Bayesian parametric models to handle missing longitudinal outcome data in trial-based health economic evaluations

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Joint work with **Andrea Gabrio (UCL)** and **Michael J Daniels (University of Florida)**

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Invited session: "Sensitivity analysis for uncheckable assumptions"

Monday 16 December 2019

Outline

1. **Health economic evaluation**
   - What is it?
   - How does it work?
2. Statistical modelling
   - Standard approach
   - The importance of being a Bayesian
3. Bayesian modelling for missing data in HTA
   - Modelling & advantages
   - Bayesian nature of dealing with missing data
4. Motivating example
   - Data (and their weird features...) & Bayesian modelling
   - Results
5. Conclusions

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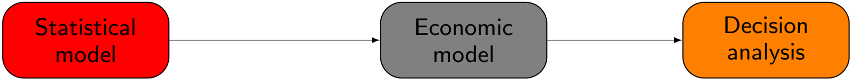
EIB $= h(\Delta_e, \Delta_c; k)$
$\ldots$



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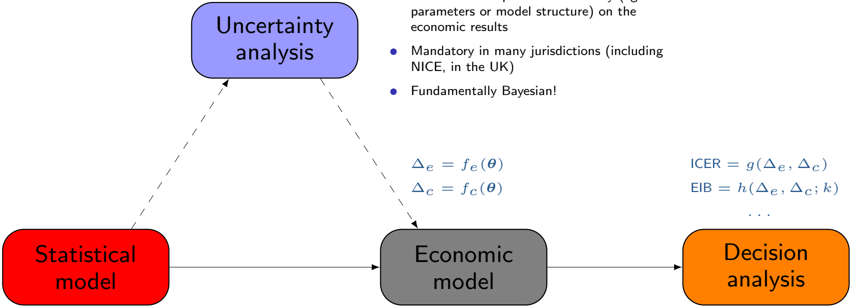

- Assesses the impact of uncertainty (eg in parameters or model structure) on the economic results
- Mandatory in many jurisdictions (including NICE, in the UK)
- Fundamentally Bayesian!

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2	1	M	21	...	0.12	0.16	...	0.38	1 204	1 808	...	877	y_{20}	y_{21}	...	y_{2J}
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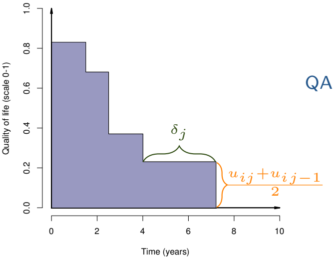
1. Compute individual QALYs and total costs as

$$e_i = \sum_{j=1}^{J} (u_{ij} + u_{ij-1}) \frac{\delta_j}{2} \quad \text{and} \quad c_i = \sum_{j=0}^{J} c_{ij}, \qquad \left[\text{with: } \delta_j = \frac{\text{Time}_j - \text{Time}_{j-1}}{\text{Unit of time}}\right]$$



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

$$\begin{aligned} e_i &= \alpha_{e0} + \alpha_{e1} u_{0i} + \alpha_{e2} \text{Trt}_i + \varepsilon_{ei} \, [+ \ldots], \qquad & \varepsilon_{ei} \sim \text{Normal}(0, \sigma_e) \\ c_i &= \alpha_{c0} + \alpha_{c1} c_{0i} + \alpha_{c2} \text{Trt}_i + \varepsilon_{ci} \, [+ \ldots], \qquad & \varepsilon_{ci} \sim \text{Normal}(0, \sigma_c) \end{aligned}$$

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

What's wrong with this?...

- Potential correlation between costs & clinical benefits [Individual Level + Aggregated Level Data]
  - Strong positive correlation — effective treatments are innovative and result from intensive and lengthy research ⇒ are associated with higher unit costs
  - Negative correlation — more effective treatments may reduce total care pathway costs e.g. by reducing hospitalisations, side effects, etc.
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  - Costs usually skewed and benefits may be bounded in $[0; 1]$
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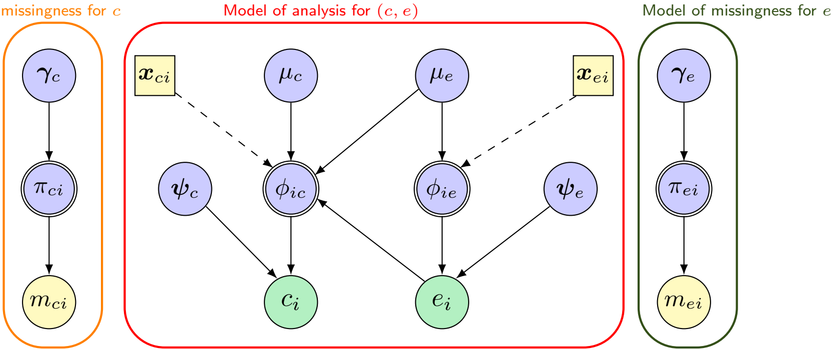
- ... and of course **Partially Observed** data
  - Can have item and/or unit non-response
  - Missingness may occur in either or both benefits/costs
  - The missingness mechanisms may also be correlated
  - Focus in decision-making, not inference — **Bayesian approach particularly suited for this!**

MCAR (e, c)



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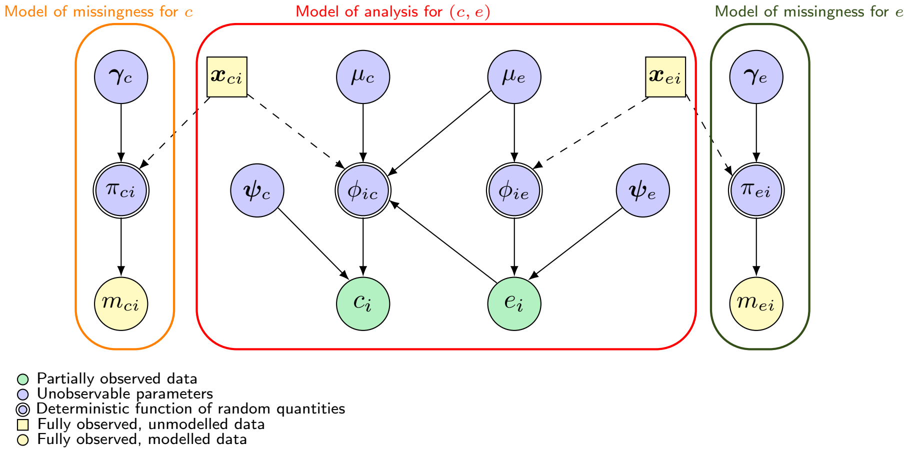

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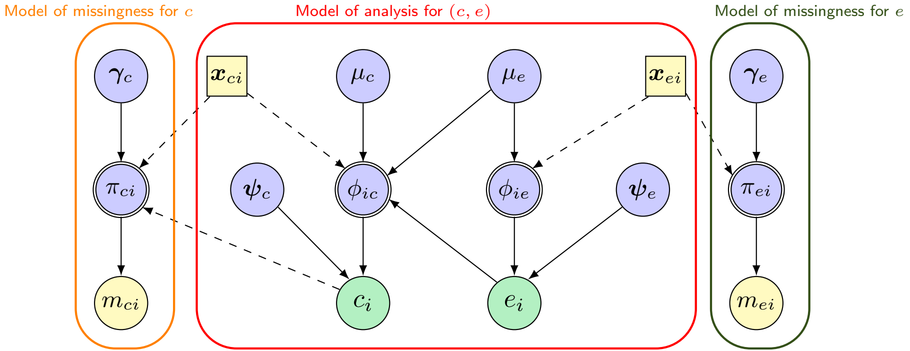

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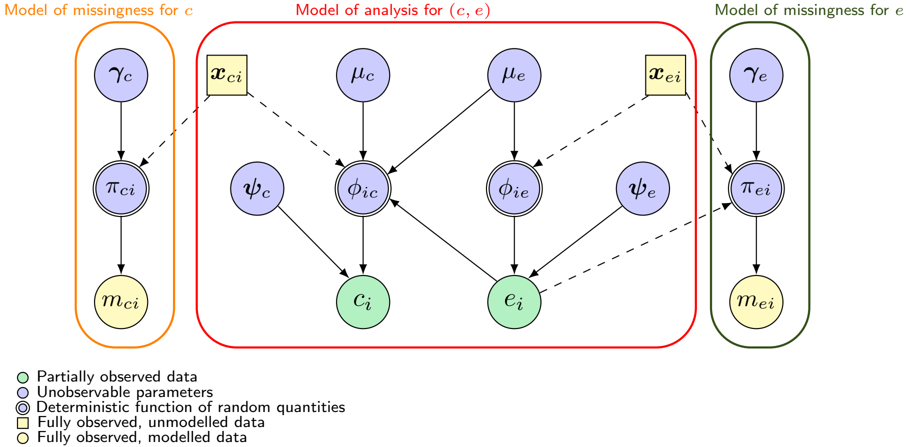

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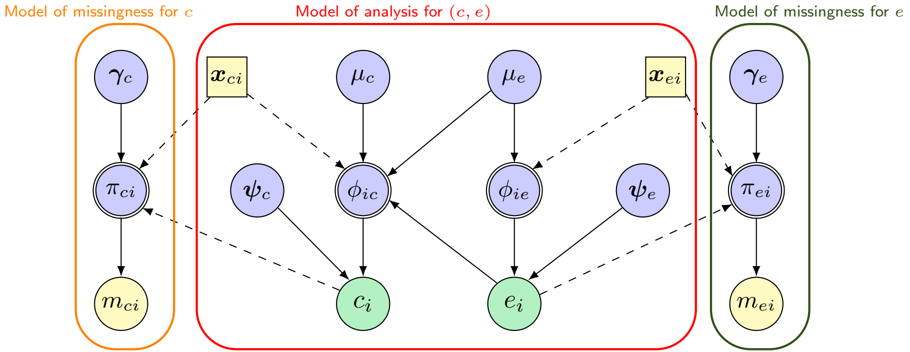

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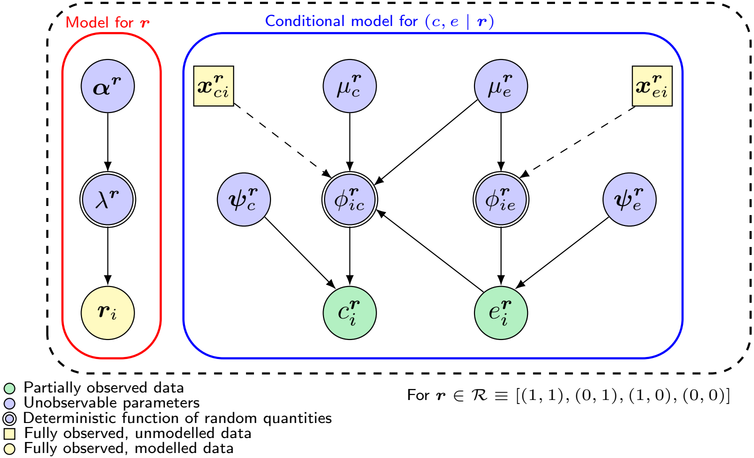

For $\boldsymbol{r} \in \mathcal{R} \equiv [(1,1),(0,1),(1,0),(0,0)]$

- $\boldsymbol{r}_i = (m_{ei}, m_{ci}) \sim \text{Multinomial}(\boldsymbol{\lambda}^{\boldsymbol{r}})$; $\mu_e = \sum_{\boldsymbol{r}\in\mathcal{R}} \mu_e^{\boldsymbol{r}}\lambda^{\boldsymbol{r}}$; $\mu_c = \sum_{\boldsymbol{r}\in\mathcal{R}} \mu_c^{\boldsymbol{r}}\lambda^{\boldsymbol{r}}$
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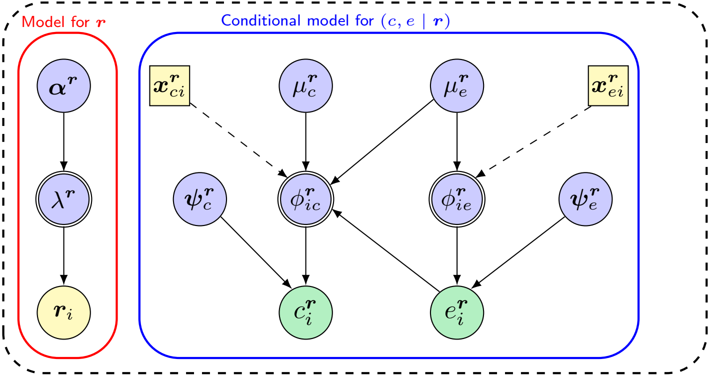

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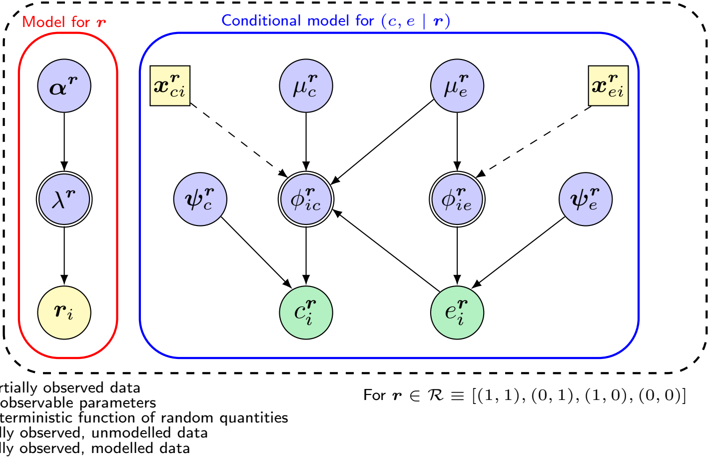

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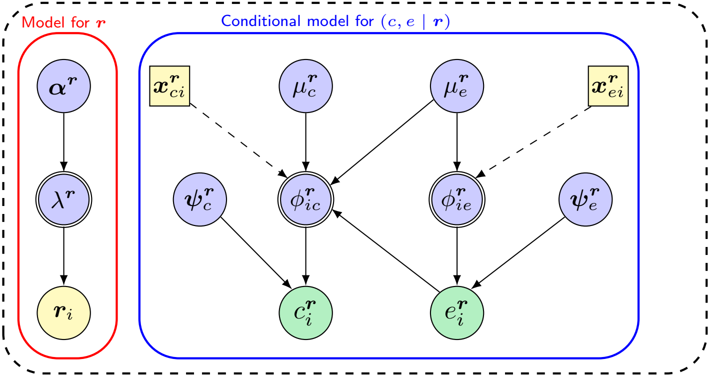

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Example: PBS trial

- Multi-centre RCT that evaluates the cost-effectiveness of a new multicomponent intervention for individuals suffering from intellectual disability and challenging behaviour
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Time	**Control** (n_1=136)		**Intervention** (n_2=108)	
	observed (%)		**observed (%)**	
	utilities	costs	utilities	costs
Baseline	127 (93%)	136 (100%)	103 (95%)	108 (100%)
6 months	119 (86%)	128 (94%)	102 (94%)	103 (95%)
12 months	125 (92%)	130 (96%)	103 (95%)	104 (96%)
complete cases	108 (79%)		96 (89%)	

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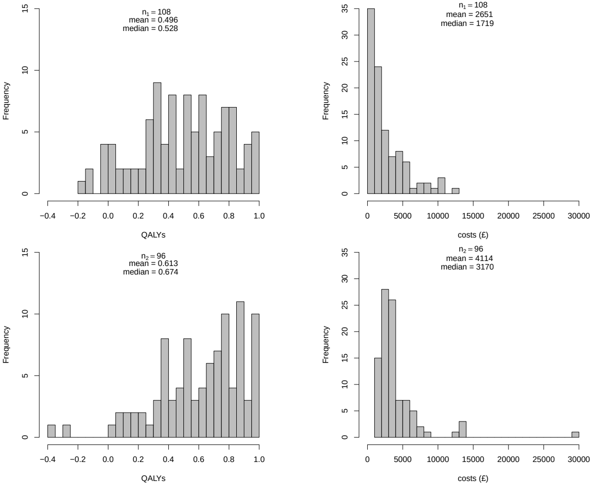

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  - Account for time dependence between outcomes $\boldsymbol{y}_{ij} = (u_{ij}, c_{ij})$
  - Use all available utility/cost data in each pattern $\boldsymbol{r}_{ij} = (r^u_{ij}, r^c_{ij})$

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- Can use **pattern mixture model**

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2. Integrate out $\boldsymbol{y}^{\boldsymbol{r}}_{mis}$ from $p(\boldsymbol{y}, \boldsymbol{r})$ and estimate the means of $\boldsymbol{y}^{\boldsymbol{r}}_{obs}$
3. Identify the means of $\boldsymbol{y}^{\boldsymbol{r}}_{mis}$ using:
   - The mean estimates of $\boldsymbol{y}^{\boldsymbol{r}}_{obs}$
   - Sensitivity parameters $\boldsymbol{\Delta} = (\Delta_u, \Delta_c)$

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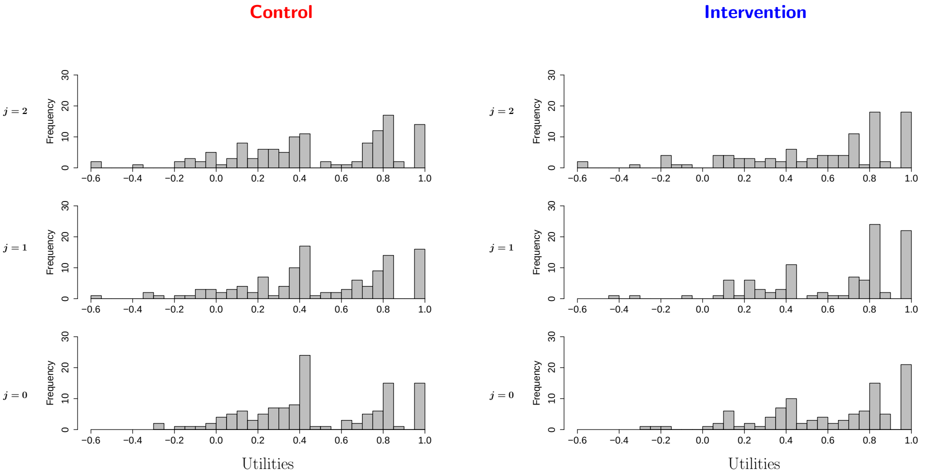
  2. Integrate out $\boldsymbol{y}^{\boldsymbol{r}}_{mis}$ from $p(\boldsymbol{y}, \boldsymbol{r})$ and estimate the means of $\boldsymbol{y}^{\boldsymbol{r}}_{obs}$
  3. Identify the means of $\boldsymbol{y}^{\boldsymbol{r}}_{mis}$ using:
     - The mean estimates of $\boldsymbol{y}^{\boldsymbol{r}}_{obs}$
     - Sensitivity parameters $\boldsymbol{\Delta} = (\Delta_u, \Delta_c)$

- Assess the robustness of the results to plausible MNAR scenarios using different informative priors on $\boldsymbol{\Delta}$

Example: PBS trial



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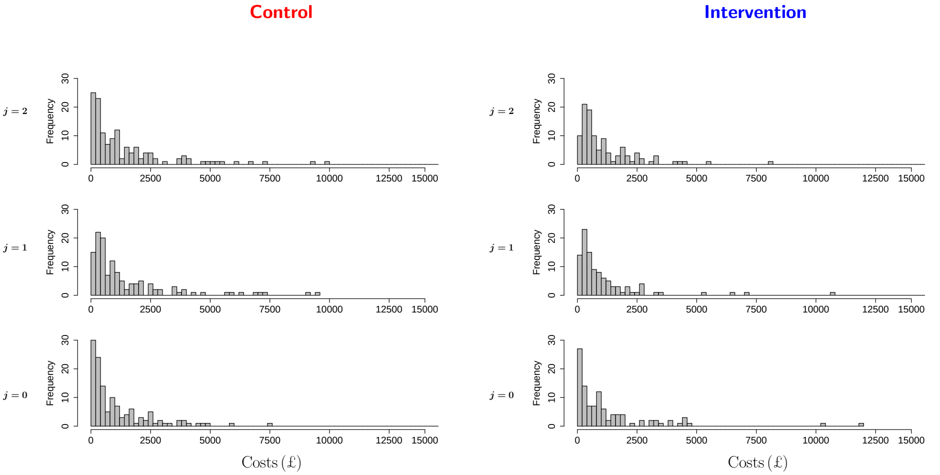
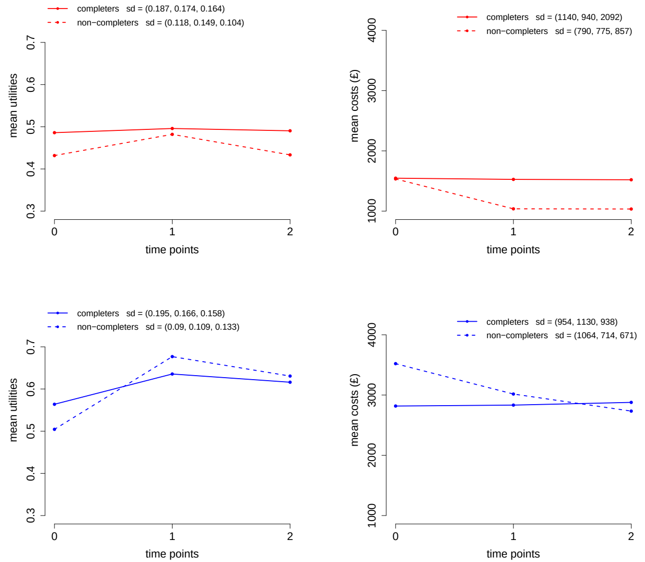


	Control ($t = 1$)							Intervention ($t = 2$)							
	u_0	c_0	u_1	c_1	u_2	c_2	n_1^r	u_0	c_0	u_1	c_1	u_2	c_2	n_2^r	
$\boldsymbol{r}$	1	1	1	1	1	1	**108**	1	1	1	1	1	1	**96**	$\rightarrow \boldsymbol{r} = 1$
mean	0.678	1546	0.684	1527	0.680	1520		0.726	2818	0.771	2833	0.759	2878		
$\boldsymbol{r}$	0	1	1	1	1	1	**7**	0	1	1	1	1	1	**5**	
mean	–	1310	0.704	1440	0.644	1858		–	2573	0.780	2939	0.849	2113		
$\boldsymbol{r}$	1	1	0	1	1	1	**4**	1	1	0	1	1	1	**1**	
mean	0.709	1620	–	1087	0.737	851		0.467	9649	–	4828	0.259	4930		
$\boldsymbol{r}$	1	1	1	1	0	1	**2**	1	1	1	1	0	1	**1**	
mean	0.564	640	0.648	512	–	286		0.817	3788	0.884	0	–	0		
$\boldsymbol{r}$	1	1	0	0	1	1	**4**	1	1	0	0	1	1	**1**	
mean	0.716	2834	–	–	0.634	679		0.501	3608	–	–	0.872	4781		$\boldsymbol{r} \neq 1$
$\boldsymbol{r}$	1	1	0	0	0	0	**4**	1	1	0	0	0	0	**4**	
mean	0.434	1528	–	–	–	–		0.760	3086	–	–	–	–		
$\boldsymbol{r}$	0	1	0	1	1	1	**2**	0	1	0	1	1	1	**0**	
mean	–	595	–	397	0.483	69		–	–	–	–	–	–		
$\boldsymbol{r}$	1	1	1	1	0	0	**2**	1	1	1	1	0	0	**0**	
mean	0.743	1434	0.705	1606	–	–		–	–	–	–	–	–		
$\boldsymbol{r}$	1	1	0	1	0	1	**3**	1	1	0	1	0	1	**0**	
mean	0.726	1510	–	432	–	976		–	–	–	–	–	–		

Example: PBS trial



- Fit model to completers $\boldsymbol{r} = \mathbf{1}$ and joint set of all other patterns $\boldsymbol{r} \neq \mathbf{1}$ separately for $t = 1, 2$

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- Account for skewness using
  - **Beta** distributions for $u^{\star}_{ij} = \dfrac{u_{ij} - \min(\boldsymbol{u}_j)}{\max(\boldsymbol{u}_j) - \min(\boldsymbol{u}_j)}$
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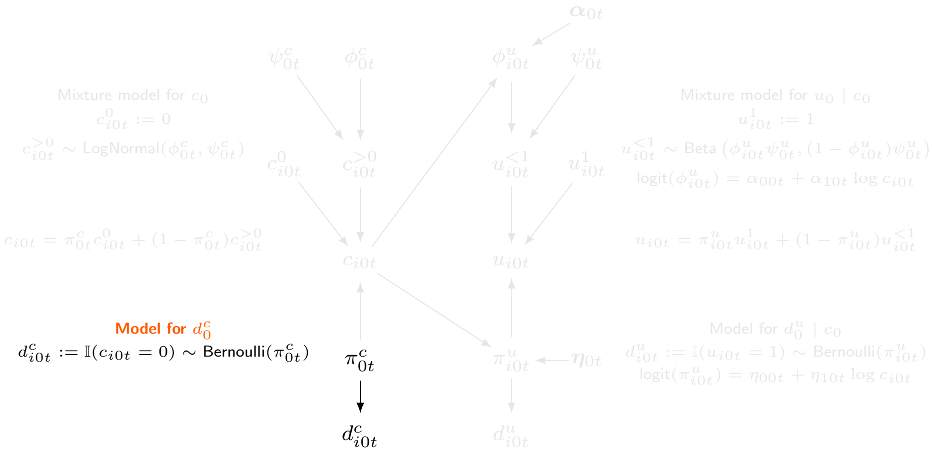
  - **LogNormal** distributions for c_{ij}
- Allow for structural **ones** in u_{ij} and **zeros** in c_{ij}
  - Define $d^u_{ij} := \mathbb{I}(u_{ij}=1)$ and $d^c_{ij} := \mathbb{I}(c_{ij}=0)$
  - Use a hurdle model to account for mixture of patients within the groups

- At $j = 0$


α_{0t}
ψ^c_{0t}
ϕ^c_{0t}
ϕ^u_{i0t}
ψ^u_{0t}
Mixture model for c_0
$c^0_{i0t} := 0$
$c^{>0}_{i0t} \sim$ LogNormal$(\phi^c_{0t}, \psi^c_{0t})$
c^0_{i0t}
$c^{>0}_{i0t}$
$u^{<1}_{i0t}$
u^1_{i0t}
Mixture model for $u_0 \mid c_0$
$u^1_{i0t} := 1$
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logit$(\phi^u_{i0t}) = \alpha_{00t} + \alpha_{10t} \log c_{i0t}$
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u_{i0t}
Model for d^c_0
$d^c_{i0t} := \mathbb{I}(c_{i0t} = 0) \sim$ Bernoulli(π^c_{0t})
π^c_{0t}
π^u_{i0t}
η_{0t}
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d^c_{i0t}
d^u_{i0t}

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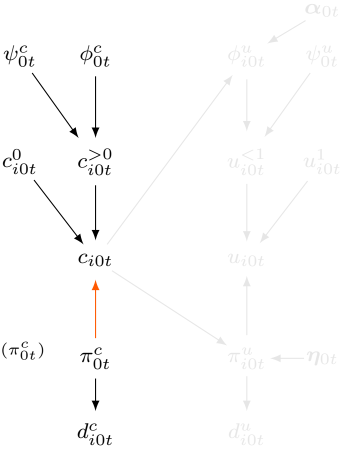

Mixture model for $u_0 \mid c_0$

$u^1_{i0t} := 1$

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Modelling

Gabrio et al. JRSS/A (2019). doi:10.1111/rssa.12522

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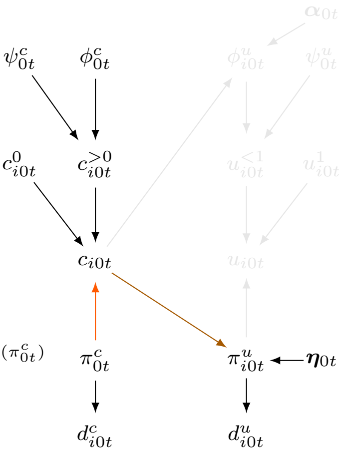

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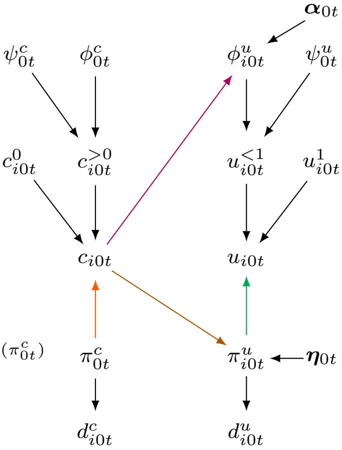

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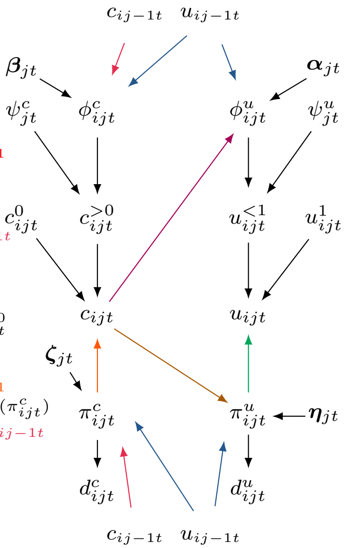

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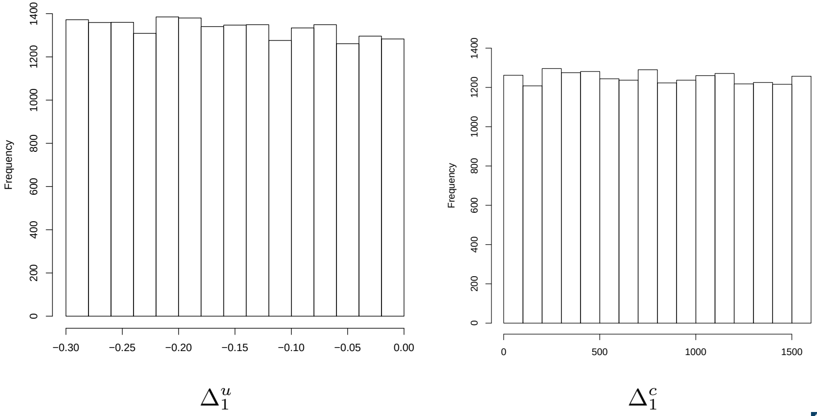
- Compute weighted average across $\boldsymbol{r}$ to derive $\boldsymbol{\mu}_{jt} = (\mu^u_{jt}, \mu^c_{jt})$
- Set $\boldsymbol{\Delta}_j = \mathbf{0}$ as benchmark assumption
- Specify three alternative priors on $\boldsymbol{\Delta}_j = (\Delta^u_j, \Delta^c_j)$, calibrated based on the variability in the observed data at each time j

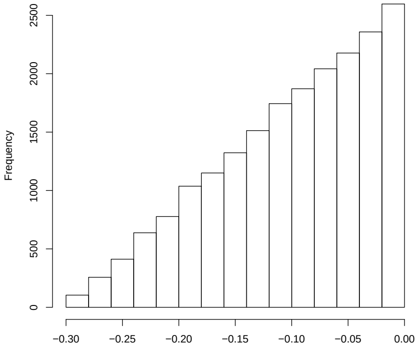
Priors on sensitivity parameters

- Assumption: $\boldsymbol{u}_{mis} < \boldsymbol{u}_{obs}$ and $\boldsymbol{c}_{mis} > \boldsymbol{c}_{obs}$
- $\boldsymbol{\Delta}^{\text{flat}}$: Flat between 0 and twice the observed standard deviation

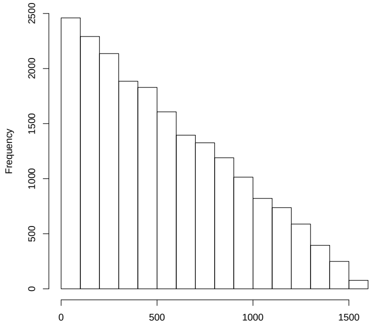


Priors on sensitivity parameters

- Assumption: $\boldsymbol{u}_{mis} < \boldsymbol{u}_{obs}$ and $\boldsymbol{c}_{mis} > \boldsymbol{c}_{obs}$
- $\boldsymbol{\Delta}^{\text{skew0}}$: Skewed towards values closer to 0 on the same range as $\boldsymbol{\Delta}^{\text{flat}}$



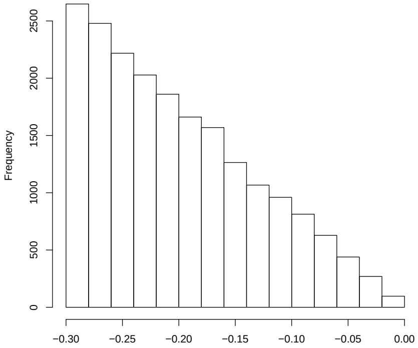
Δ_1^u



Δ_1^c

Priors on sensitivity parameters

- Assumption: $u_{mis} < u_{obs}$ and $c_{mis} > c_{obs}$
- Δ^{skew1}: Skewed towards values far from 0 on the same range as Δ^{flat}



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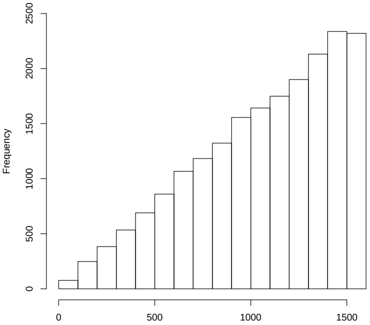
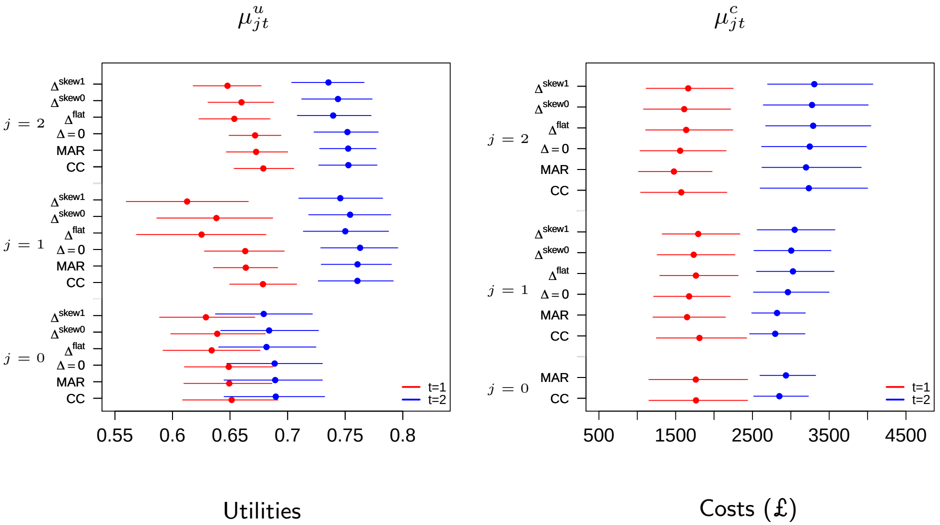
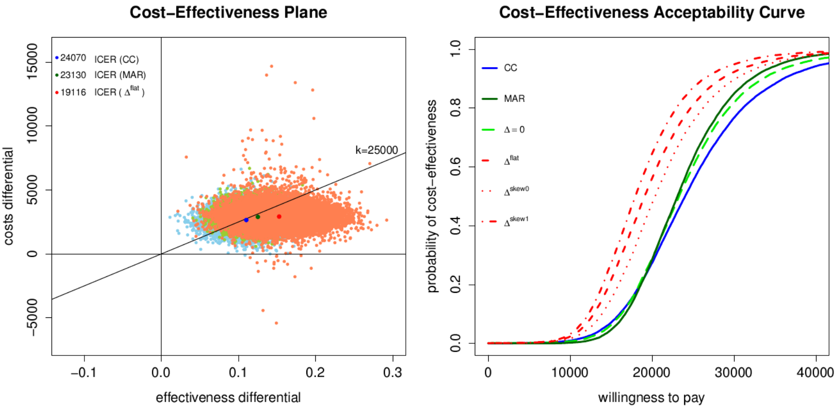


Δ_1^c

Results: means utilities and costs



Cost-effectiveness analysis



1. **Flexibility** of the modelling framework
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3. Principled incorporation of **external evidence** through priors
   - Crucial for conducting sensitivity analysis to MNAR
   - Useful in small/pilot trials where there is limited evidence

Thank you!