Statistical Issues in small/pilot Cost-Effectiveness Analysis

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(Thanks to Gianluca Baio and Alexina J. Mason)

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Outline

Health Economic Evaluation

Objective: Combine costs & benefits of a given intervention into a rational scheme for allocating resources, increasingly often under a Bayesian framework

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Statistical model → Economic model → Decision analysis

- Estimates relevant **population** parameters $\boldsymbol{\theta}$
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- Summarises the economic model by computing suitable measures of "cost-effectiveness"

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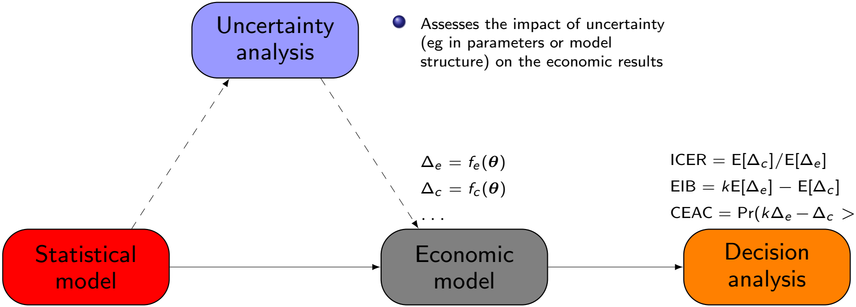

- Assesses the impact of uncertainty (eg in parameters or model structure) on the economic results

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"Standard" statistical modelling — **individual level data**

- The available data usually look something like this:

		Demographics				HRQL data				Resource use data		
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and the **typical** analysis is based on the following steps:

1. Compute individual QALYs and total costs as

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

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

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

What's wrong with this?

- Potential **correlation** between costs & clinical benefits
  - Strong positive correlation — effective treatments are innovative and 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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- Joint/marginal **normality** not realistic
  - Costs usually skewed and benefits may be bounded in $[0;1]$
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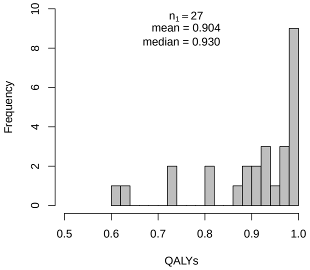
- ... and of course **Partially Observed** data
  - Missingness may occur in either or both benefits/costs
  - Important to explore the impact on the results of a range of plausible missingness assumptions in sensitivity analysis

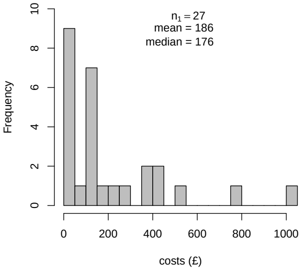
The MenSS Trial: Partially-observed data

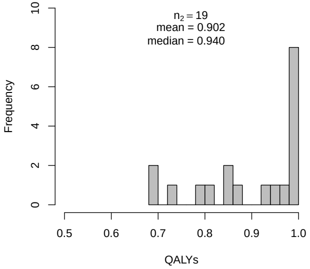
- The MenSS pilot RCT evaluates the cost-effectiveness of a new digital intervention to reduce the incidence of STI in young men with respect to the SOC
  - QALYs calculated from utilities (EQ-5D 3L)
  - Total costs calculated from different components (no baseline)

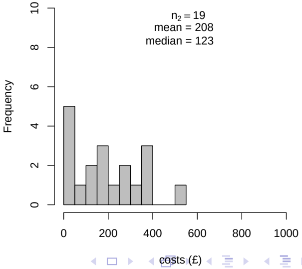
Time	**Type of outcome**	**observed (%)**	**observed (%)**
		Control (n_1=75)	Intervention (n_2=84)
Baseline	utilities	72 (96%)	72 (86%)
3 months	utilities and costs	34 (45%)	23 (27%)
6 months	utilities and costs	35 (47%)	23 (27%)
12 months	utilities and costs	43 (57%)	36 (43%)
Complete cases	utilities and costs	27 (44%)	19 (23%)

The MenSS Trial: Empirical Distributions









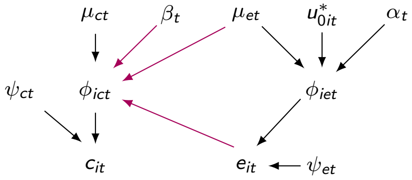
Modelling

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

1. **Bivariate Normal**
   - Account for correlation between QALYs and costs

Conditional model for $c \mid e$

$$c_{it} \mid e_{it} \sim \text{Normal}(\phi_{cit}, \psi_{ct})$$
$$\phi_{cit} = \mu_{ct} + \beta_t (e_{it} - \mu_{et})$$



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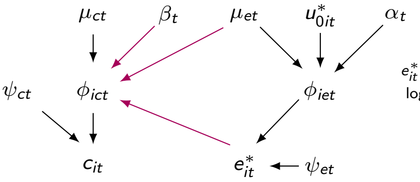

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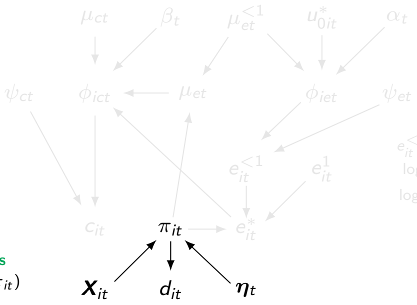

Mixture model for e

$e^1_{it} := 1$

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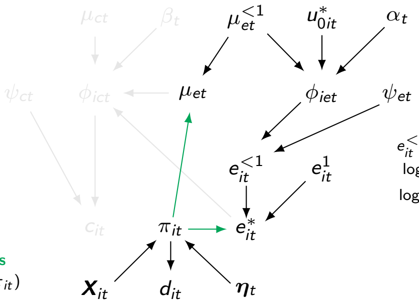

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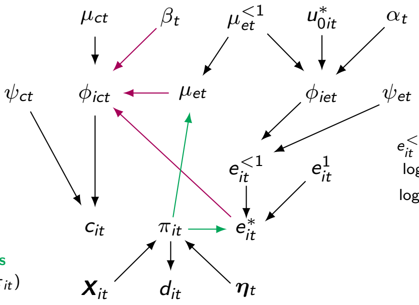

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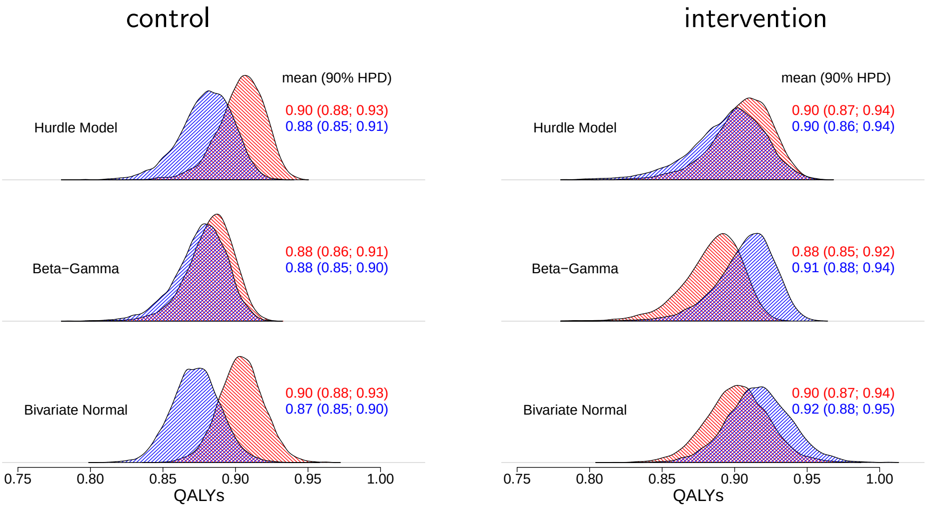
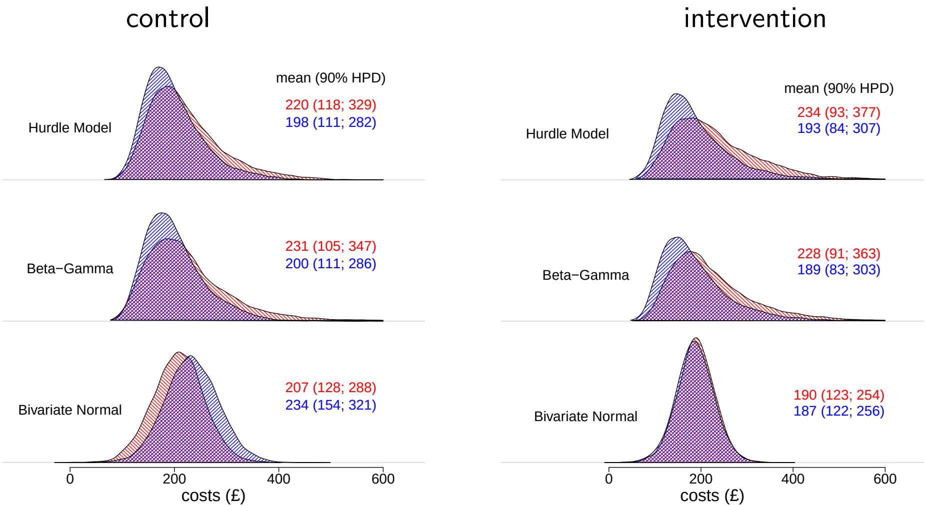
Results: QALYs



Complete Cases

All cases (Missing At Random)

Results: Costs



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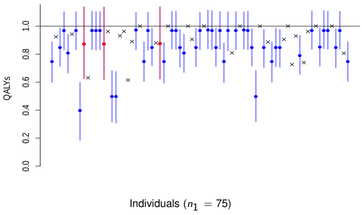
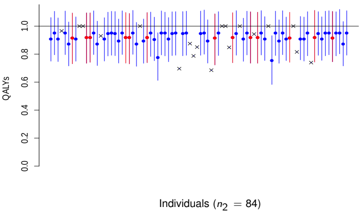
Imputations (under MAR)

Bivariate Normal





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Imputed, missing baseline
× Observed

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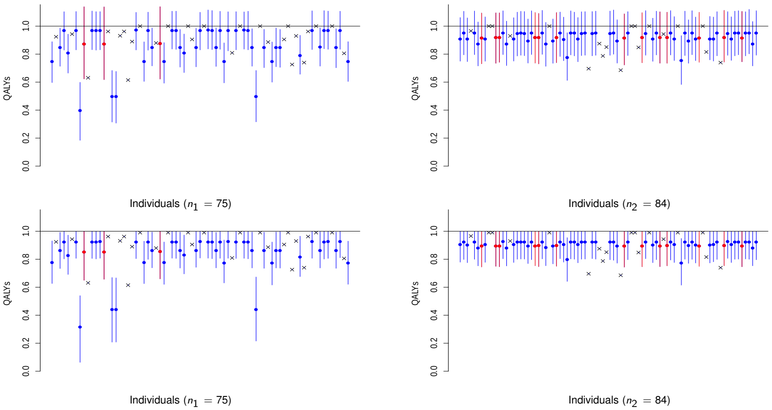

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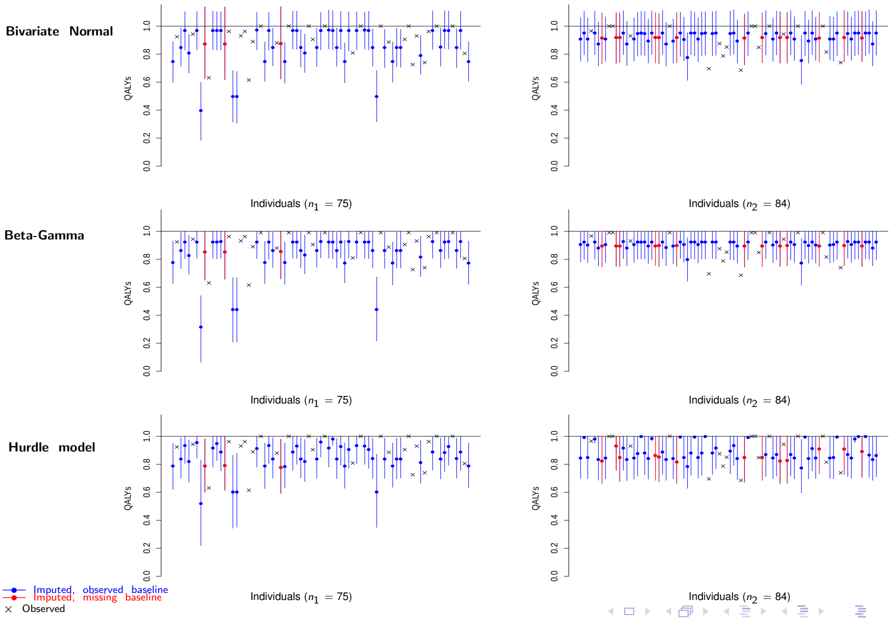


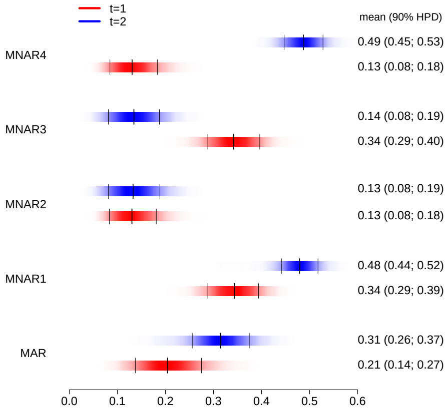
MNAR

- We observe $n^*_{01} = 13$ and $n^*_{02} = 22$ individuals with $u_{0it} = 1$ and $u_{jit} = \texttt{NA}$, for $j = 1, 2, 3$
- For those individuals, we cannot compute directly the structural one indicator d_{it} and so need to make assumptions/model this
  - Sensitivity analysis to alternative departures from MAR

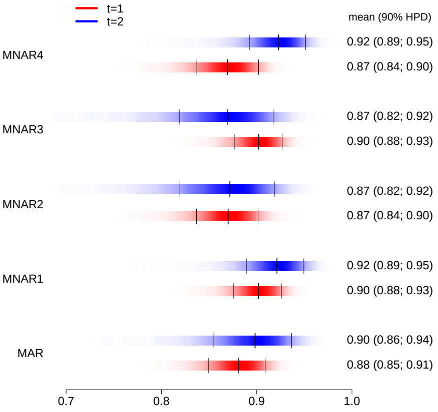
Scenario	**Control** $(n^*_1 = 13)$	**Intervention** $(n^*_2 = 22)$
MNAR1	$d_{ie} = 1$	$d_{ie} = 1$
MNAR2	$d_{ie} = 0$	$d_{ie} = 0$
MNAR3	$d_{ie} = 1$	$d_{ie} = 0$
MNAR4	$d_{ie} = 0$	$d_{ie} = 1$

Results — MNAR

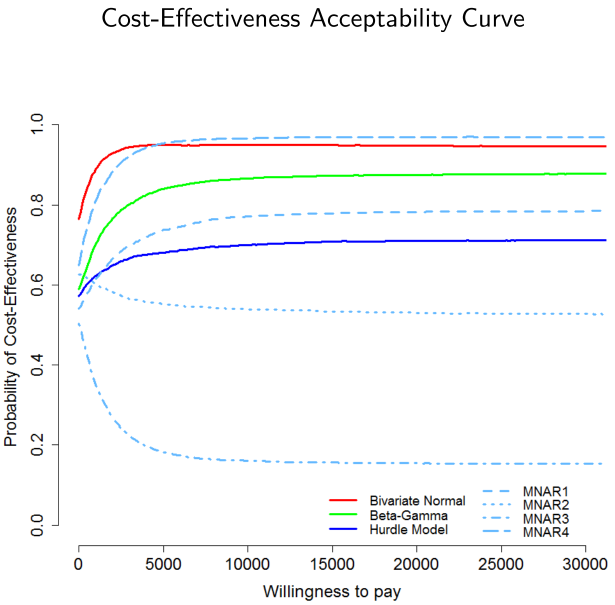
Probability of $e = 1$



QALYs mean



Cost-effectiveness analysis



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    - Can consider MAR and MNAR with relatively little expansion to the basic model
- Missingness assumptions cannot be tested
    - Necessary to explore plausible MNAR departures
    - Assess and quantify impact of uncertainty on inferences and (more importantly) on the decision process

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- Model partially-observed outcomes at the longitudinal level (u_{ij}, c_{ij})
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  - Flexible model for the observed data distribution (e.g. semi-parametric)
  - Identify distribution of missing data with sensitivity parameters
- Perform sensitivity analysis
  - Naturally falls within a Bayesian approach
  - Calibrate priors on expert opinion or the observed data
  - Assess the robustness of the results to a range of plausible assumptions