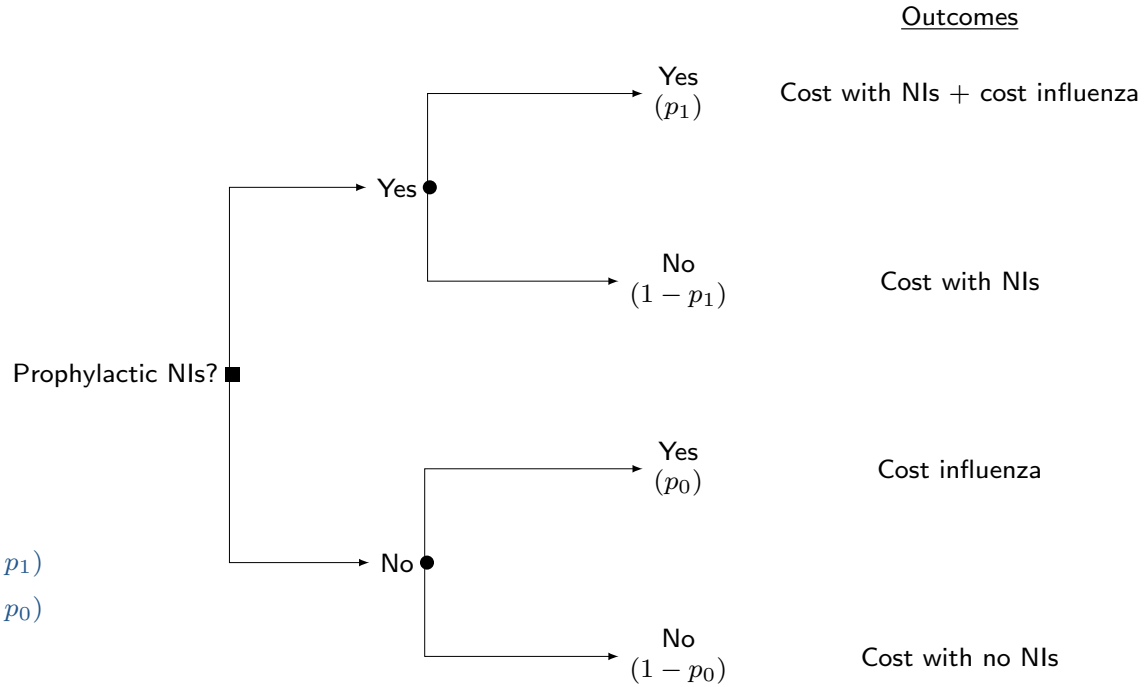

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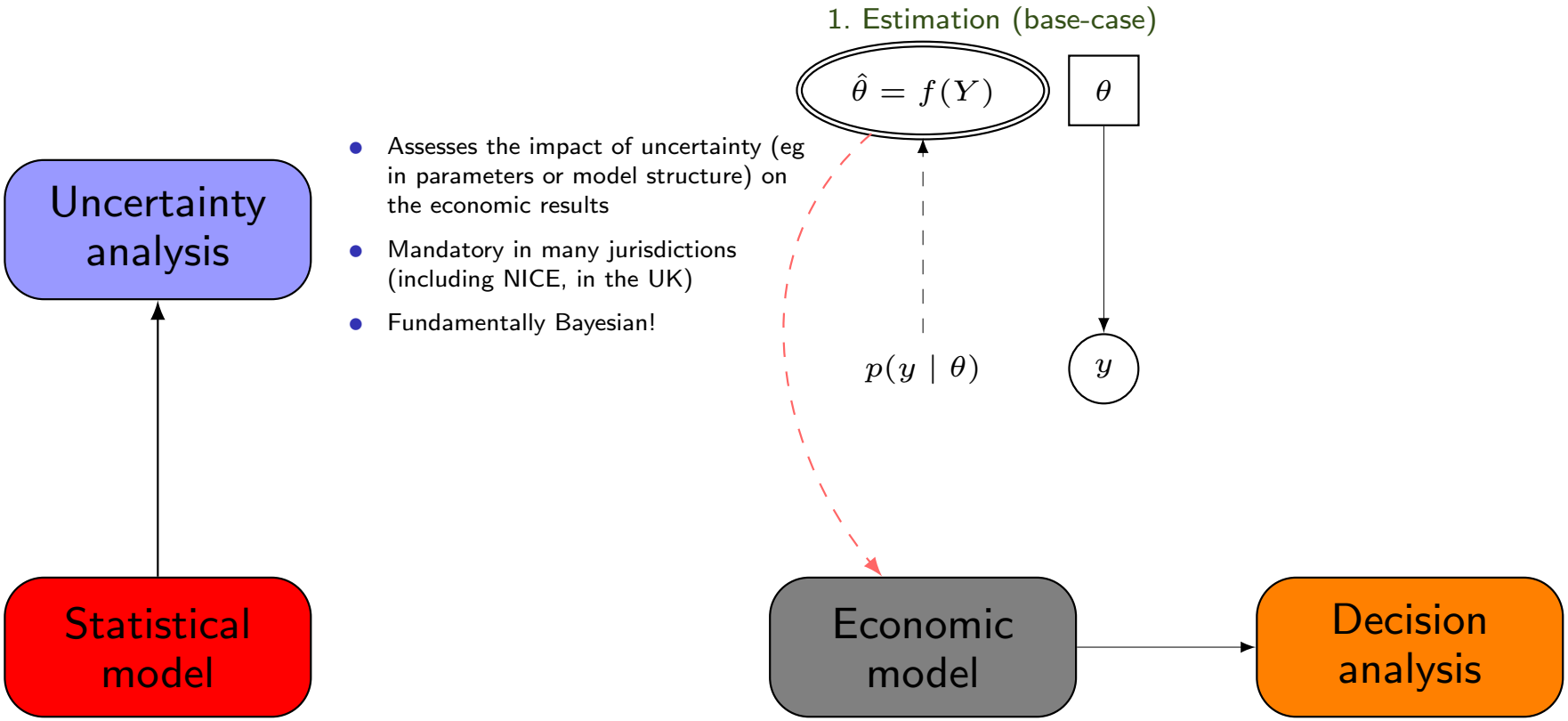
"Standard" approach to HTA — "Two-stage"



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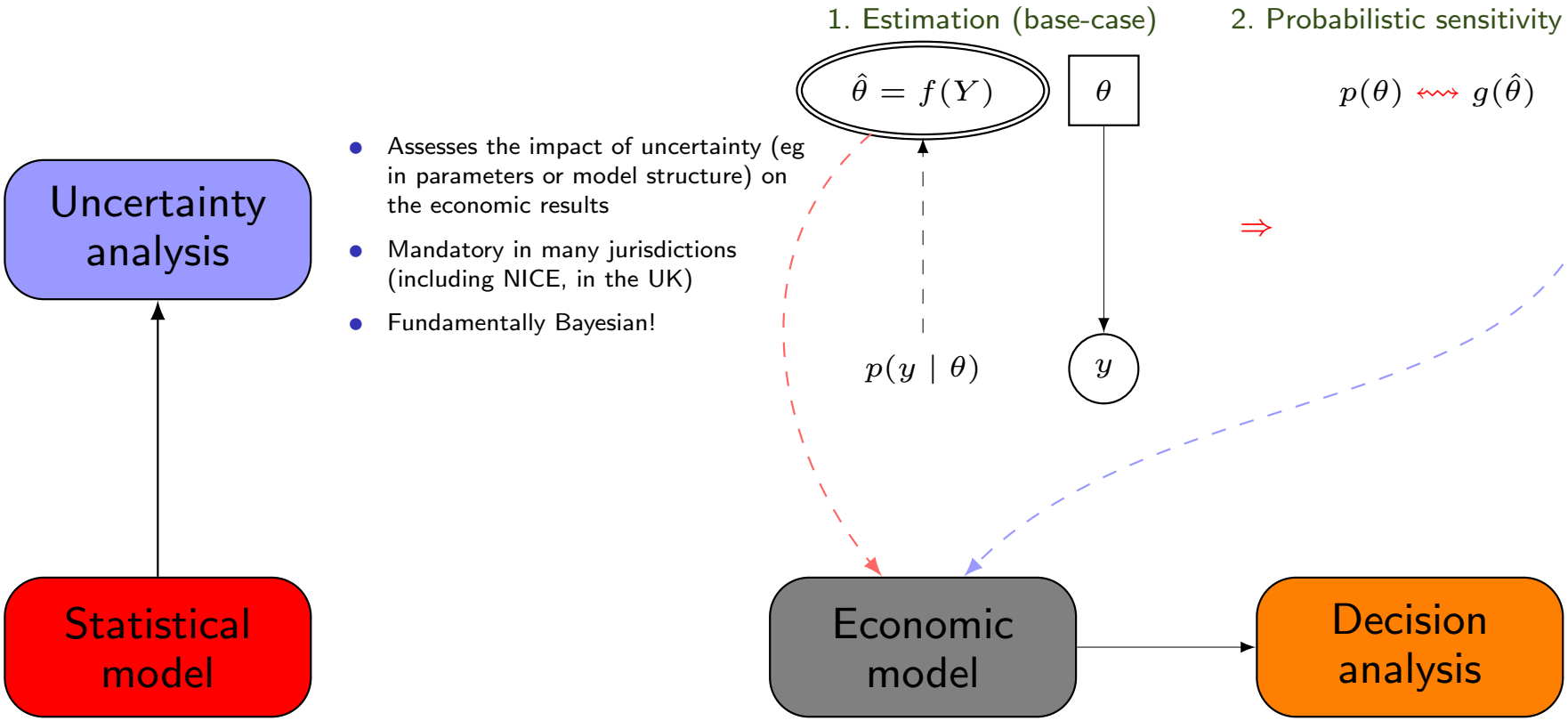

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"Two-stage approach" (Spiegelhalter, Abrams & Myles, 2004)

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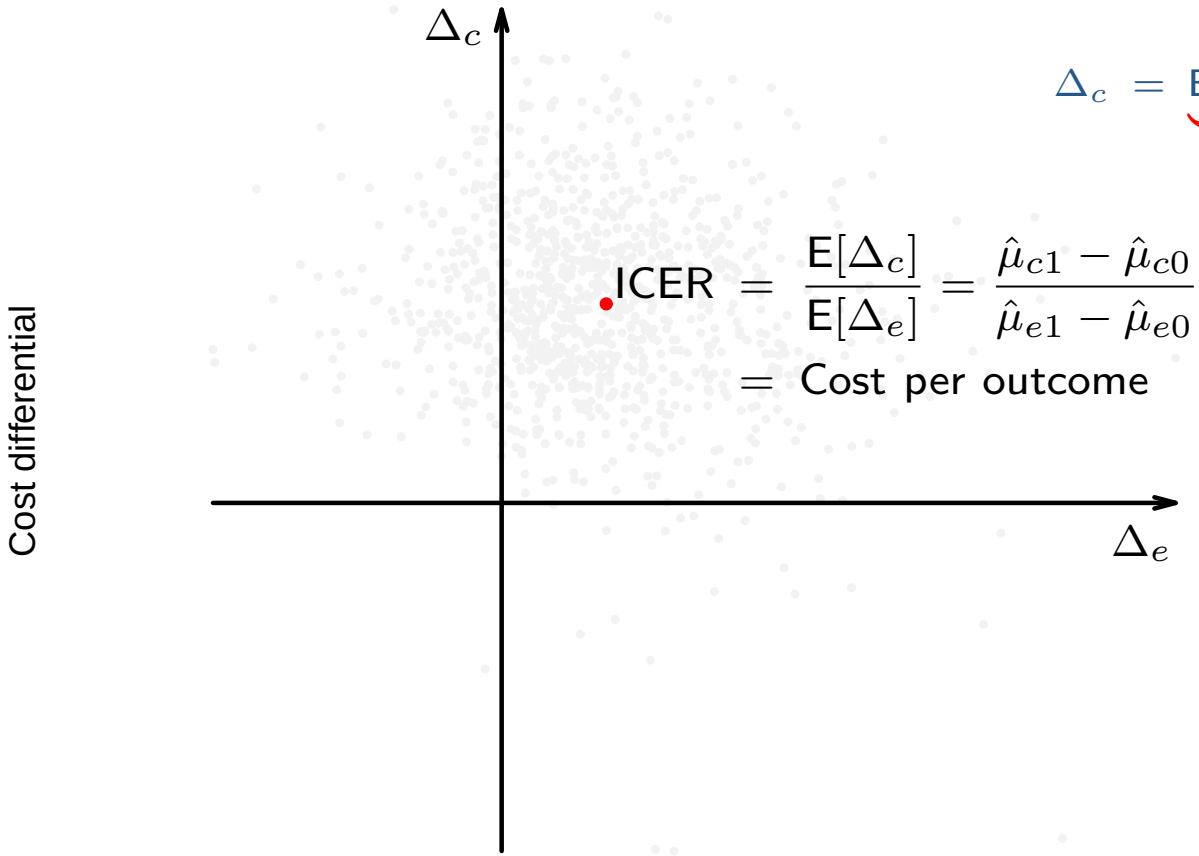

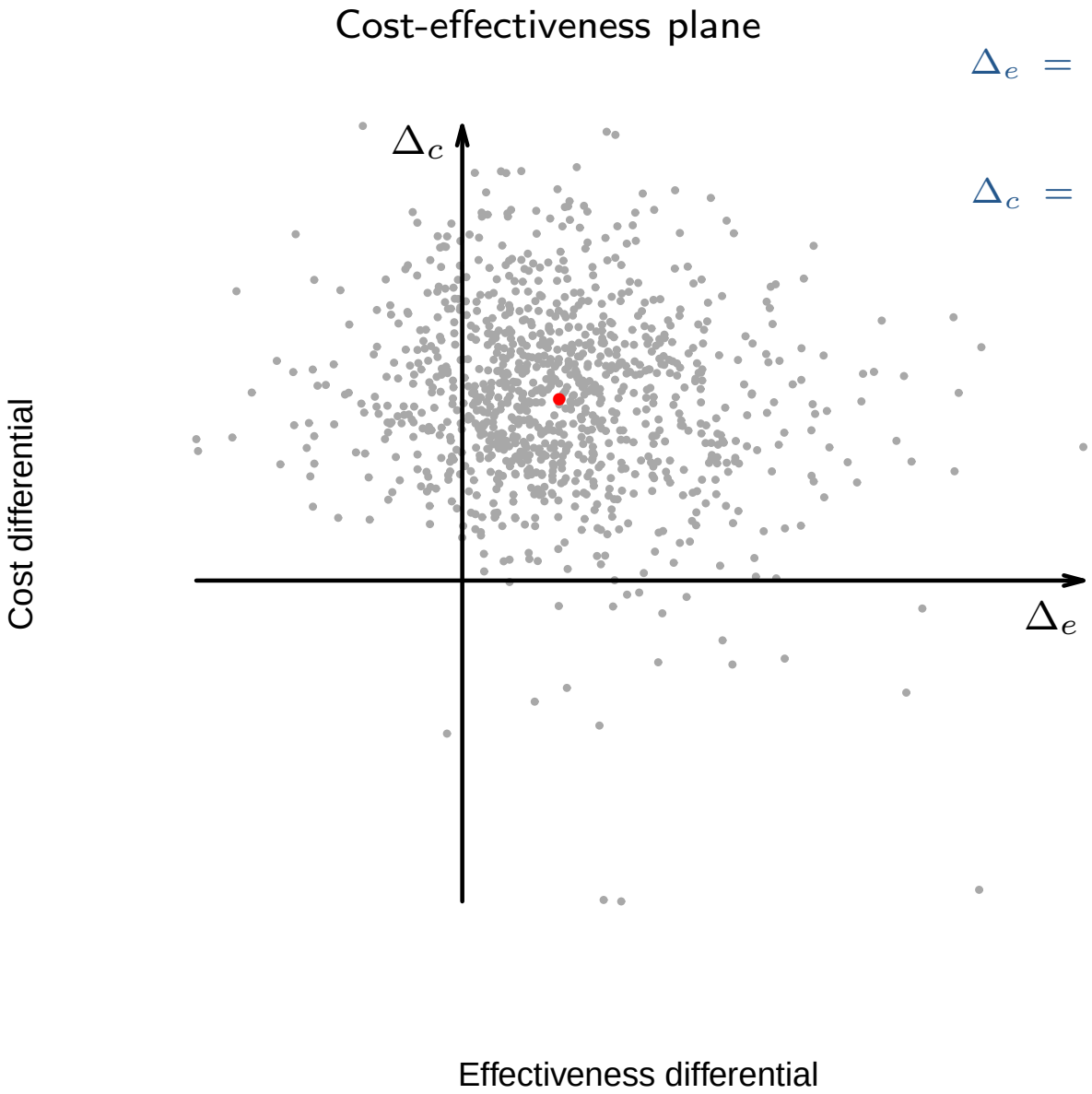

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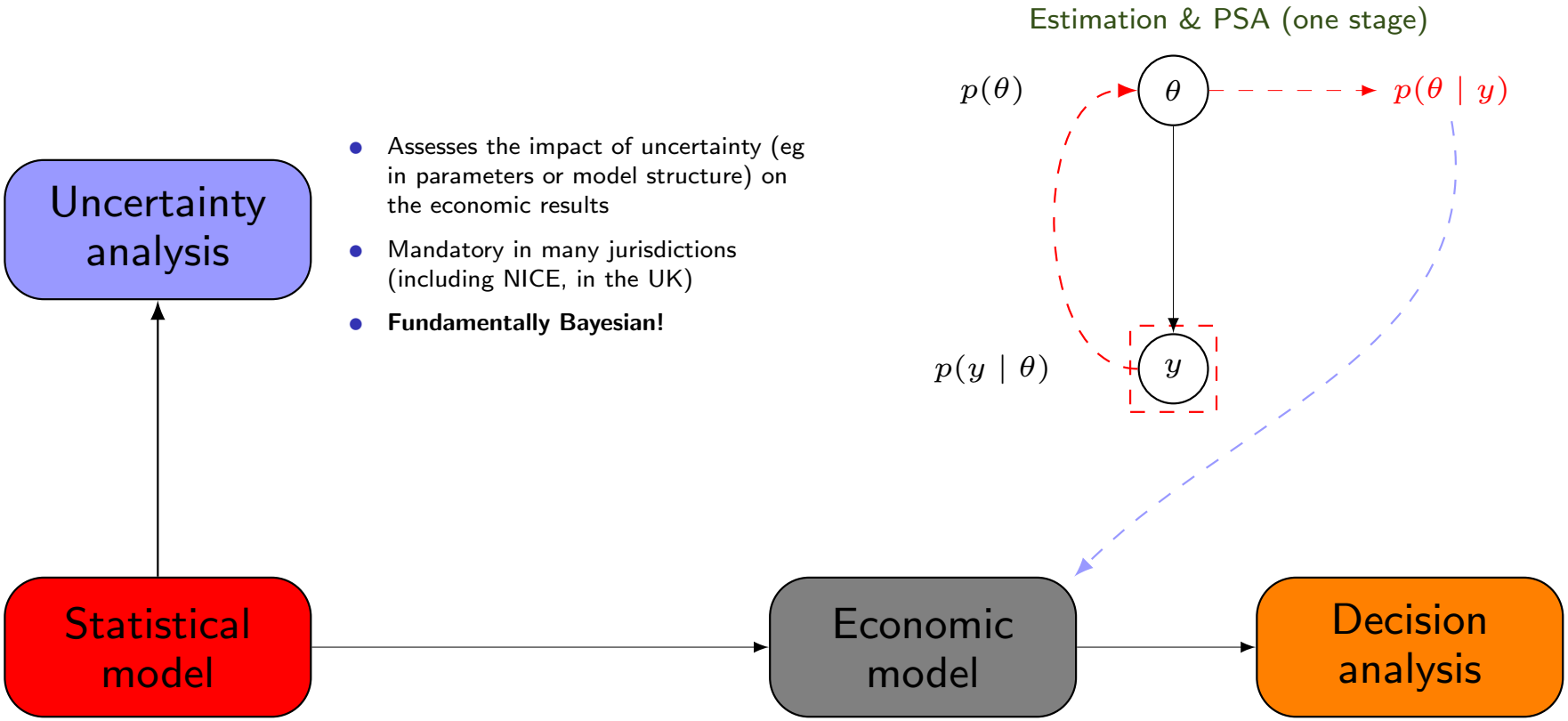
Bayesian approach to HTA



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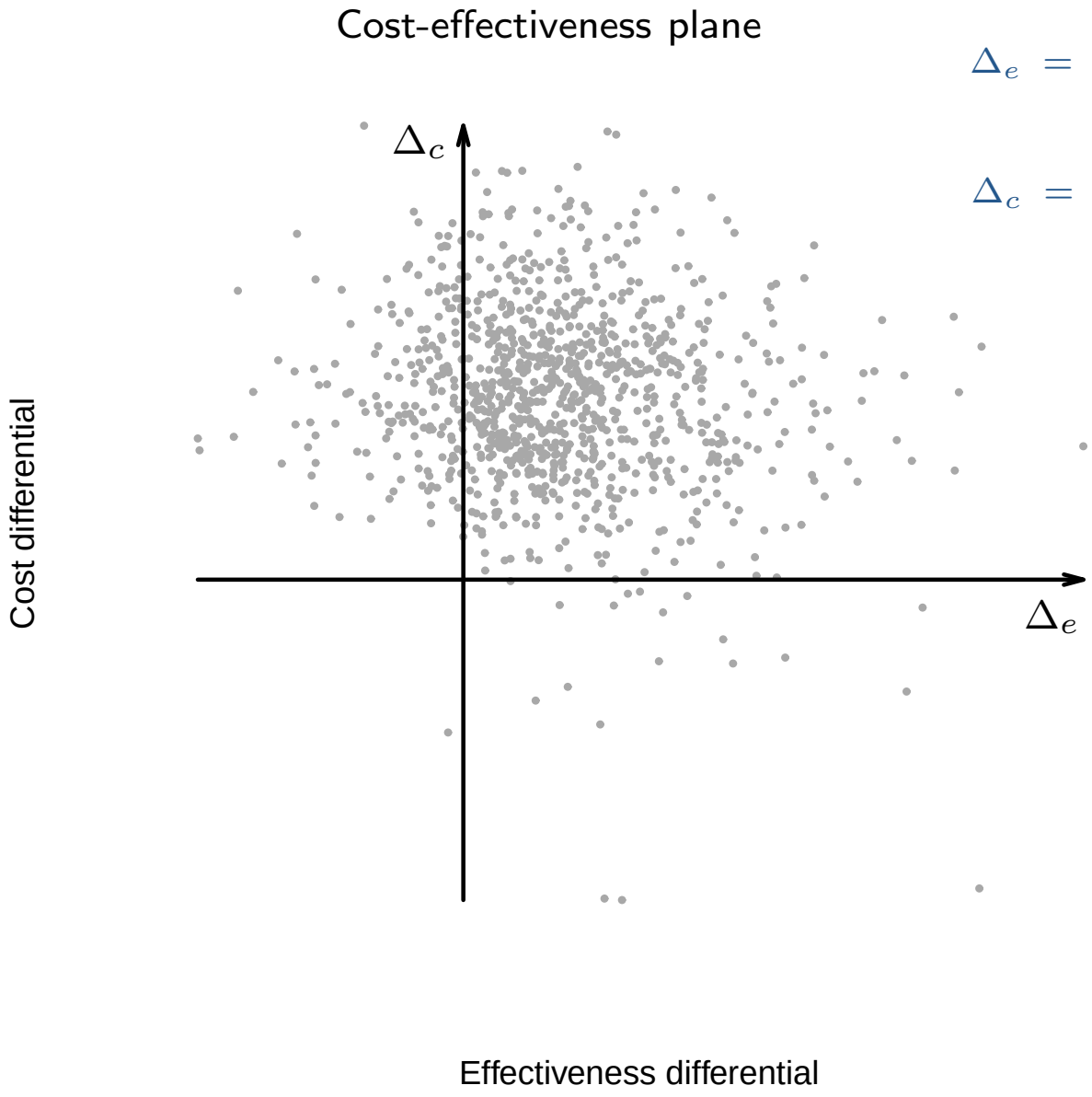
"Integrated approach" Spiegelhalter, Abrams & Myles (2004)
Baio, Berardi & Heath (2017)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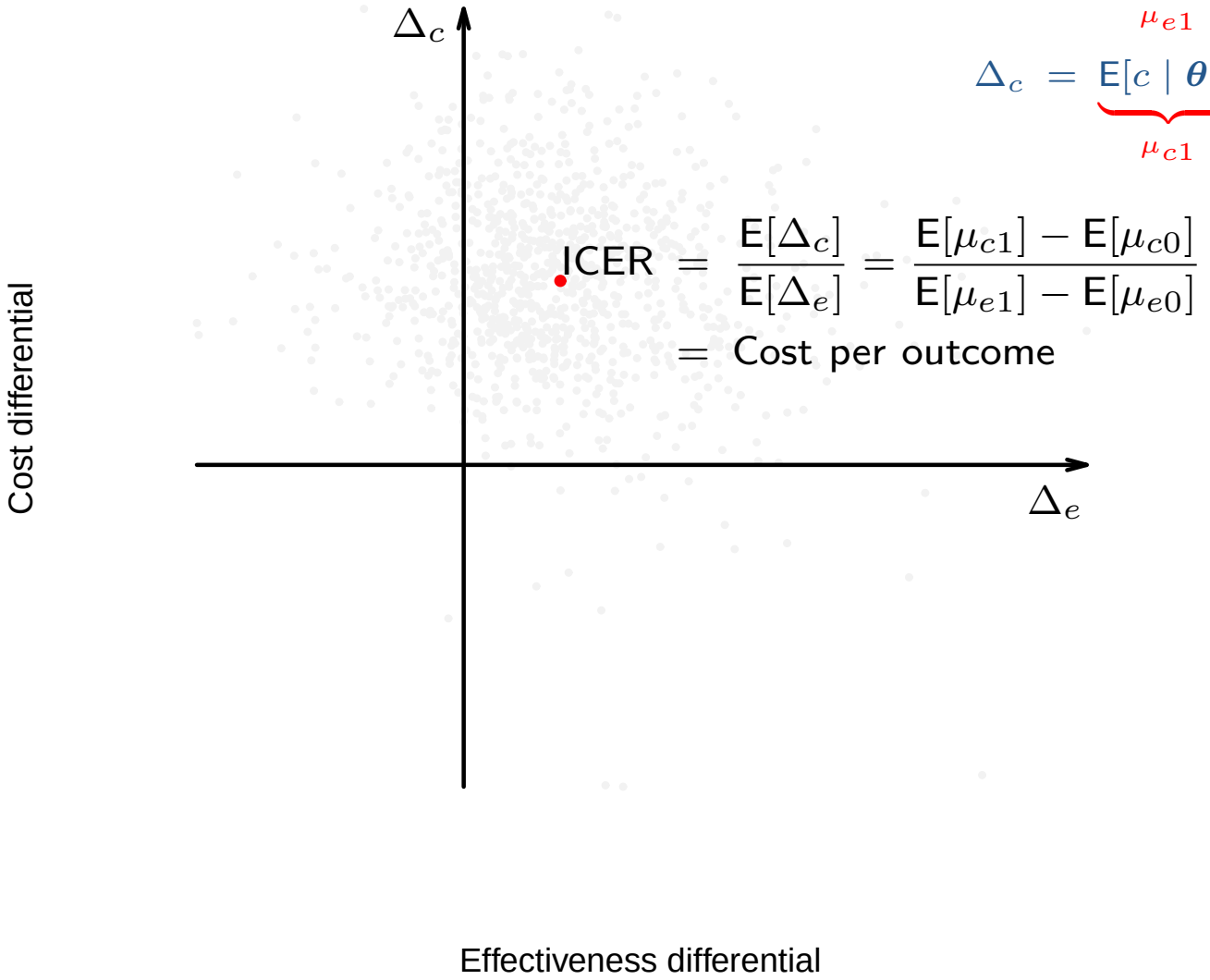

Bayesians do it better...

- Potential correlation between costs & clinical benefits [Both ILD and ALD]
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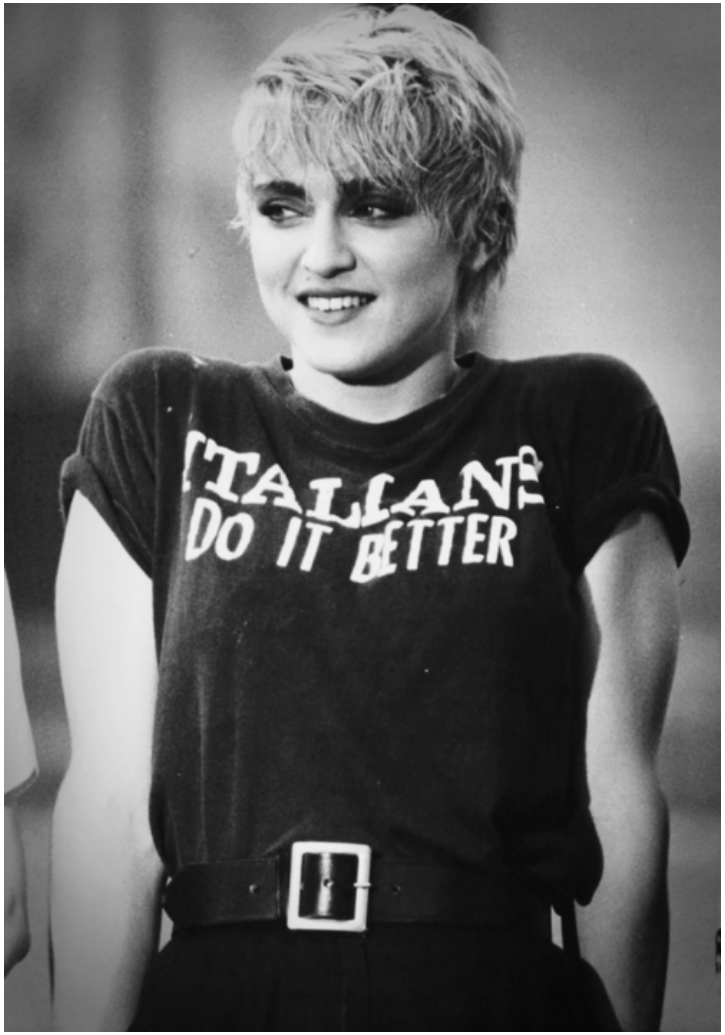
- Particularly as the focus is on decision-making (rather than just inference), we need to use **all** available evidence to fully characterise current uncertainty on the model parameters and outcomes [Mainly ALD]
  - A Bayesian approach is helpful in combining different sources of information
  - **Propagating uncertainty is a fundamentally Bayesian operation!**

Bayesians do it better...



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ILD+Missing data

Survival analysis

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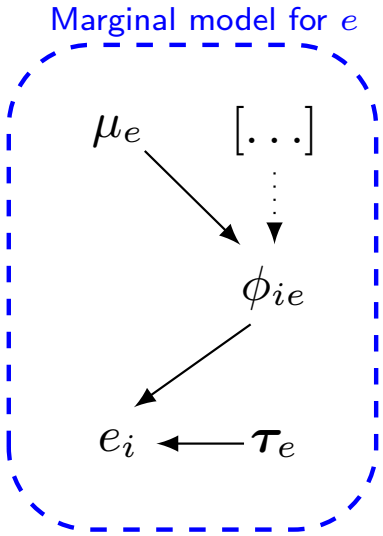

$$e_i \sim p(e \mid \phi_{ei}, \boldsymbol{\tau}_e)$$
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ϕ_{ei} = location
$\boldsymbol{\tau}_e$ = ancillary

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- In general, can represent the joint distribution as $p(e, c) = p(e)p(c \mid e) = p(c)p(e \mid c)$

$c_i \sim p(c \mid e, \phi_{ci}, \boldsymbol{\tau}_c)$

$g_c(\phi_{ci}) = \beta_0 + \beta_1(e_i - \mu_e)\,[+\ldots]$

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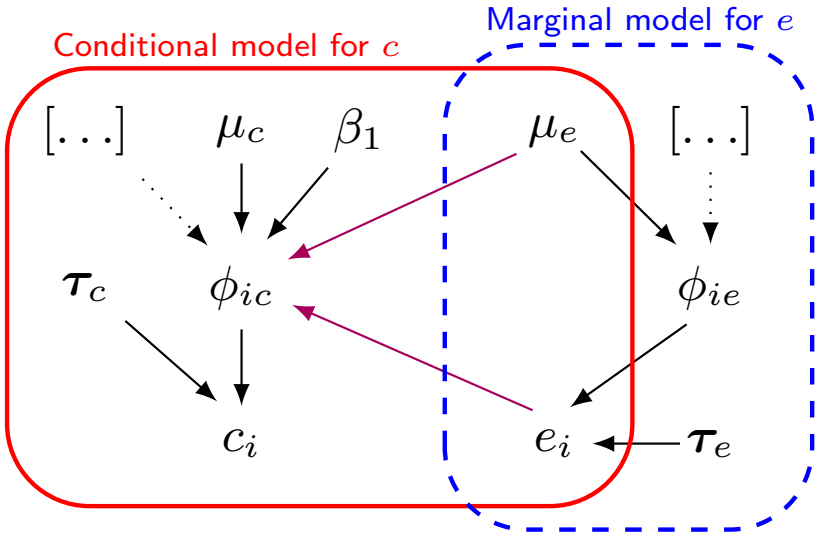

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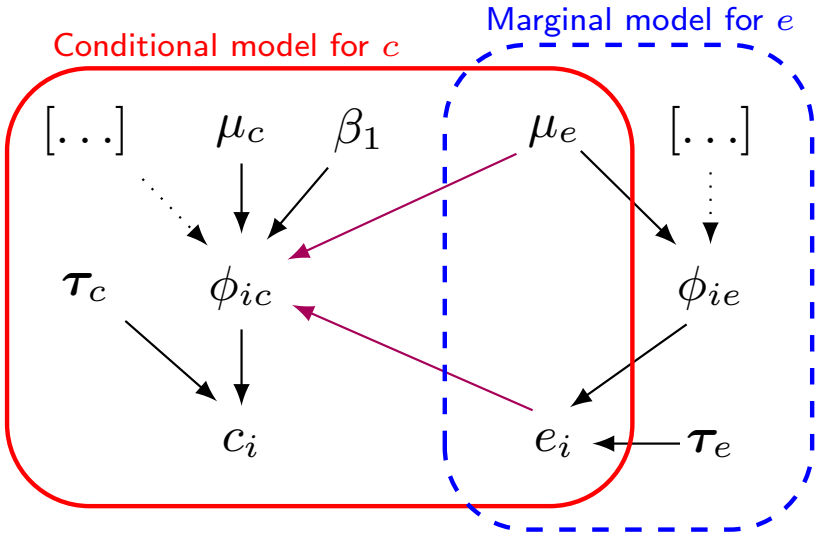

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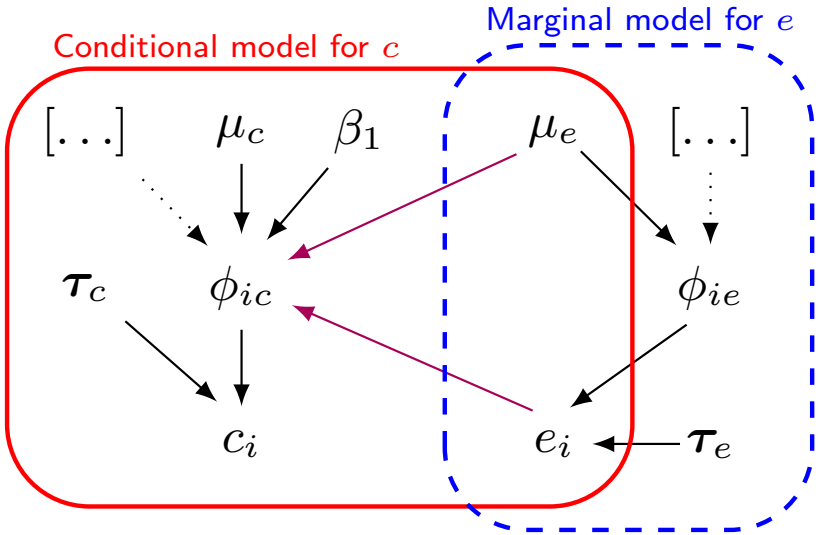

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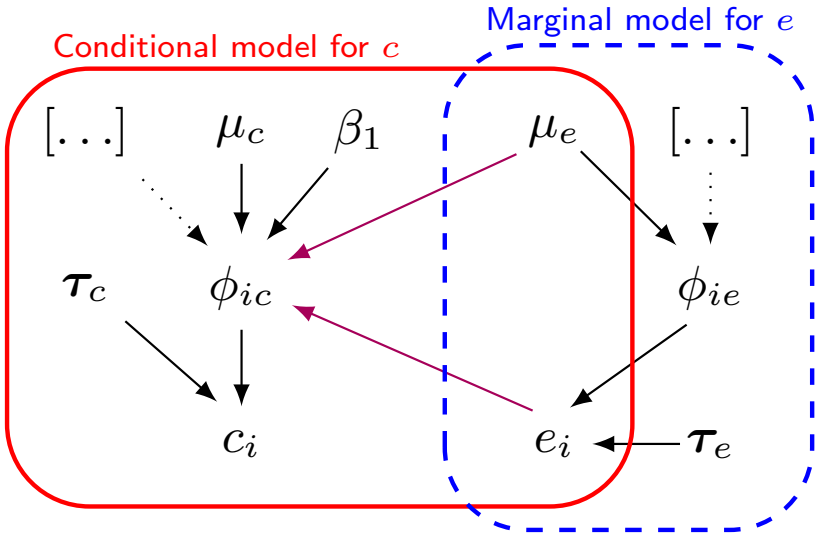

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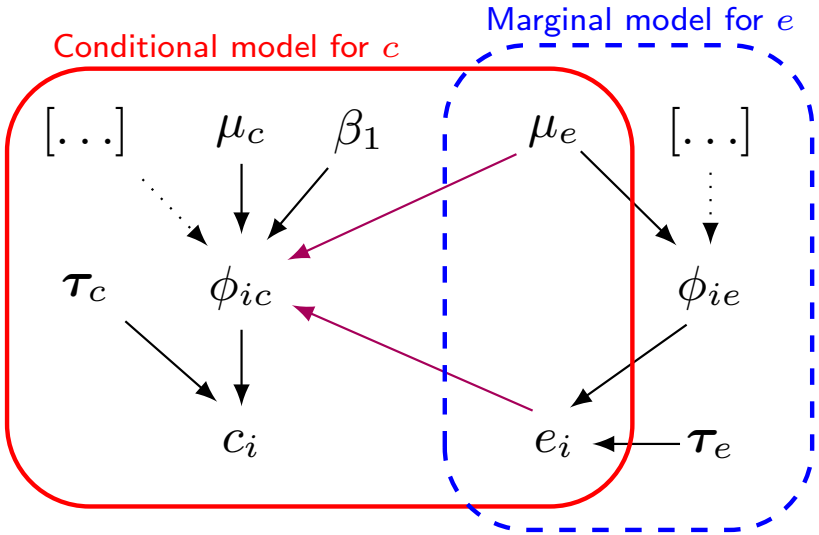

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- Combining "modules" and fully characterising uncertainty about deterministic functions of random quantities is relatively straightforward using MCMC
- Prior information can help stabilise inference (especially with sparse data!), eg
  - Cancer patients are unlikely to survive as long as the general population
  - ORs are unlikely to be greater than ± 5

Example: MenSS trial

- The MenSS pilot RCT evaluates the cost-effectiveness of a new digital intervention to reduce the incidence of STI in young men with respect to the SOC
  - QALYs calculated from utilities (EQ-5D 3L)
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Time	**Type of outcome**	**observed (%)**	**observed (%)**
		Control (n_1=75)	Intervention (n_2=84)
Baseline	utilities	72 (96%)	72 (86%)
3 months	utilities and costs	34 (45%)	23 (27%)
6 months	utilities and costs	35 (47%)	23 (27%)
12 months	utilities and costs	43 (57%)	36 (43%)
Complete cases	utilities and costs	27 (44%)	19 (23%)

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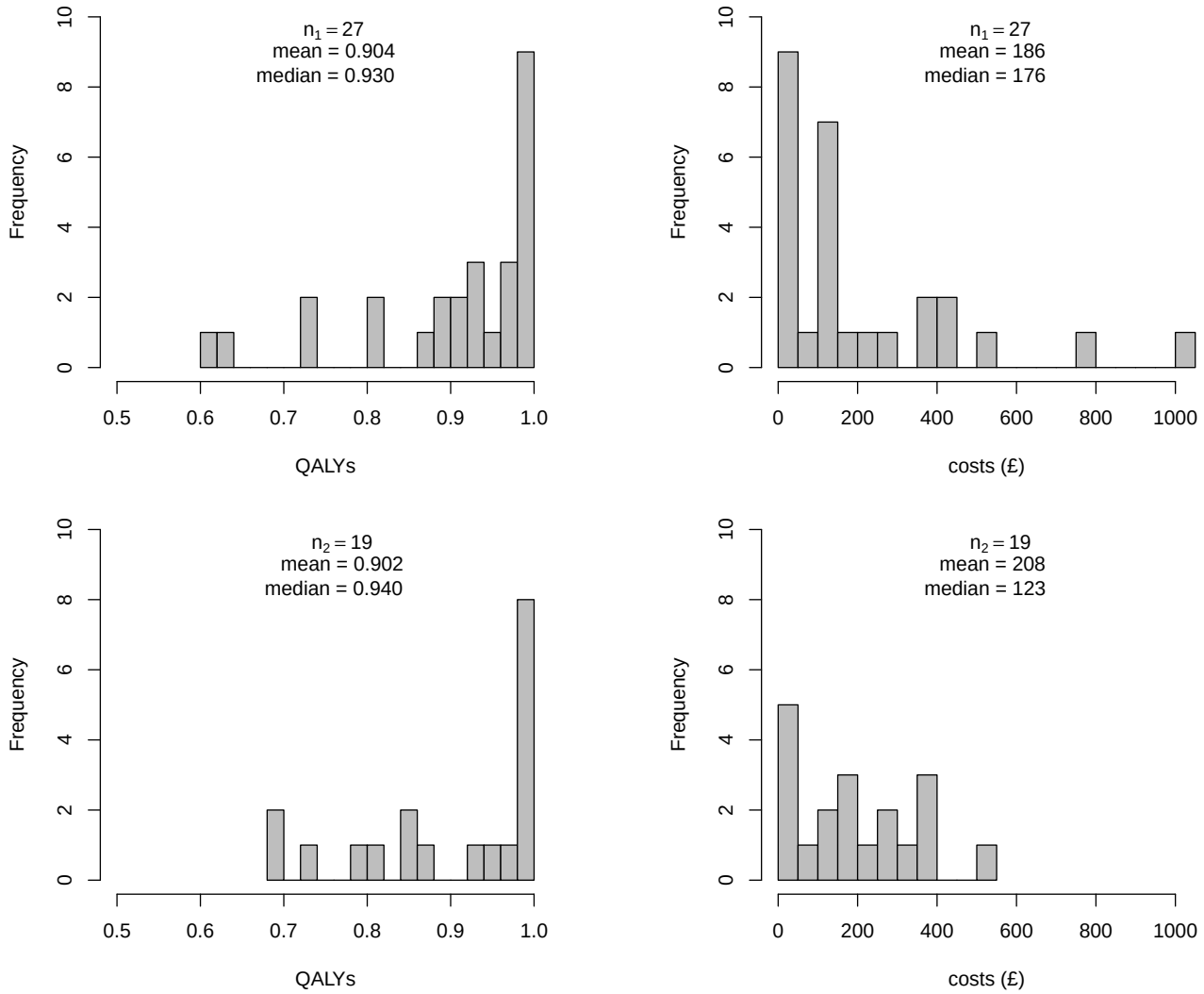

Gabrio et al. (2018). https://arxiv.org/abs/1801.09541

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   - Simpler and closer to "standard" frequentist model
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Conditional model for $c \mid e$

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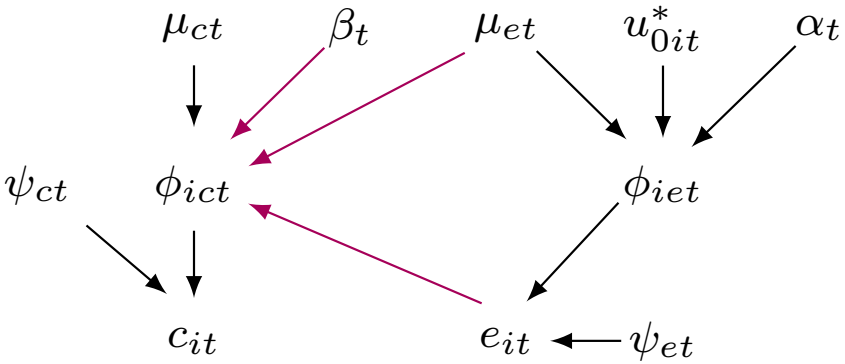

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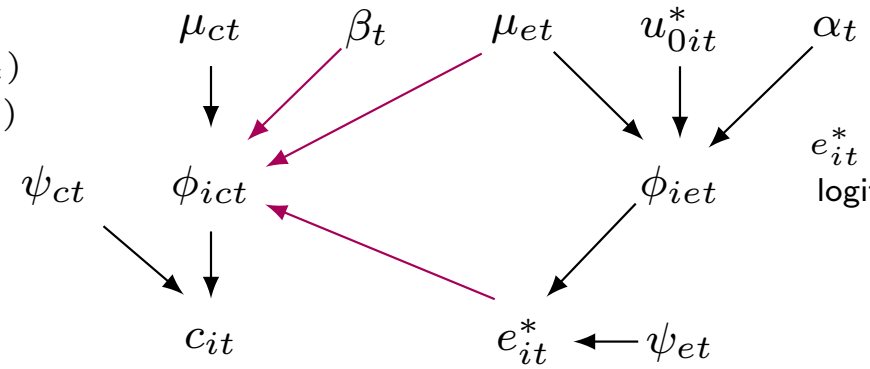

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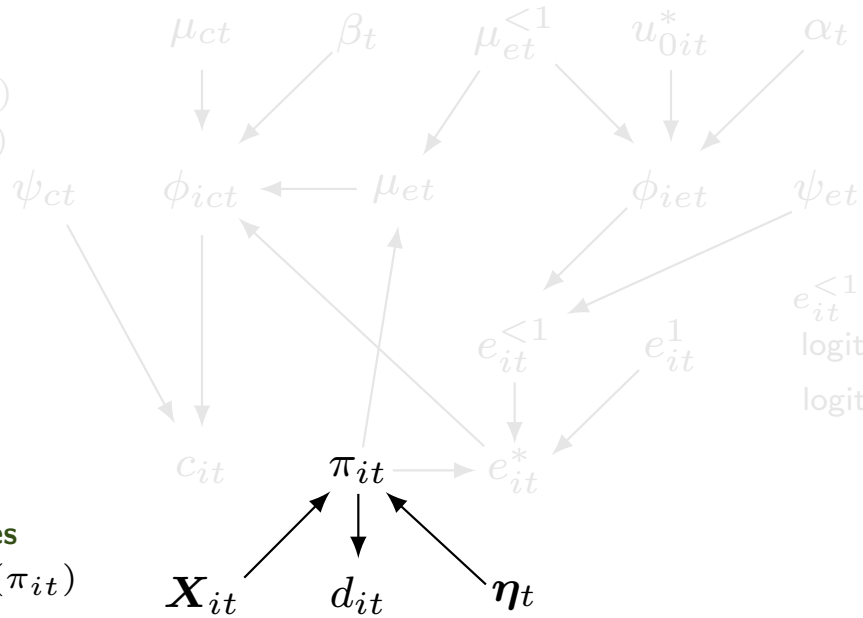

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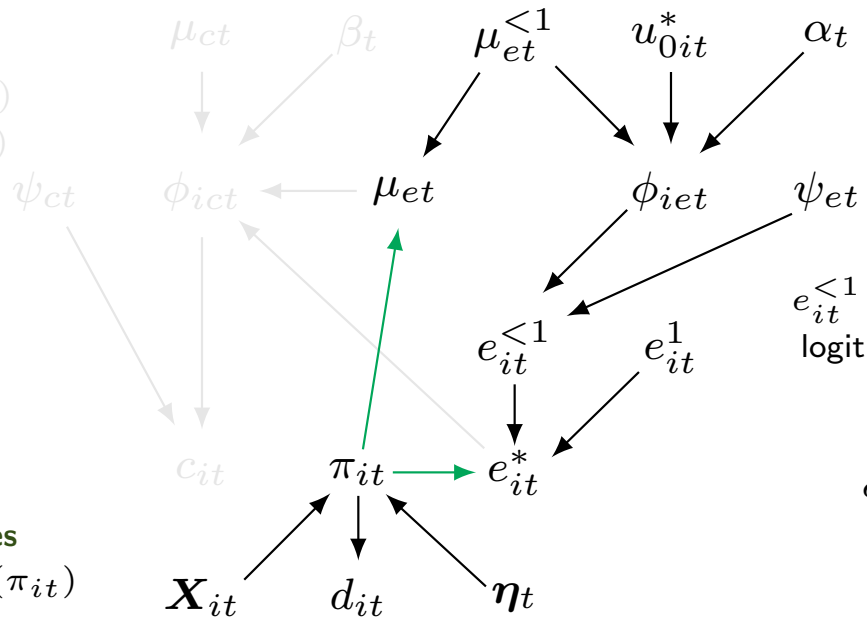

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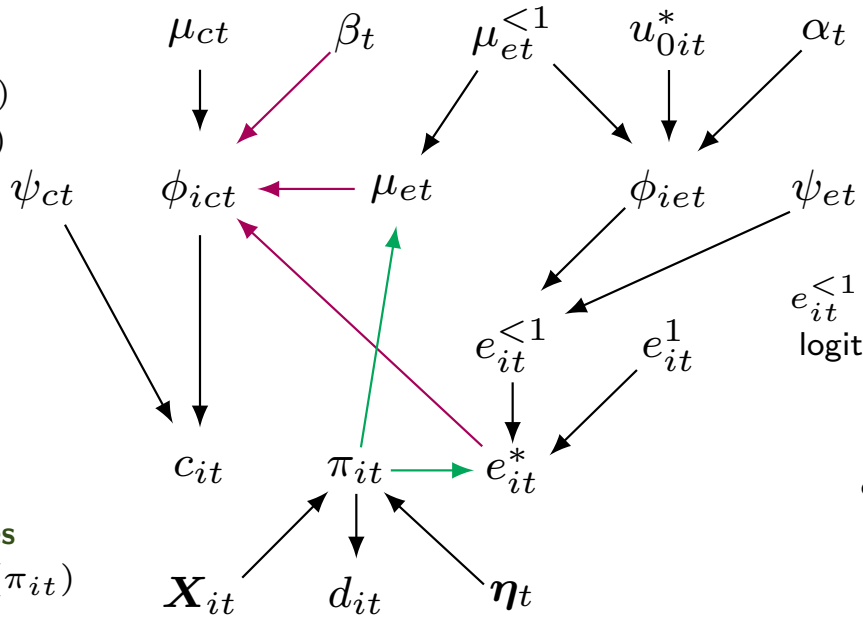

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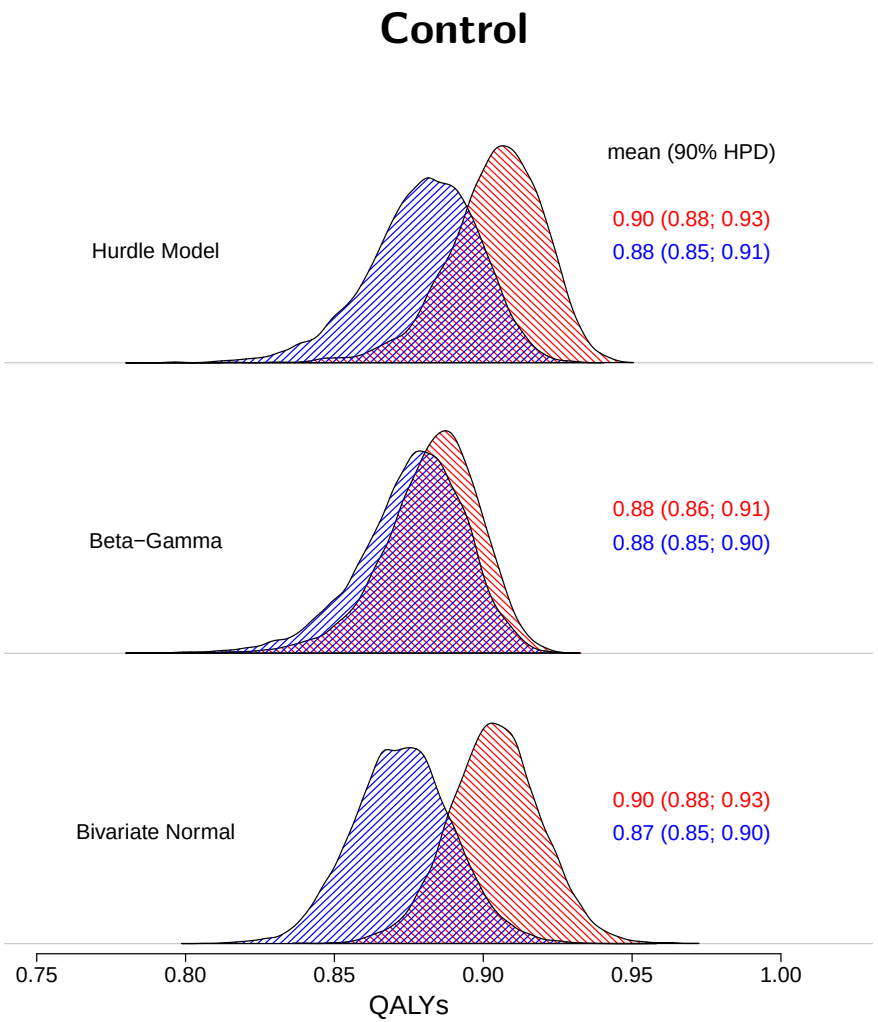
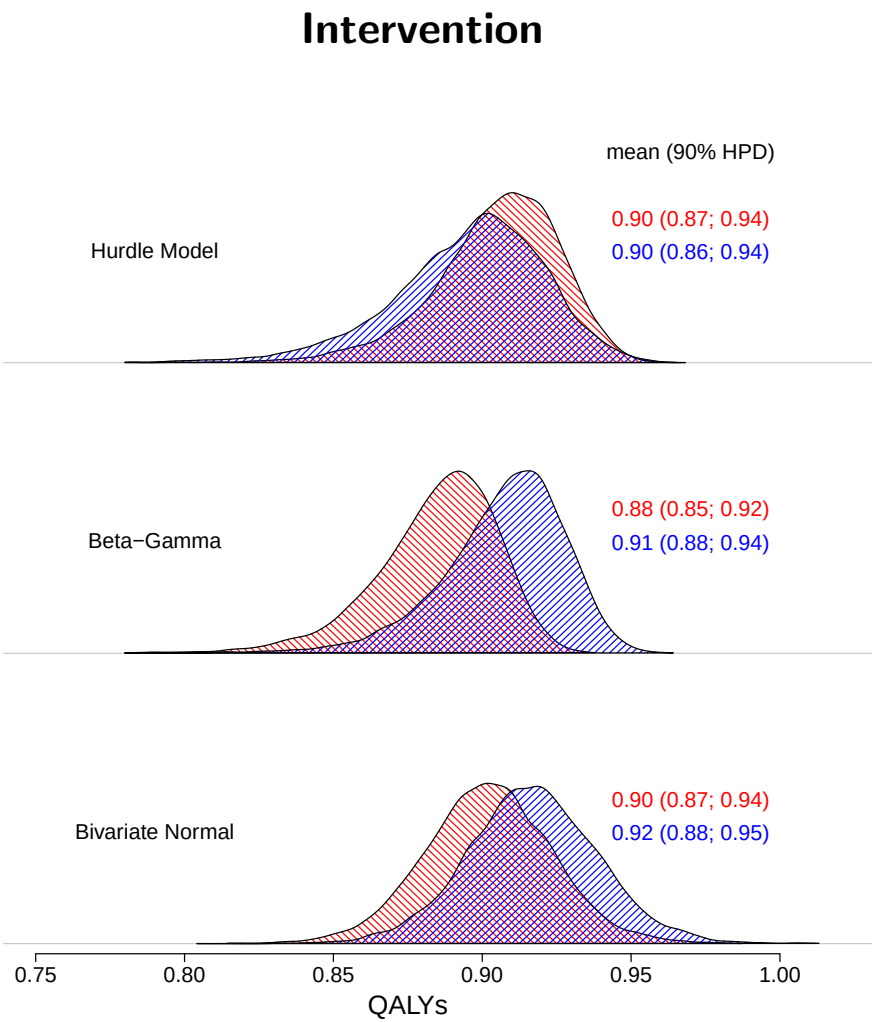
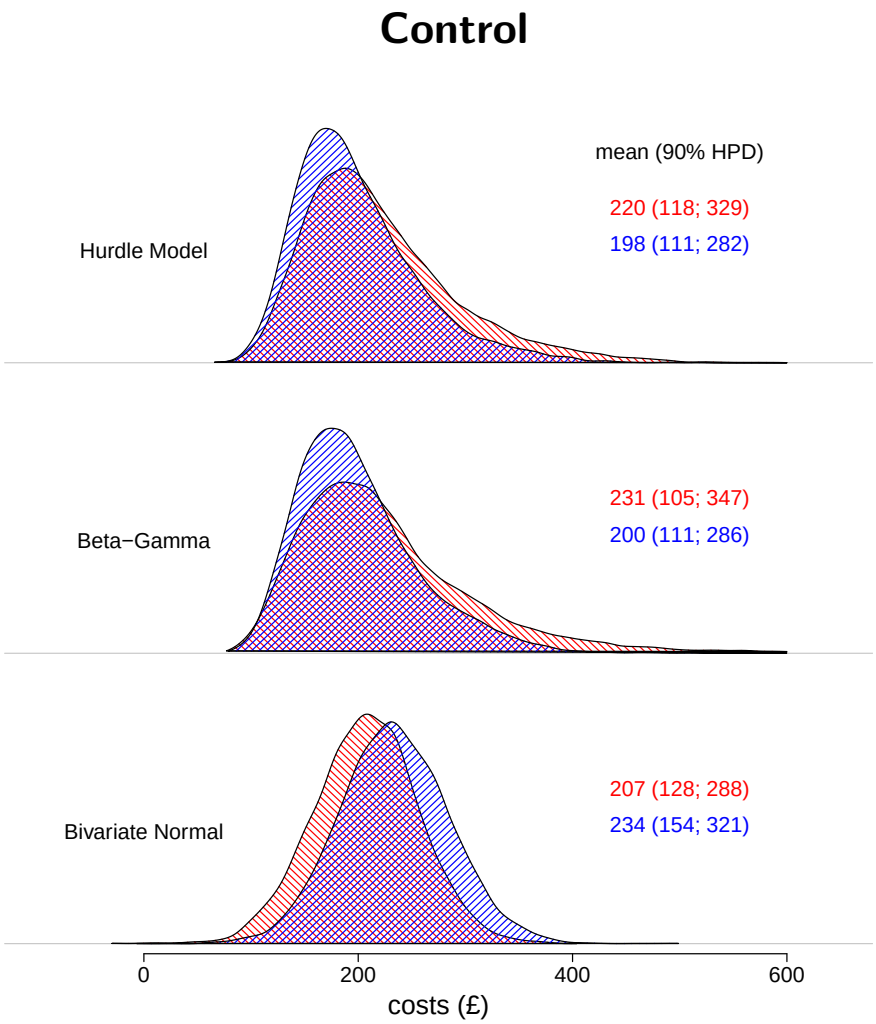
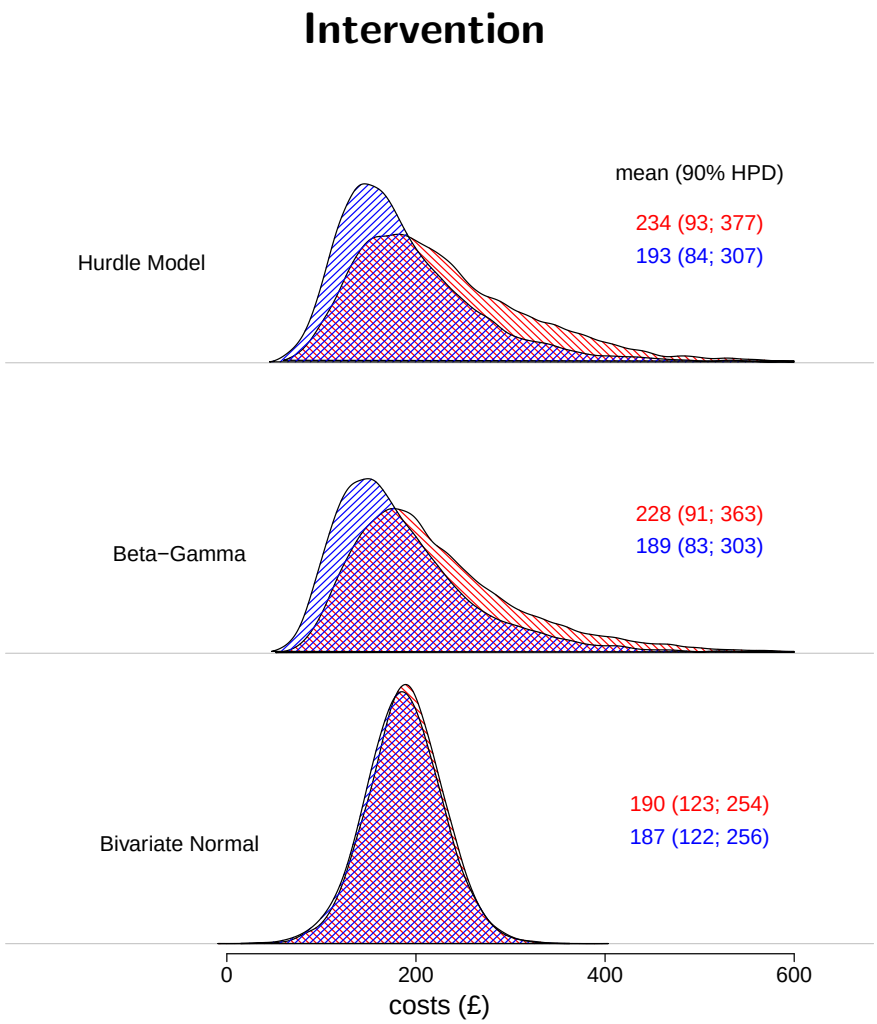




Complete cases only
All cases (missing at random, MAR)





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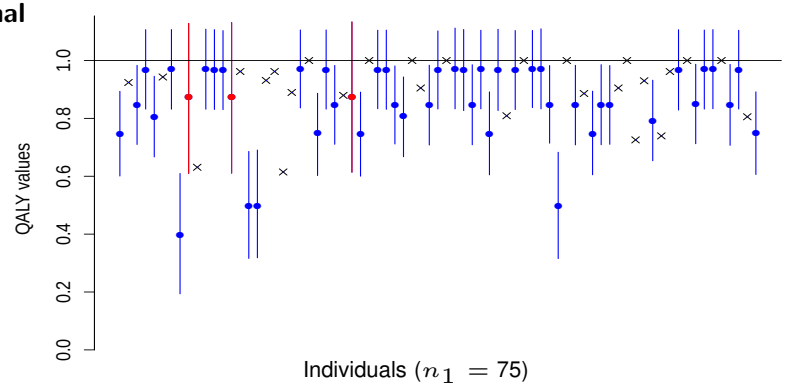
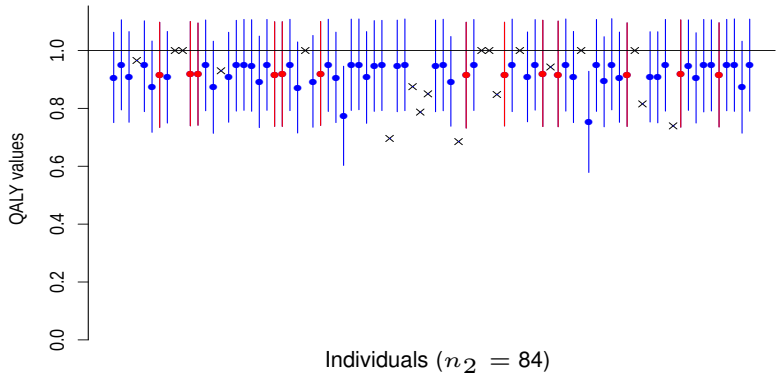
Bayesian multiple imputation (under MAR)

Bivariate Normal





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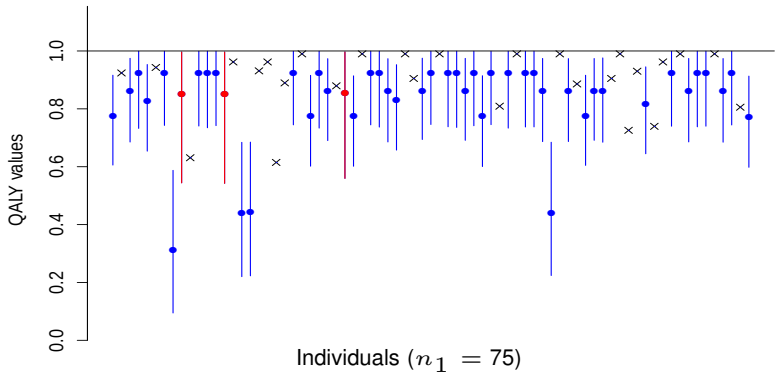
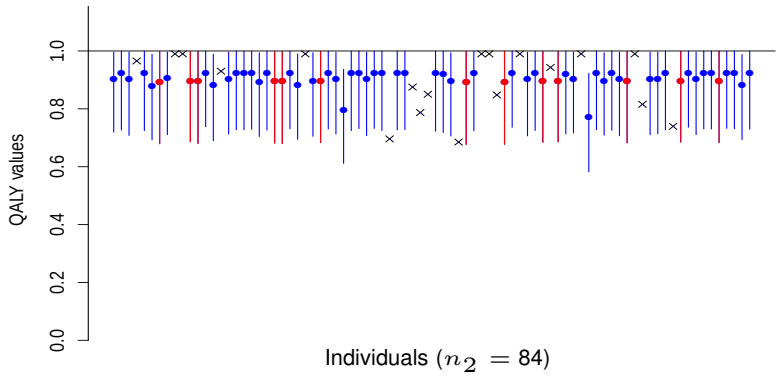
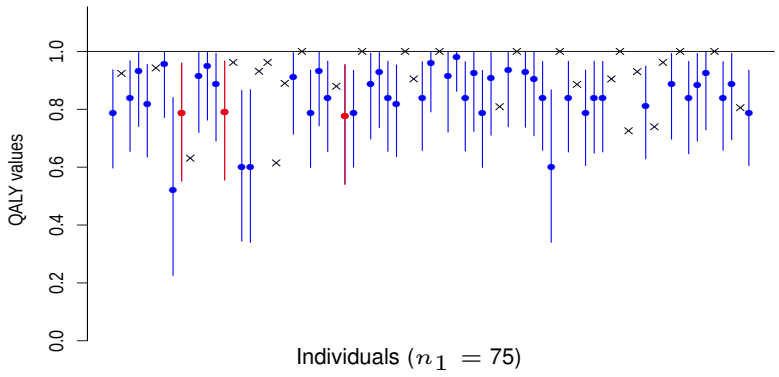
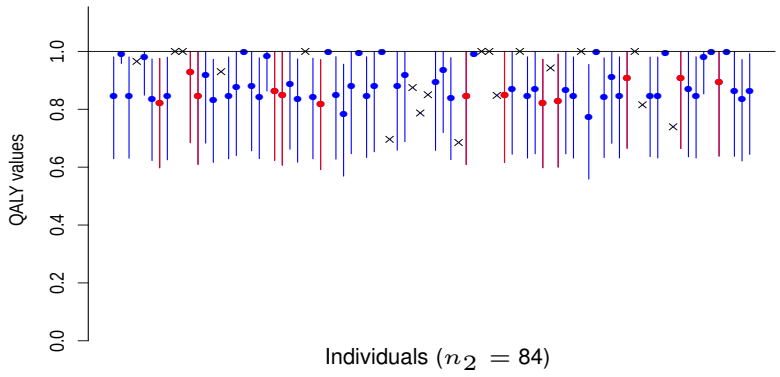




Hurdle model





Imputed, observed baseline
Imputed, missing baseline
× Observed

End

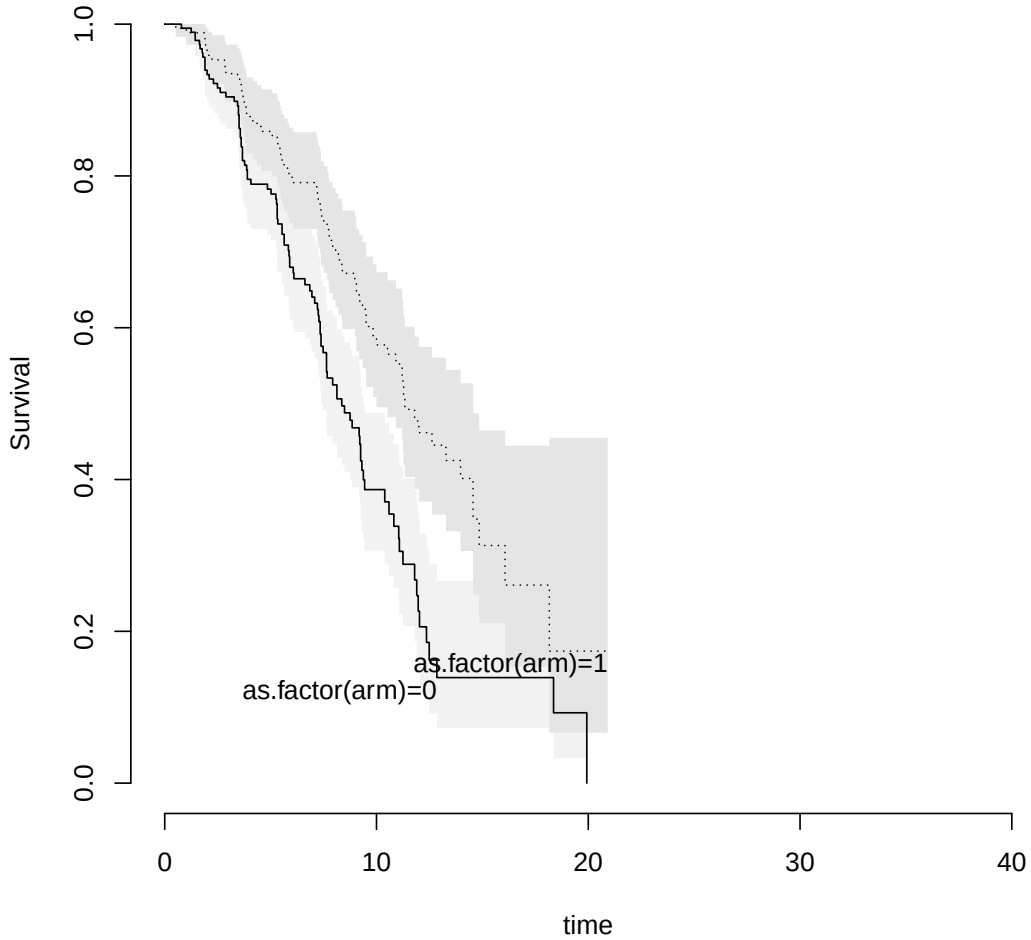
Outline

1. Health economic evaluation
   - What is it?
   - How does it work?
2. Statistical modelling
   - Individual-level vs aggregated data
   - The importance of being a Bayesian
3. **Some examples**
   - Individual level & partially observed data
   - Survival analysis in HTA
   - Value of information
4. Conclusions

Survival analysis

Value of information

- Survival data are often the main outcome in clinical studies relevant for HTA
  - Cancer drugs (progression-free/overall survival time): $\approx$ 40% of NICE appraisals!
  - Need to **extrapolate**, for economic modelling purposes. **BUT**: Limited follow up from trials, not consistent with time horizon of economic model



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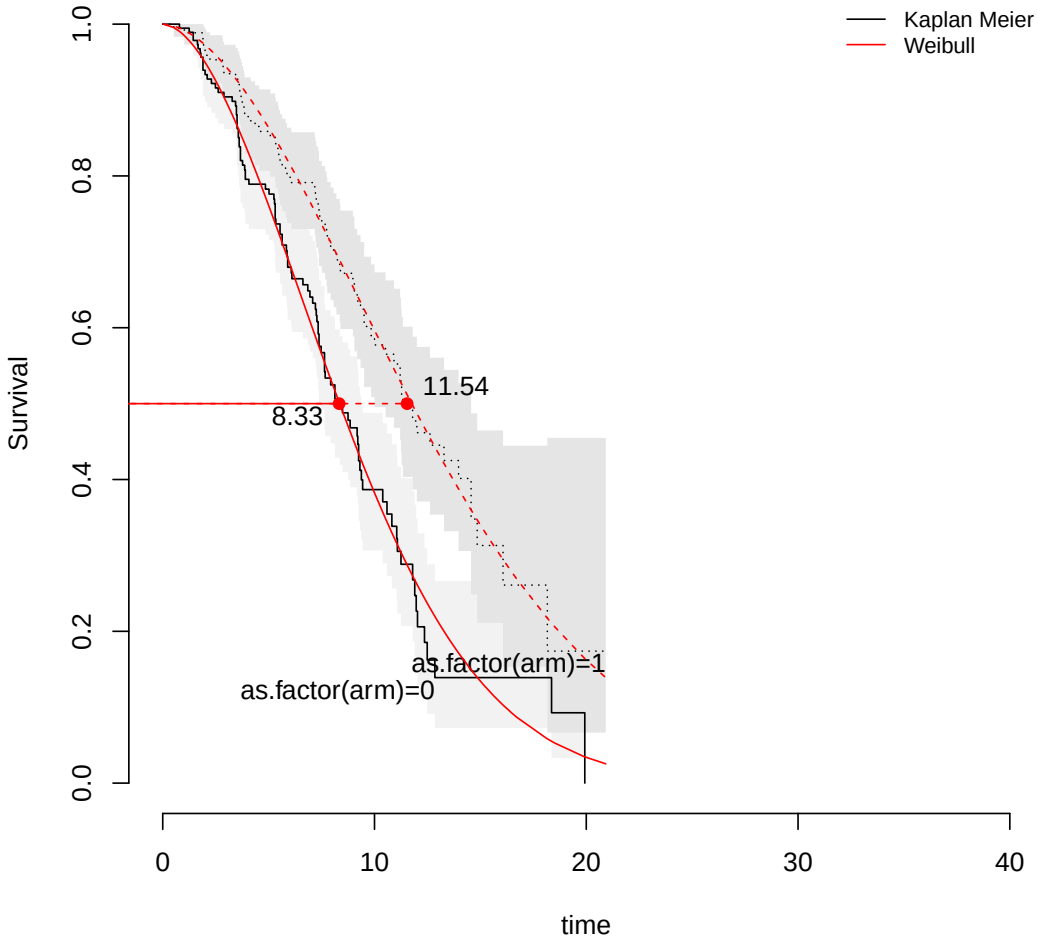

Mean time: $\int_0^\infty S(t)dt$

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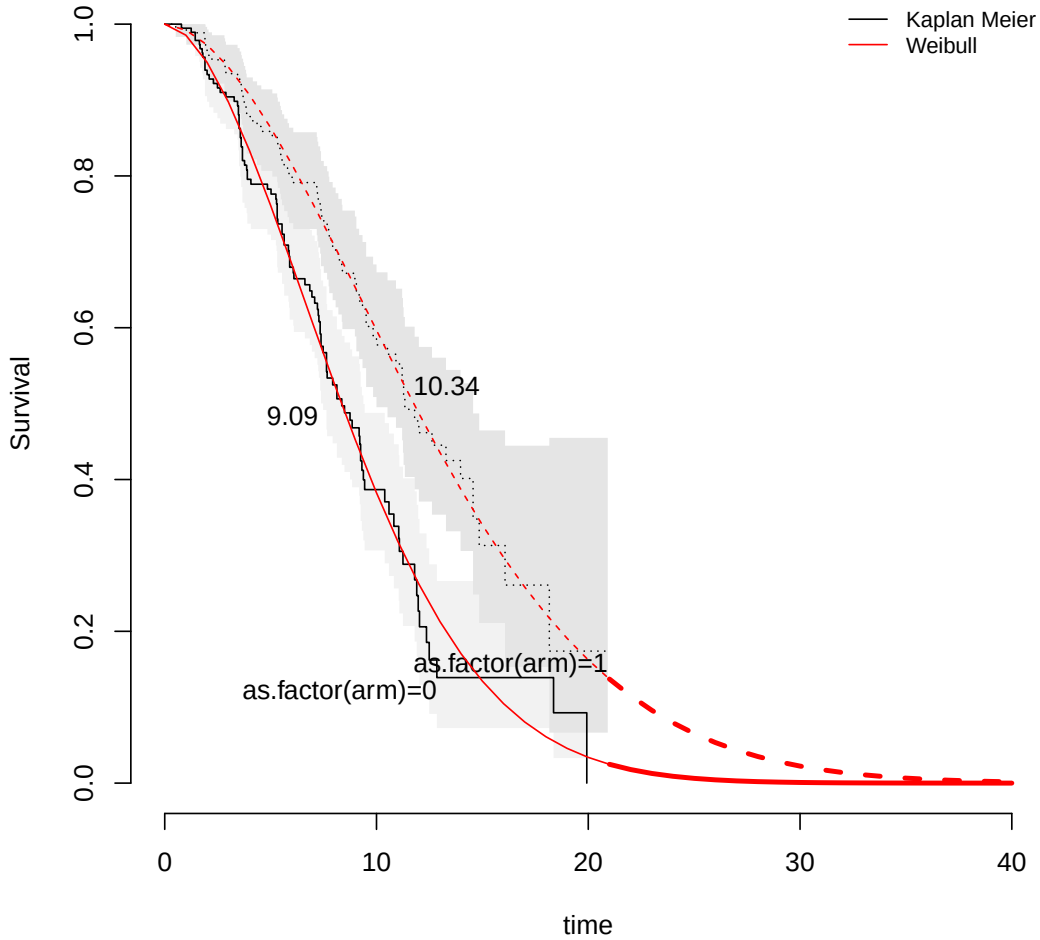

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- When there is strong correlation among the survival parameters, the results of uncertainty analysis may be (strongly) biased under a more simplistic frequentist model
  - This matters most in health economics, because this bias carries over the economic modelling, optimal decision making and assessment of the impact of parametric uncertainty!
  - **A full Bayesian approach propagates directly correlation and uncertainty in the model parameters through to the survival curves and the economic model**

- For more complex models, MLE-based estimates may fail to converge
  - This may be an issue for multi-parameter models, where limited data (not compounded by relevant prior information) are not enough to fit all the model parameters
  - **NB**: you would normally need to fit more complex models for cases where the survival curves are "strange" and so the usual parametric models fail to provide sufficient fit

- Survival data are often the main outcome in clinical studies relevant for HTA
  - Cancer drugs (progression-free/overall survival time): $\approx$ 40% of NICE appraisals!
  - Need to **extrapolate**, for economic modelling purposes. **BUT**: Limited follow up from trials, not consistent with time horizon of economic model

```
Model fit for the Generalised F model, obtained using Flexsurvreg
(Maximum Likelihood Estimate). Running time: 1.157 seconds

                       mean         se         L95%         U95%
mu                2.29139696 0.0798508 2.13489e+00 2.44790e+00
sigma             0.58729598 0.0725044 4.61076e-01 7.48069e-01
Q                 0.84874994 0.2506424 3.57500e-01 1.34000e+00
P                 0.00268265 0.0902210 6.33197e-32 1.13655e+26
as.factor(arm)1 0.34645851 0.0877892 1.74395e-01 5.18522e-01
```

```
Model fit for the Generalised F model, obtained using Stan
(Bayesian inference via Hamiltonian Monte Carlo). Running time: 26.692 seconds

                     mean         se       L95%       U95%
mu                2.256760 0.3455163 0.0897086 0.0865904
sigma             0.507861 0.0762112 0.3608566 0.6582047
Q                 0.700062 0.3358360 0.0786118 1.3880582
P                 1.131968 0.5837460 0.3908284 2.6342762
as.factor(arm)1 0.345516 0.0865904 0.1745665 0.5176818
```

Set up/interventions

- ICD (Implantable Cardioverter Defibrillators) compared to anti-arrhythmic drugs (AAD) for prevention of sudden cardiac death in people with cardiac arrhythmia

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Data

- Individual data from cohort of 535 UK cardiac arrhythmia patients implanted with ICDs between 1991 and 2002
- Meta-analysis of three (non-UK) RCTs providing published HRs
  - Relatively short-term follow-up: approximately 75% people, followed for less than 5 years, maximum 10 years
- UK population mortality statistics by age, sex, cause of death

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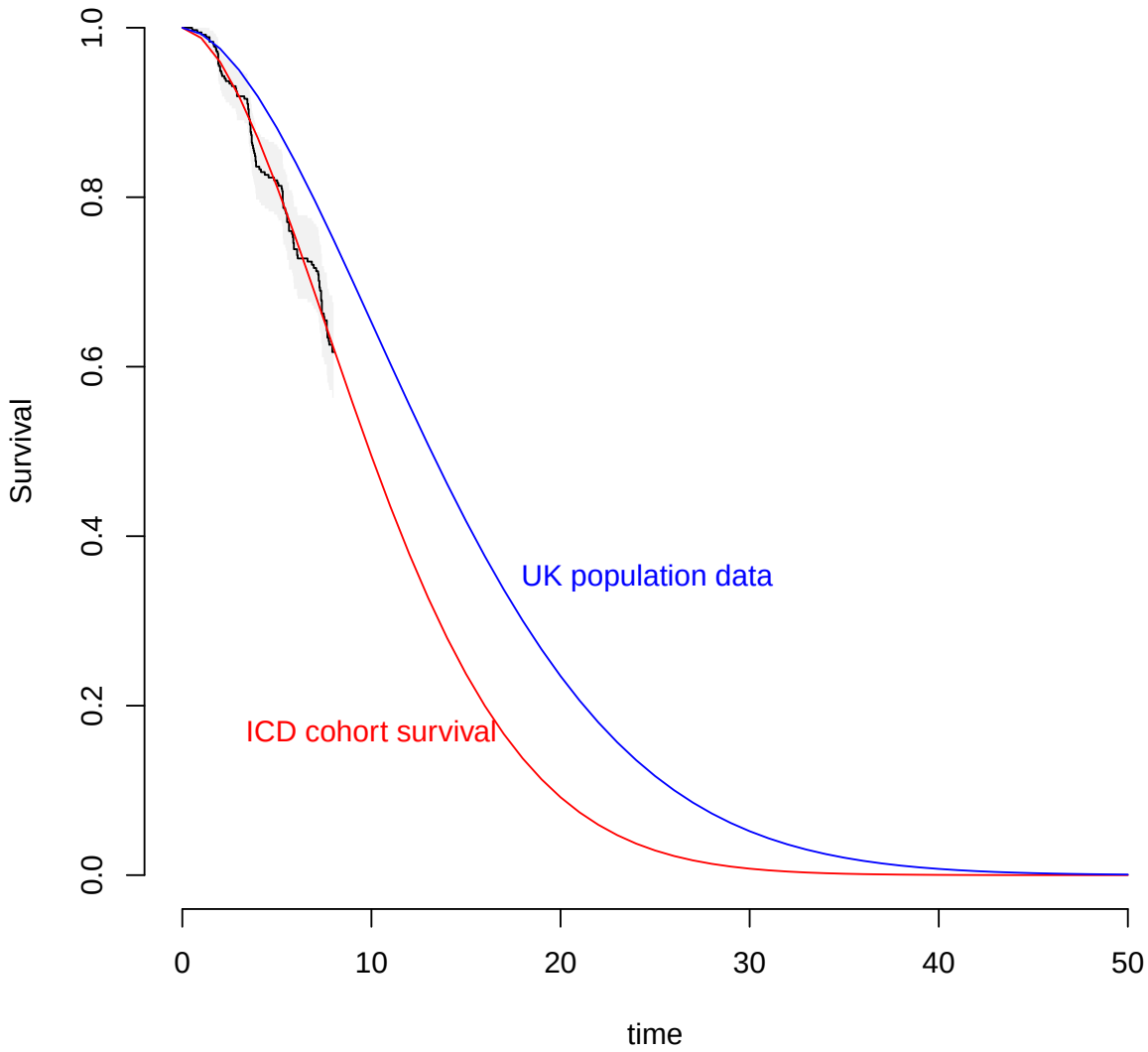
Objective

- Estimate the survival curve **over the lifetime** of ICD and AAD patients in UK
- Extrapolate the output to inform the wider economic model

Basic idea

Use UK population data (matched by age/sex) to "**anchor**" the ICD population risk



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Use UK population data (matched by age/sex) to "**anchor**" the ICD population risk

- Perhaps the easiest way of doing this anchoring is to relate the hazards between the two populations — eg **proportional hazard ratio**:

$$h_{\text{ICD}}(t) = e^{\beta} h_{\text{UK}}(t) \qquad \Leftrightarrow \qquad \text{HR} = \frac{h_{\text{ICD}}(t)}{h_{\text{UK}}(t)} = e^{\beta} = \text{Constant}$$

- Relatively easy to model — but probably very unrealistic!
  - ICD patients are at (much?) greater risk of arrhythmia death
  - If the proportion of deaths caused by arrythmia changes over time, we would induce bias, because we would be extrapolate a constant HR for all causes mortality

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- Formally account for multiple mortality causes (**Poly-Weibull** model):

$$\begin{aligned} h_{\text{ICD}}(t) &= h^{\text{arr}}_{\text{ICD}}(t) + h^{\text{oth}}_{\text{ICD}}(t) \\ &= e^{\beta} h^{\text{arr}}_{\text{UK}}(t) + h^{\text{oth}}_{\text{UK}}(t) \\ &= e^{\beta} \alpha_1 \mu_1 t^{\alpha_1 - 1} + \alpha_2 \mu_2 t^{\alpha_2 - 1} \end{aligned}$$

- This assumes that:
  - Arrhythmia hazard is **proportional** to matched UK population
  - Other causes hazard is **identical** to matched UK population

♪ You don't know what you're doing!... ♪

https://youtu.be/fOSU59DP760

- To set up a full Bayesian model including a reasonable specification of the priors can be a hard task
- Often people claim that they have "no prior information".

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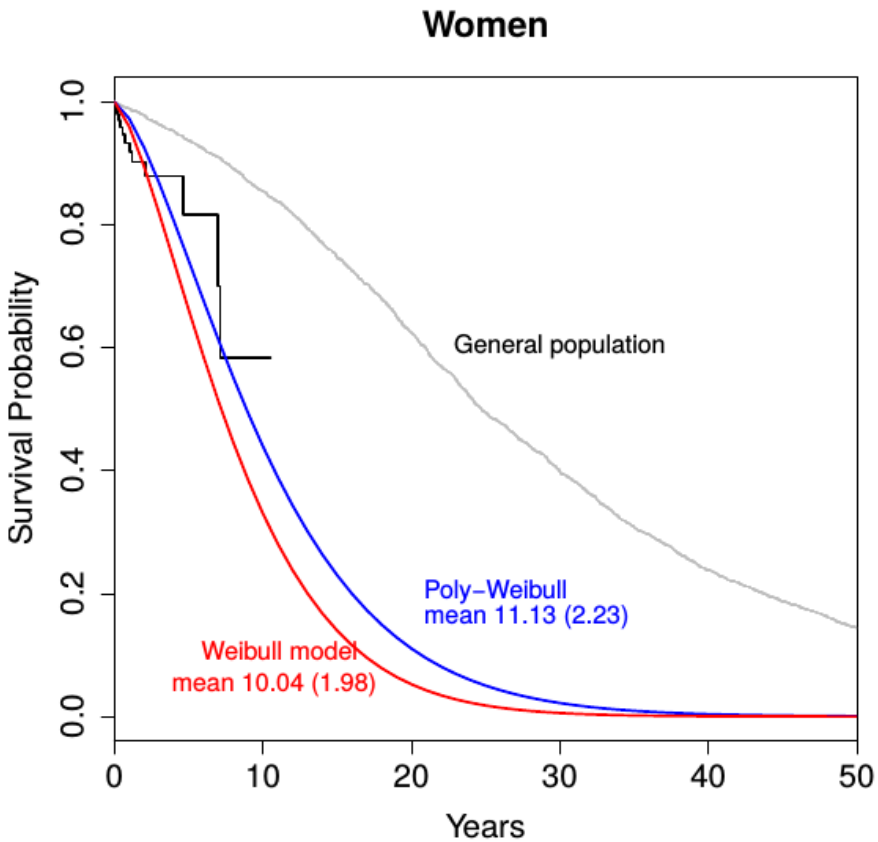
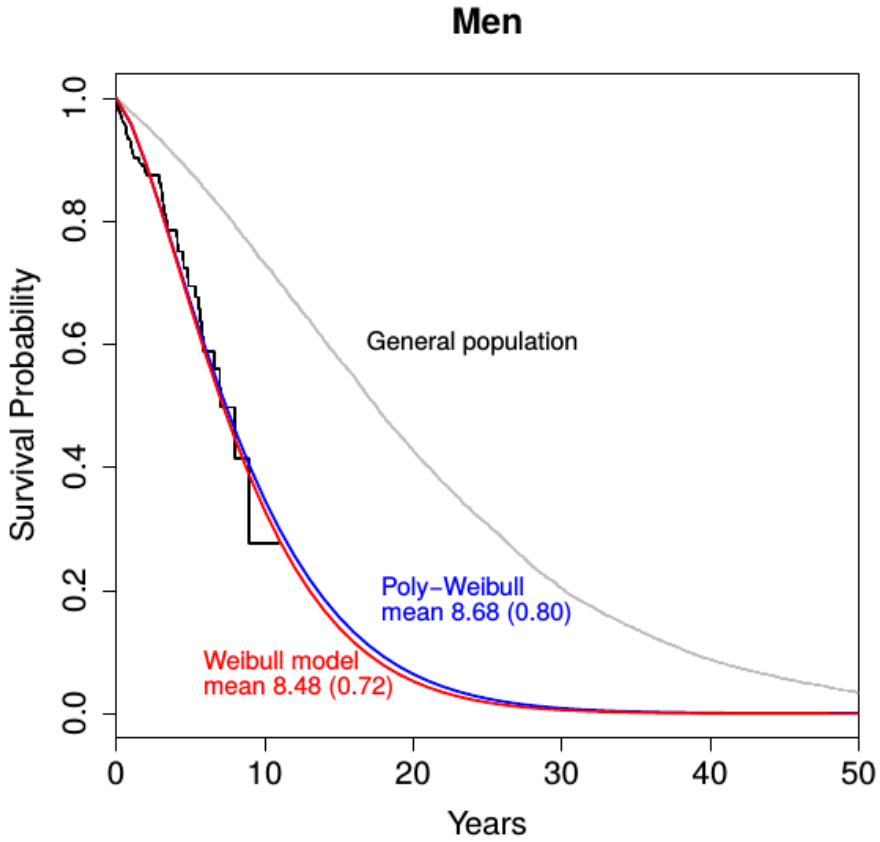
- In the ICD case, age at entry is around 60 — we **know** that people won't survive for more than other 60 years
  - Setting a prior for the scale $\mu_i \sim \text{Uniform}(0, 100)$ implies that the prior mean survival of the resulting Weibull distribution is

$$\mu_i \Gamma\left(1 + \frac{1}{\alpha}\right) < 60$$

- Can also include some knowledge on the shape α and the coefficient β to limit their variations in reasonable ranges

Results





- Ignoring cause-specific mortality (Weibull) results in larger bias, especially for females (because the arrhythmia proportion of deaths does vary over time in that subgroup)

End

Outline

1. Health economic evaluation
   - What is it?
   - How does it work?
2. Statistical modelling
   - Individual-level vs aggregated data
   - The importance of being a Bayesian
3. **Some examples**
   - Individual level & partially observed data
   - Survival analysis in HTA
   - Value of information
4. Conclusions

ILD+Missing data

Value of information

Knowledge *is* power?...

(A tale of two stupid examples)

- **Example 1**: Intervention $t = 1$ is the most cost-effective, given current evidence
  - $\Pr(t = 1 \text{ is cost-effective}) = 0.51$
  - If we get it wrong: Increase in costs = £3
    Decrease in effectiveness = 0.000001 QALYs
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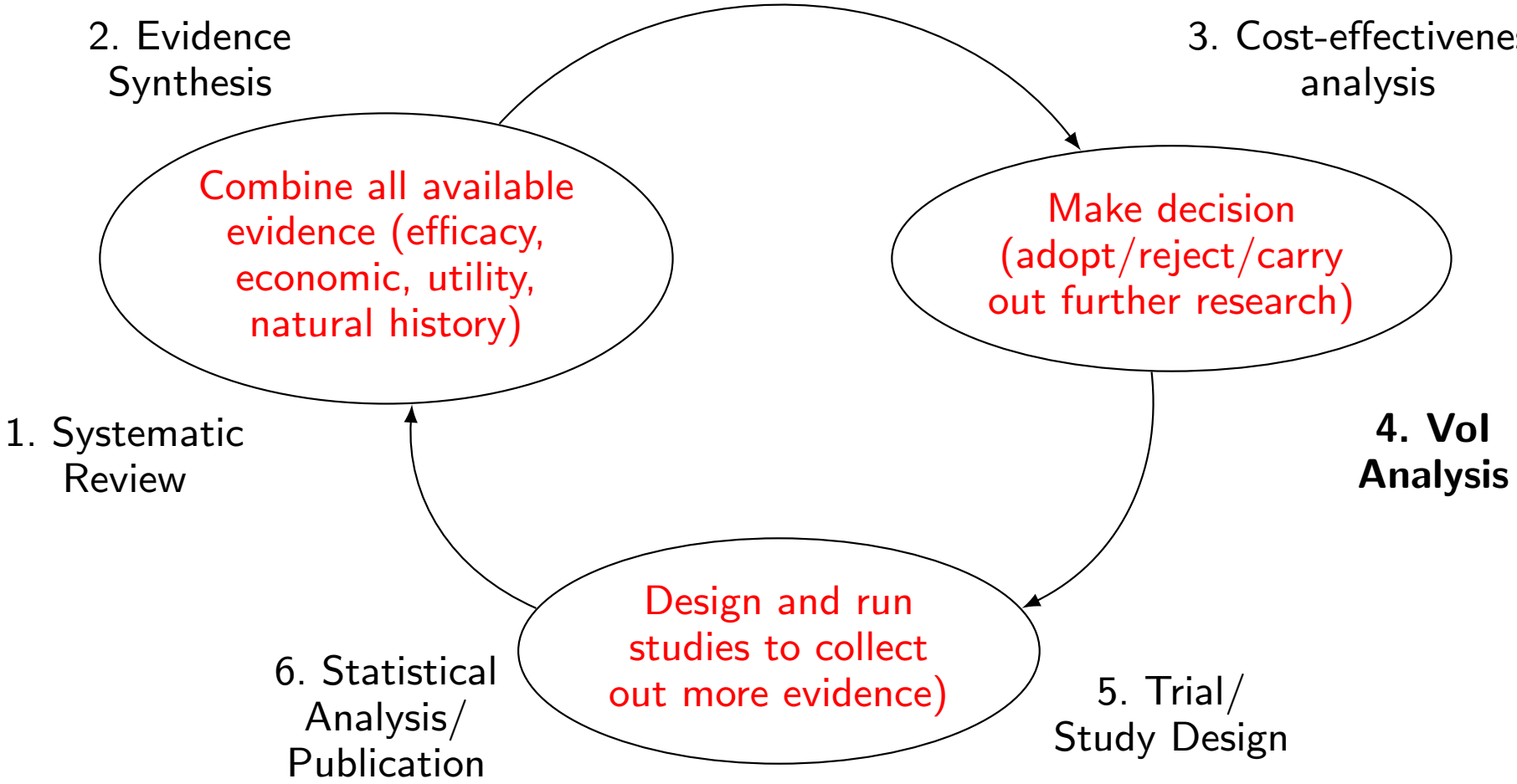
- **Example 2**: Intervention $t = 1$ is the most cost-effective, given current evidence
  - $\Pr(t = 1 \text{ is cost-effective}) = 0.999$
  - If we get it wrong: Increase in costs $=$ £1 000 000 000
    Decrease in effectiveness $= 999999$ QALYs
  - Tiny uncertainty/dire consequences $\Rightarrow$ **probably should think about it...**

Evidence Based Decision-Making and Value of Information (VoI)



Process inherently Bayesian!

VoI: Basic idea

- A new study will provide new data
  - Reducing (or even eliminating) uncertainty in a subset of model parameters
- Update the cost-effectiveness model
  - If the optimal decision changes, gain in monetary net benefit (NB = utility) from using new optimal treatment
  - If optimal decision unchanged, no gain in NB
- **Expected** VOI is the average gain in NB

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1. **Expected Value of Perfect Information** (EVPI)
   - Value of completely resolving uncertainty in all input parameters to decision model
   - Infinite-sized long-term follow-up trial measuring everything!
   - Gives an upper-bound on the value of new study — if EVPI is low, suggests we can make our decision based on existing information

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3. **Expected Value of Sample Information** (EVSI)
   - Value of reducing uncertainty by conducting a study of given design
   - Can compare the benefits and costs of a study with given design
   - Is the proposed study likely to be a good use of resources? What is the optimal design?

Parameters simulations

Iter/n	π_0	ρ	...	γ
1	0.365	0.076	...	0.162
2	0.421	0.024	...	0.134
3	0.125	0.017	...	0.149
4	0.117	0.073	...	0.120
5	0.481	0.008	...	0.191
6	0.163	0.127	...	0.004
...		...		
1000	0.354	0.067	...	0.117

- Characterise uncertainty in the model parameters
  - In a full Bayesian setting, these are draws from the joint posterior distribution of $\boldsymbol{\theta}$
  - In a frequentist setting, these are typically Monte Carlo draws from a set of univariate distributions that describe some level of uncertainty around MLEs (two-step/hybrid)

	Parameters simulations				Expected utility	
Iter/n	π_0	ρ	...	γ	$\text{NB}_0(\boldsymbol{\theta})$	$\text{NB}_1(\boldsymbol{\theta})$
1	0.365	0.076	...	0.162	19 214 751	*19 647 706*
2	0.421	0.024	...	0.134	*17 165 526*	17 163 407
3	0.125	0.017	...	0.149	18 710 928	16 458 433
4	0.117	0.073	...	0.120	16 991 321	*18 497 648*
5	0.481	0.008	...	0.191	*19 772 898*	18 662 329
6	0.163	0.127	...	0.004	17 106 136	*18 983 331*
...		...				...
1000	0.354	0.067	...	0.117	*18 043 921*	16 470 805
				Average	18 659 238	*19 515 004*

- Uncertainty in the parameters induces a distribution of decisions
  - Typically based on the **net benefits**: $\text{NB}_t(\boldsymbol{\theta}) = k\mu_{et} - \mu_{ct}$
  - In each parameters configuration can identify the *optimal strategy*
- Averaging over the uncertainty in $\boldsymbol{\theta}$ provides t^*, the overall optimal decision *given current uncertainty* (= choose the intervention associated with ***highest* expected utility**)

	Parameters simulations				Expected utility		Maximum	Opportunity
Iter/n	π_0	ρ	...	γ	$\text{NB}_0(\boldsymbol{\theta})$	$\text{NB}_1(\boldsymbol{\theta})$	net benefit	loss
1	0.365	0.076	...	0.162	19 214 751	*19 647 706*	19 647 706	0
2	0.421	0.024	...	0.134	*17 165 526*	17 163 407	17 165 526	2 119.3
3	0.125	0.017	...	0.149	18 710 928	16 458 433	18 710 928	2 252 495.5
4	0.117	0.073	...	0.120	16 991 321	*18 497 648*	18 497 648	0
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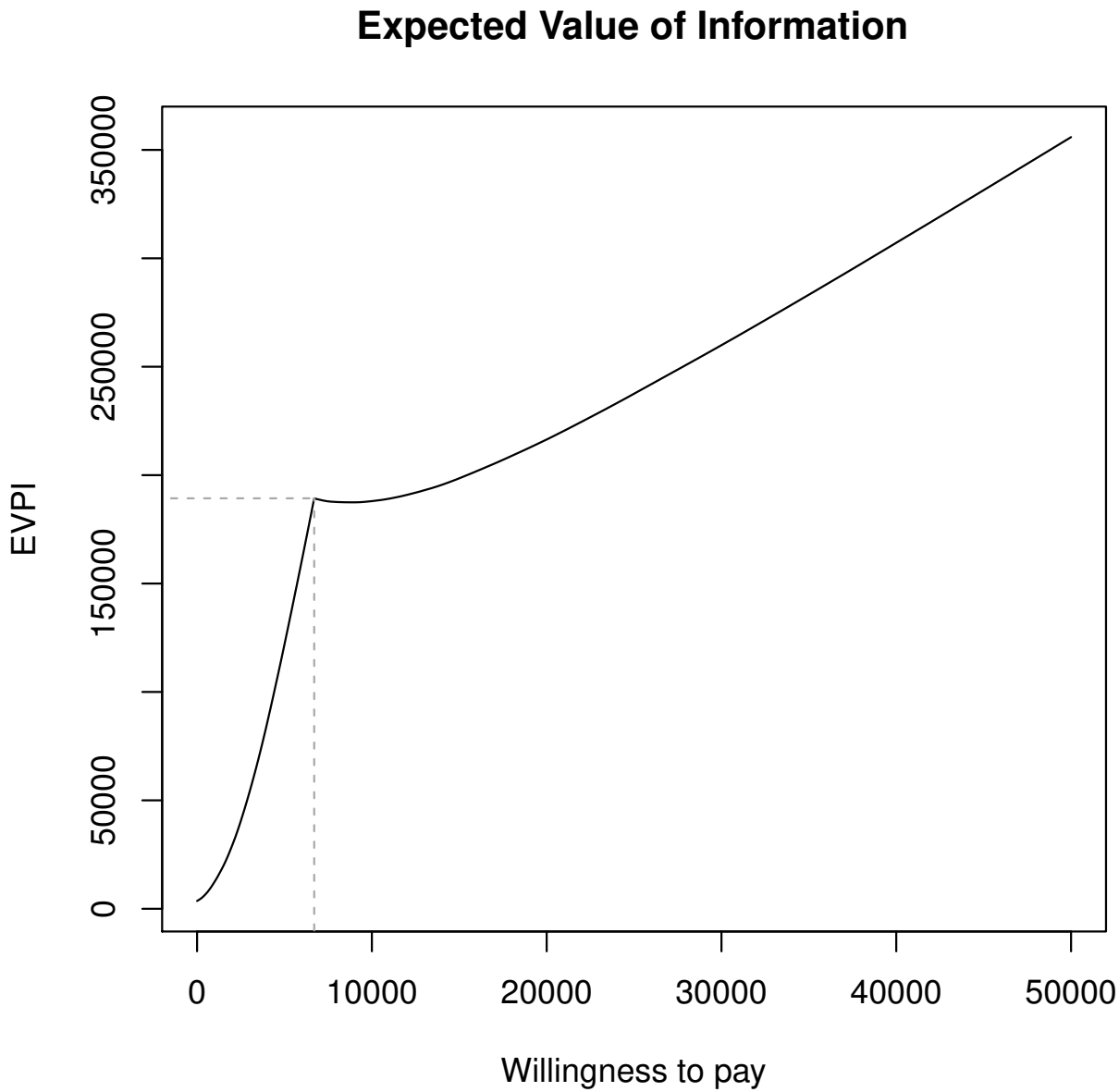
6	0.163	0.127	...	0.004	17 106 136	*18 983 331*	18 983 331	0
...		...				...	...	
1000	0.354	0.067	...	0.117	*18 043 921*	16 470 805	18 043 921	1 573 116.0
				Average	18 659 238	*19 515 004*	**19 741 589**	**226 585**

- **Expected Value of "Perfect" Information** (EVPI) summarises uncertainty in the decision
  - Defined as the **average Opportunity Loss**
  - Can also be computed as the difference between the **average maximum expected utility under "perfect" information** and the **maximum expected utility overall**:

$$\text{EVPI} = \text{E}_{\boldsymbol{\theta}}\underbrace{\left[\max_t \text{NB}_t(\boldsymbol{\theta})\right]}_{\substack{\text{Value of decision}\\ \text{if we knew } \boldsymbol{\theta}}} - \underbrace{\max_t \text{E}_{\boldsymbol{\theta}}\left[\text{NB}_t(\boldsymbol{\theta})\right]}_{\substack{\text{Value of decision based}\\ \text{on current information}}} = \text{E}_{\boldsymbol{\theta}}\underbrace{\left[\max_t \text{NB}_t(\boldsymbol{\theta}) - \text{NB}_{t^*}(\boldsymbol{\theta})\right]}_{\substack{\text{Opportunity lost from using } t^*\\ \text{instead of the optimal } t \text{ for } \boldsymbol{\theta}}}$$


Expected Value of Information
EVPI
0
50000
150000
250000
350000
0
10000
20000
30000
40000
50000
Willingness to pay

Summarising PSA + Research priority: Expected Value of **Partial** Perfect Information

- $\boldsymbol{\theta}$ = all the model parameters; can be split into two subsets
  - The "**parameters of interest**" ϕ, e.g. prevalence of a disease, HRQL measures, length of stay in hospital, ...
  - The "**remaining parameters**" ψ, e.g. cost of treatment with other established medications,
- We are interested in quantifying the value of gaining more information on ϕ, while leaving the current level of uncertainty on ψ unchanged

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- In formulæ:
  - First, consider the expected utility (EU) **if** we were able to learn ϕ but not ψ

$$\mathrm{E}_{\psi|\phi}\left[\mathrm{NB}_t(\boldsymbol{\theta})\right]$$

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$$\mathrm{E}_{\phi}\left[\max_{t}\mathrm{E}_{\psi|\phi}\left[\mathrm{NB}_{t}(\boldsymbol{\theta})\right]\right]-\max_{t}\mathrm{E}_{\boldsymbol{\theta}}\left[\mathrm{NB}_{t}(\boldsymbol{\theta})\right]$$

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  - And compare this with the **maximum expected utility overall**
  - This is the EVPPI!

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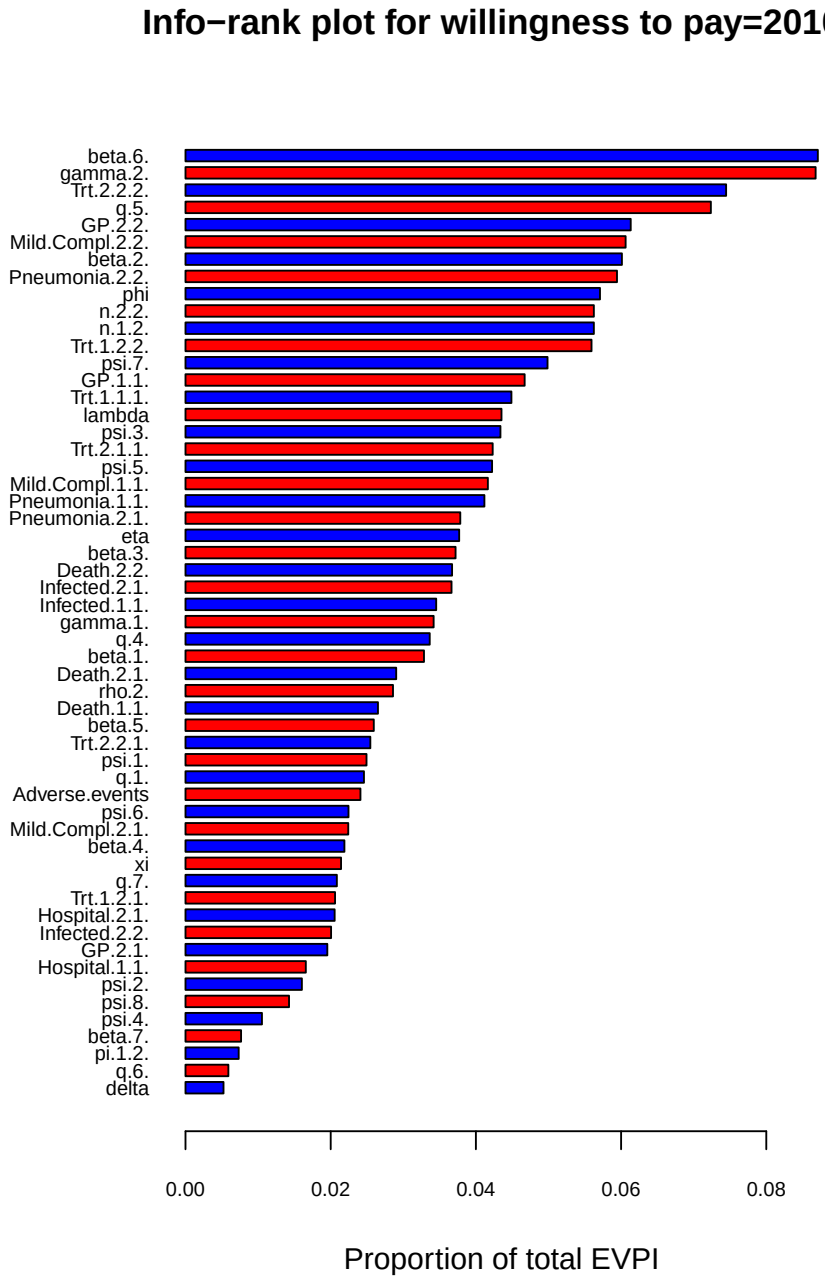
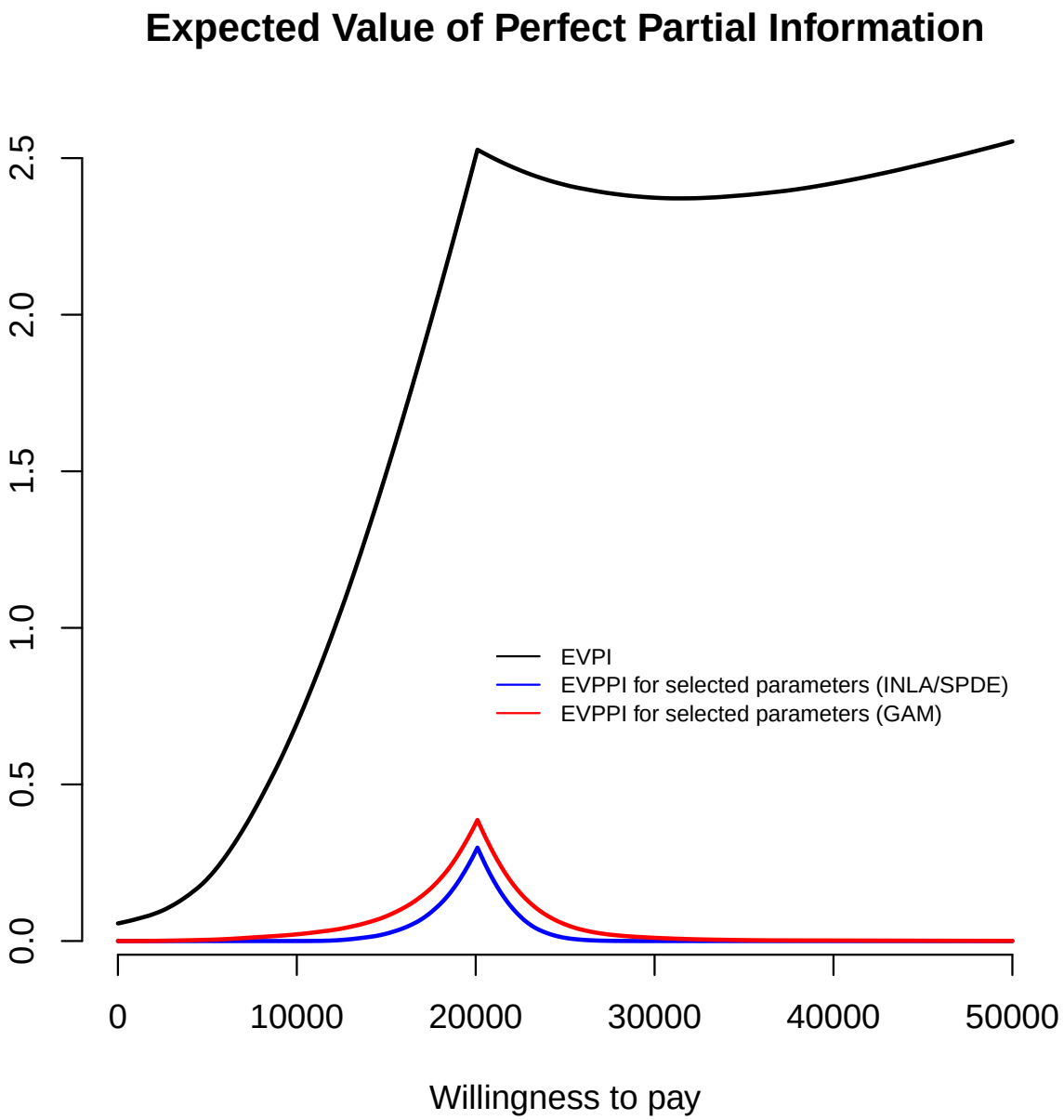
- **That's** the difficult part!
  - Can do nested Monte Carlo, but takes forever to get accurate results
  - **Recent methods** based on **Gaussian Process regression** very efficient & quick!

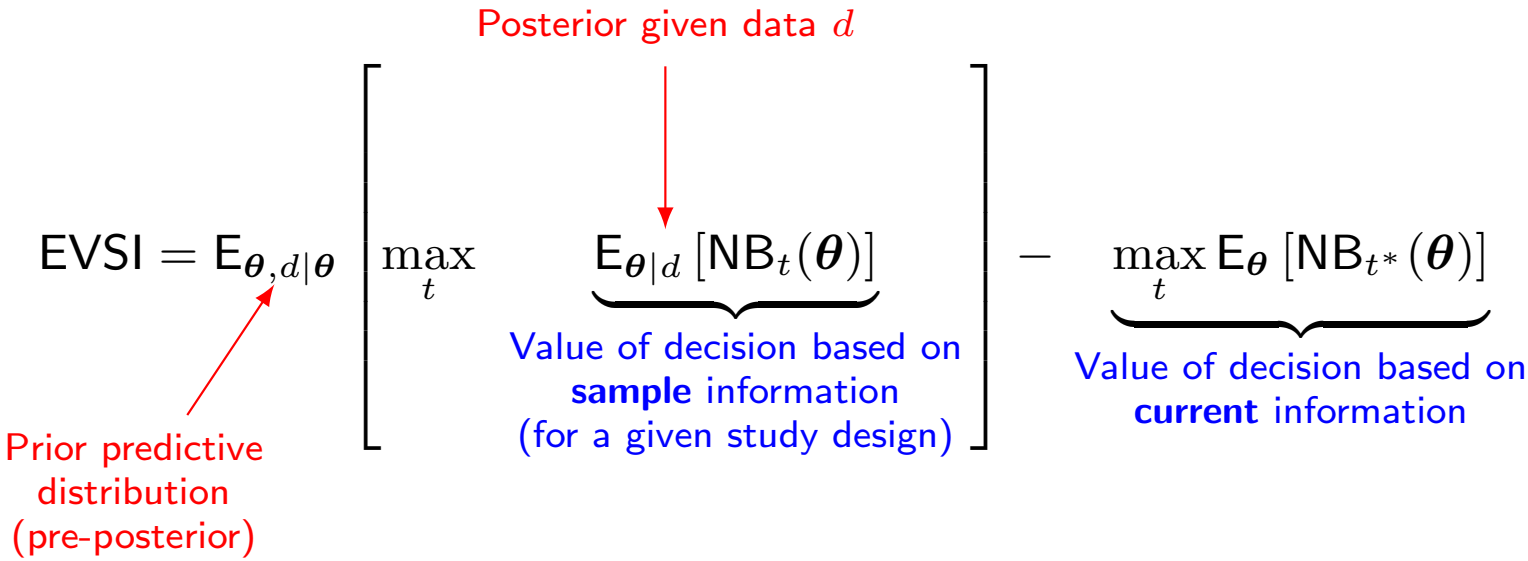
Strong et al *Medical Decision Making*. 2014; **34(3)**: 311-26.
Heath et al *Statistics in Medicine*. 2016; **35(23)**: 4264-4280.

http://savi.shef.ac.uk/SAVI/
https://egon.stats.ucl.ac.uk/projects/EVSI/

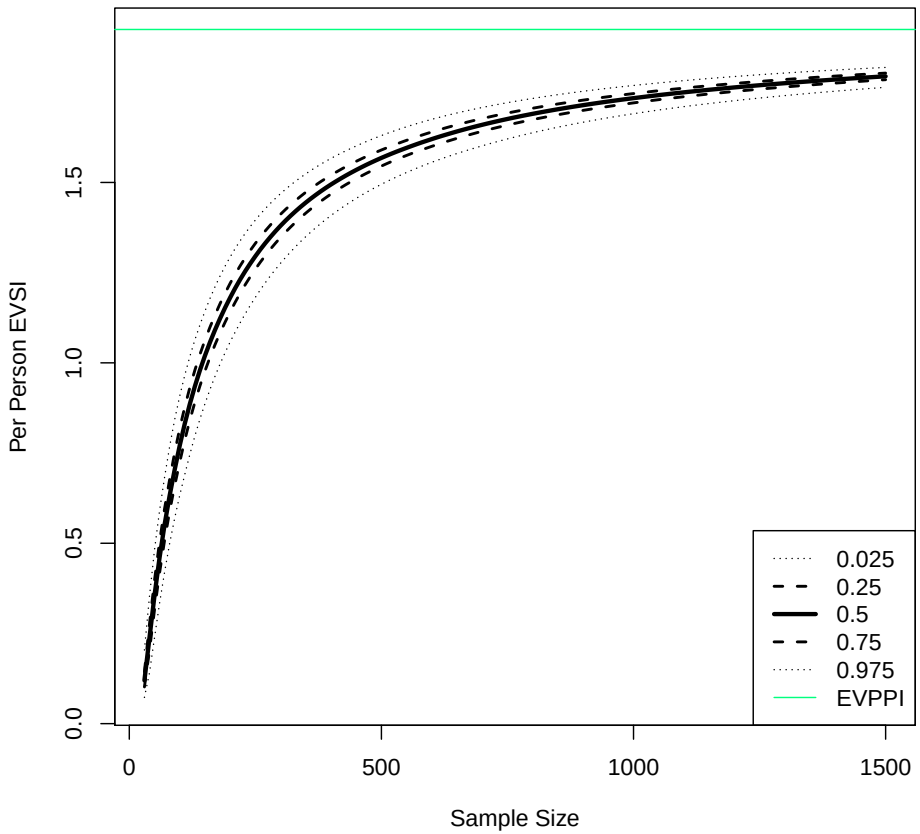
Summarising PSA + Research priority: Expected Value of **Partial** Perfect Information

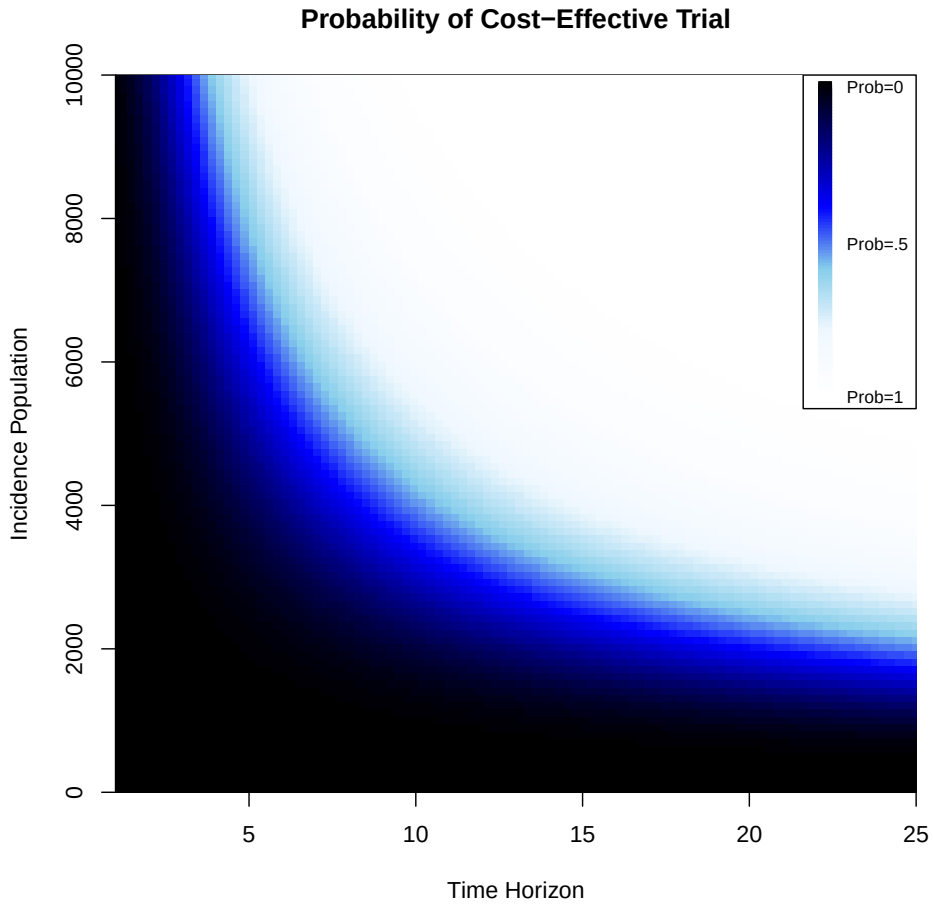



Expected Value of Perfect Partial Information
0.0
0.5
1.0
1.5
2.0
2.5
0
10000
20000
30000
40000
50000
Willingness to pay
EVPI
EVPPI for selected parameters (INLA/SPDE)
EVPPI for selected parameters (GAM)

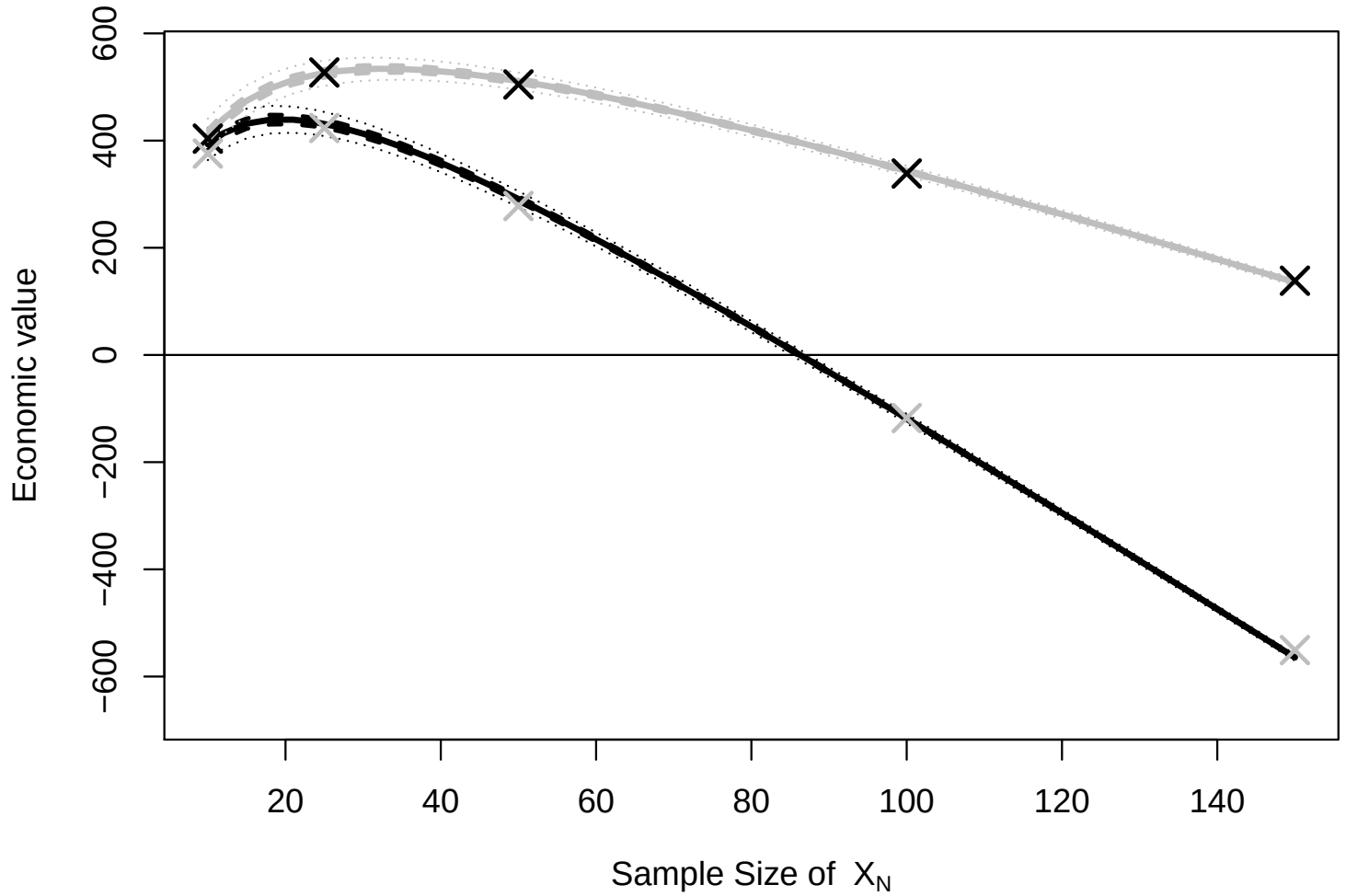


- Computationally complex
  - Requires specific knowledge of the model for (future/hypothetical) data collection
  - Again, recent methods have improved efficiency
- Can be used to drive design of new study (eg sample size calculations)





https://github.com/giabaio/EVSI
https://egon.stats.ucl.ac.uk/projects/EVSI
Heath et al (2018). https://arxiv.org/abs/1804.09590
Heath et al *Medical Decision Making*. 2017. **38(2)**: 163-173


Economic value
600
400
200
0
−200
−400
−600
20
40
60
80
100
120
140
Sample Size of X_N

End

Outline

1. Health economic evaluation
   - What is it?
   - How does it work?
2. Statistical modelling
   - Individual-level vs aggregated data
   - The importance of being a Bayesian
3. **Some examples**
   - Individual level & partially observed data
   - Survival analysis in HTA
   - Value of information
4. Conclusions

ILD+Missing data

Survival analysis

Conclusions

- Bayesian modelling particularly effective in health economic evaluations
- Allows the incorporation of external, additional information to the current analysis
  - Previous studies
  - Elicitation of expert opinions

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Conclusions

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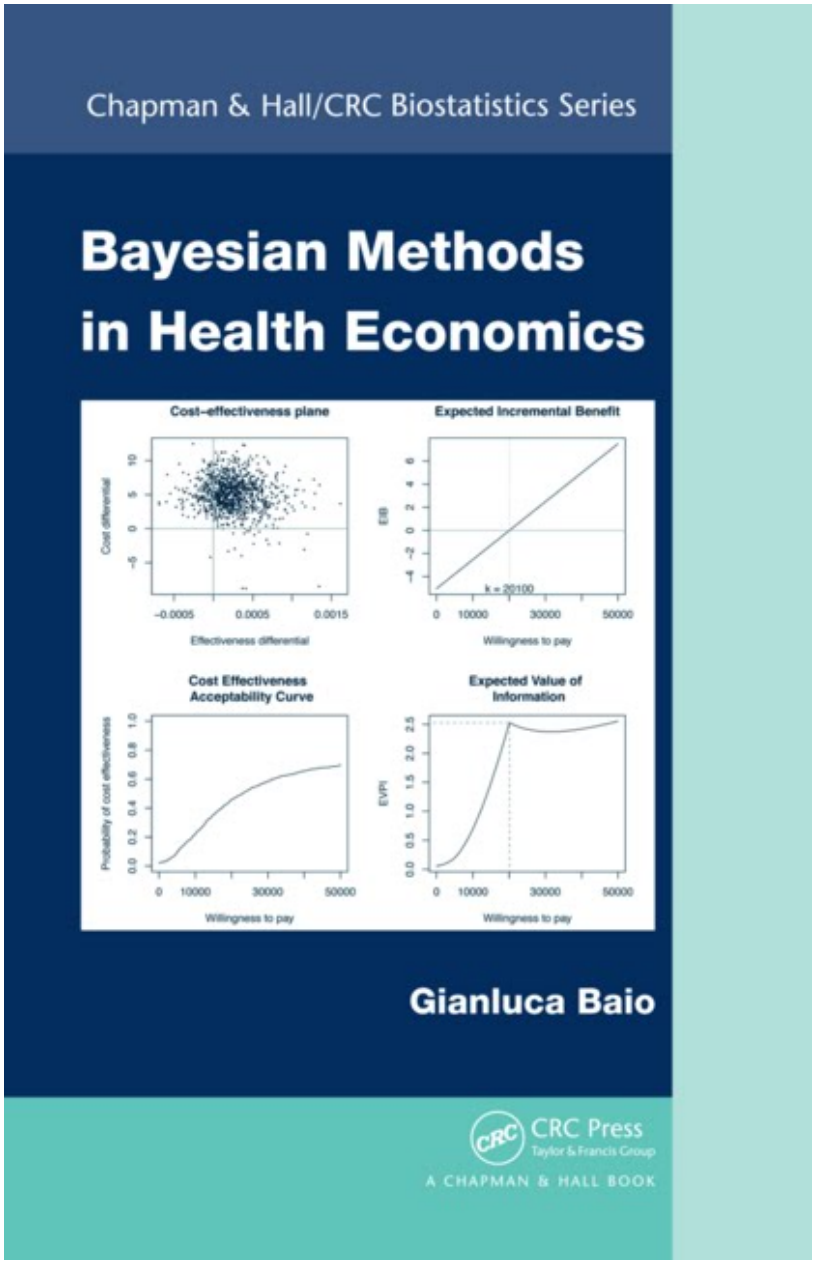
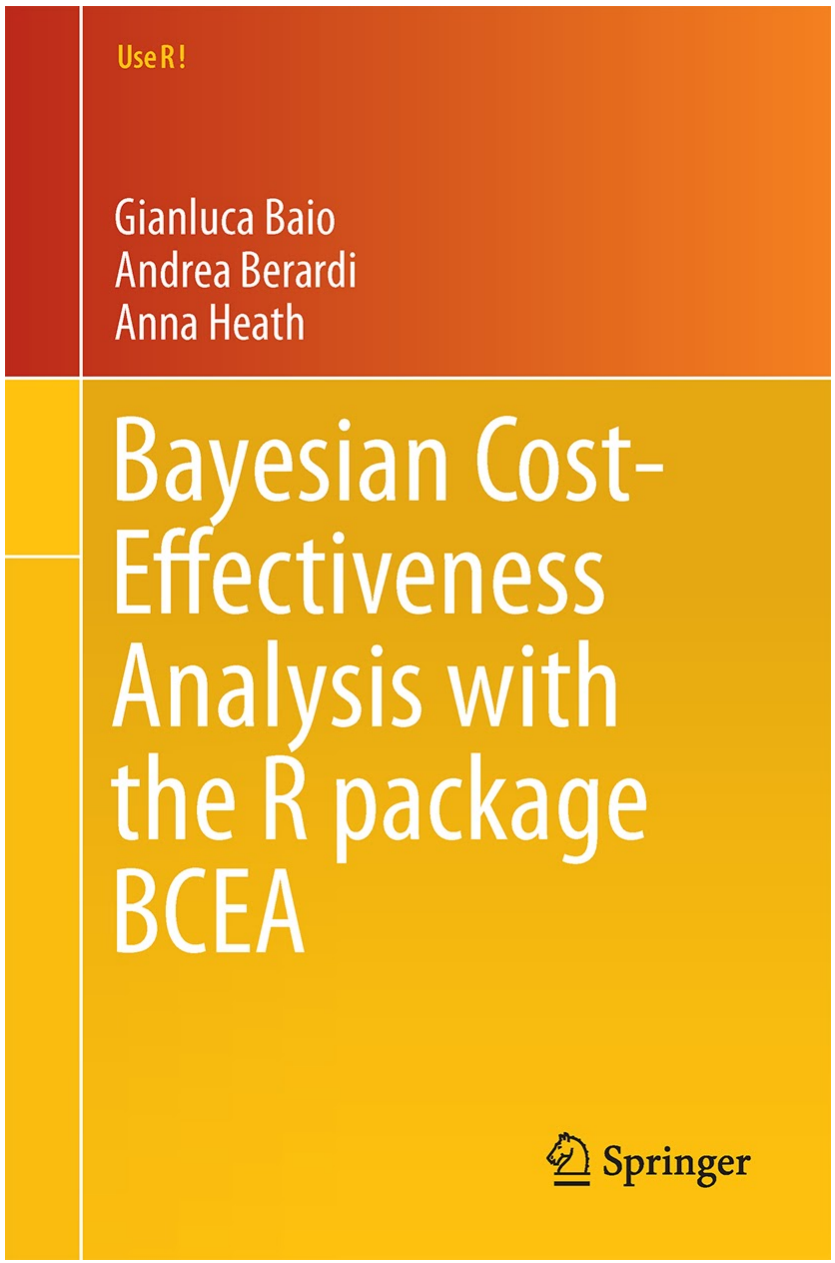
  - Useful in the case of individual-level data (eg from Phase III RCT)
- Using MCMC methods, it is possible to produce the results in terms of simulations from the posterior distributions
  - These can be used to build suitable variables of cost and benefit
  - Particularly effective for running "probabilistic sensitivity analysis"

Shameless self marketing





Ευχαριστώ!