A Full Bayesian Model to Handle Structural Ones and Missingness in Economic Evaluations from Individual-Level Data

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Andrea Gabrio[1], Alexina J. Mason[2], and Gianluca Baio[1]

[1] *Department of Statistical Science, University College London*

[2] *Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine*

1 Introduction

In routine analyses, trial-based CEAs typically assume normality and independence for the underlying cost and effectiveness data $(e; c)$. There are several potential issues with this setting:

- Clinical outcome (e.g. QALYs) and costs tend to be correlated, as more effective treatments have typically higher unit costs, but may also reduce overall implementation cost;
- Joint/marginal normality is not realistic as costs are usually skewed and benefits may be bounded in $[0; 1]$ and, possibly, bimodal;
- Data may exhibit spikes at one or both of the boundaries of the range for the underlying distribution. For example, some patients in a trial may not accrue any cost at all (i.e. $c_i = 0$) or may be associated with perfect health, i.e. unit QALY;
- Individual level outcome data from RCTs are almost invariably affected by a substantial proportion of missingness ($> 25\%$) and simple methods discarding the missing values (e.g. CCA) may lead to biased results.

Objective: Provide a general Bayesian framework that can jointly handle a number of features affecting effectiveness and cost data while assessing the impact of missingness uncertainty on decision-making.

2 Example – The MenSS trial

The MenSS trial is a pilot RCT conducted in the UK to evaluate the cost-effectiveness of a new digital intervention to reduce the incidence of Sexually Transmitted Infections (STIs) in young men. A total of 159 men at risk of STIs were randomised to receive either usual clinical care only ($n_1 = 75$), or a combination of usual care and the new intervention ($n_2 = 84$). Utility (u_{ij}) and resource use (c_{ij}) data are computed from participant responses to questionnaires collected at baseline ($j = 0$ – only for the utilities) and 3, 6 and 12 months ($j = 1, 2, J = 3$). QALYs and Total costs derived from these measures show:

- A high degree of skewness in the distributions of QALYs and costs in both treatment groups;
- High spikes at 1 in the QALYs for both groups due to many individuals incurring a perfect health status;
- High levels of missingness which lead to 27 (control group) and 19 (intervention group) complete cases.

3 Modelling Framework

We can specify the joint distribution of the effectiveness and cost variables $p(e, c)$ as:

$$p(e, c) = p(c)p(e \mid c) = p(e)p(c \mid e),$$

where, for example, $p(e)$ is the *marginal* distribution of the effectiveness and $p(c \mid e)$ is the *conditional* distribution of costs given the effectiveness.

3.1 Marginal Model for the Effectiveness

For each individual we consider a marginal distribution $p(e_i \mid \boldsymbol{\theta}_e)$ indexed by a set of parameters $\boldsymbol{\theta}_e$ comprising a *location* ϕ_{ie} and a set of *ancillary* parameters $\boldsymbol{\psi}_e$ typically including some measure of *marginal* variance, σ^2_e. We can model the location parameter using a generalised linear structure, e.g.

$$g_e(\phi_{ie}) = \alpha_0 \; [+ \ldots],$$

where α_0 is the intercept and the notation $[+ \ldots]$ indicates that other terms may or may not be included in the model. In the absence of covariates or assuming that a centered version $x^*_i = (x_i - \bar{x})$ is used, the parameter $\mu_e = g_e^{-1}(\alpha_0)$ represents the population average effectiveness.

3.2 Conditional Model for the Costs

For the costs, we consider a conditional model $p(c_i \mid e_i, \boldsymbol{\theta}_c)$, which explicitly depends on the effectiveness, as well as on a set of quantities $\boldsymbol{\theta}_c$, again comprising a location and ancillary parameters. The location can be modelled as a function of the effectiveness variable as:

$$g_c(\phi_{ic}) = \beta_0 + \beta_1(e_i - \mu_e) \; [+ \ldots].$$

Here, $(e_i - \mu_e)$ is the centered version of the effectiveness, while β_1 quantifies the correlation between c and e. Assuming other covariates are either also centered or absent, $\mu_c = g_c^{-1}(\beta_0)$ is the population average cost.

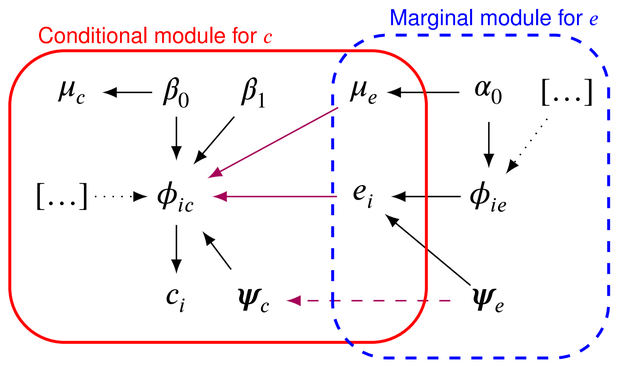


Figure 1: Graphical representation of the framework

4 Analysis Models

Three alternative specifications of the general structure depicted in Figure 1 are compared for modelling the QALYs and costs from the MenSS trial. In all cases, baseline utilities are included in the model of the QALYs as covariates. The models are:

1) Normal marginal for e and Normal conditional for c – **Bivariate Normal**

2) Beta marginal for e and Gamma conditional for c – **Beta-Gamma**

3) Beta marginal for e and Gamma conditional for c with hurdle approach for $e = 1$ – **Hurdle Model**

4.1 Hurdle Model

Hurdle models are mixture models defined by two components: the first one is a mass distribution at the spike, while the second is a parametric model applied to the natural range of the relevant variable. We can expand the model by defining an indicator variable d_{ie} taking value 1 if the $i-$th individual is associated with a unit QALYs ($e_i = 1$) and 0 otherwise ($e_i < 1$). This is then modelled as

$$\begin{aligned} d_{ie} := \mathbb{I}(e_i = 1) &\sim \text{Bernoulli}(\pi_{ie}) \\ \text{logit}(\pi_{ie}) &= \gamma_0 + \gamma_1(u_{i0} - \bar{u}_0) \; [+ \ldots], \end{aligned}$$

where π_{ie} is the individual probability of unit QALYs, which is estimated on the logit scale as a function of a baseline parameter γ_0 and the centred baseline utilities, whose effect is captured by the parameter γ_1. The quantity $\bar{\pi}_e = \frac{\exp(\gamma_0)}{1+\exp(\gamma_0)}$ represents the estimated marginal probability of unit QALYs.

4.2 Missingness Scenarios

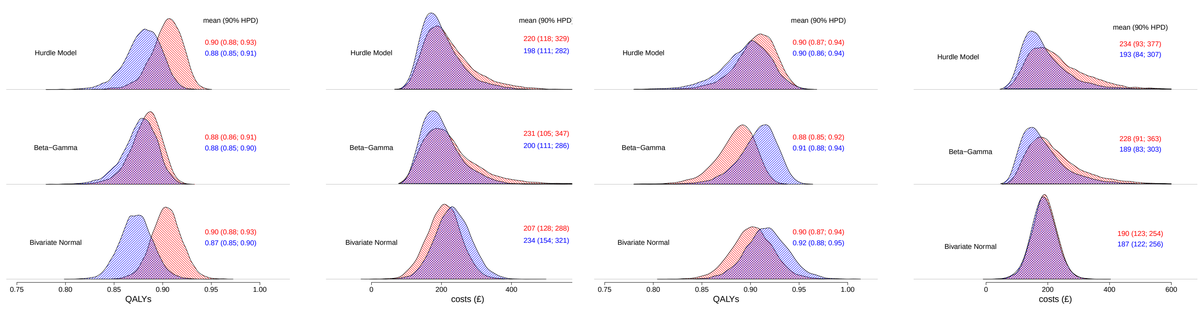
For each model we assume a complete cases scenario and then extend the structure to all cases (complete and missing), considering both MAR (for all models) or alternative MNAR scenarios (for the Hurdle Model only).

- **MAR** – No change to the model structure is required under MAR, but baseline utilities (u_{i0}) need to be explicitly modelled using suitable distributions to impute the missing values (Normal, Beta and Beta-Hurdle for the three specifications, respectively);
- **MNAR** – We observe that $n^*_1 = 13$ (control) and $n^*_2 = 22$ (intervention) individuals have $u_{i0} = 1$ and $u_{ij} = NA$, for $j > 1$. For those individuals, we cannot compute directly the value of d_{ie} and so need to make assumptions/model this → Sensitivity analysis to alternative MNAR departures from MAR. Table 1 shows the four MNAR scenarios considered:

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	$d_{ie} = 0$	$d_{ie} = 1$

Table 1: MNAR scenarios considered in the MenSS study for the Hurdle Model.

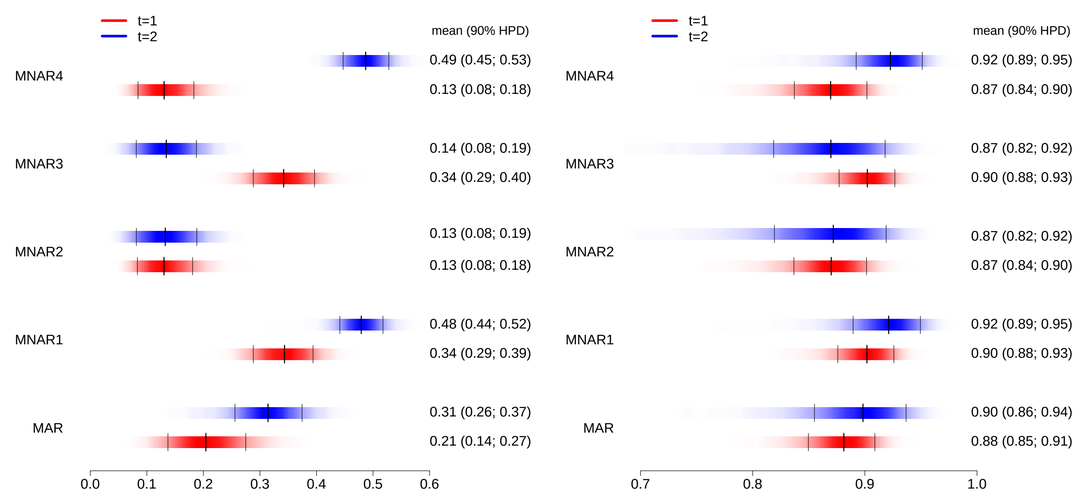
5 Results (Complete and All Cases – MAR)



(a) Control (b) Intervention

Figure 2: Posterior mean QALYs and costs distributions in both arms for the three models

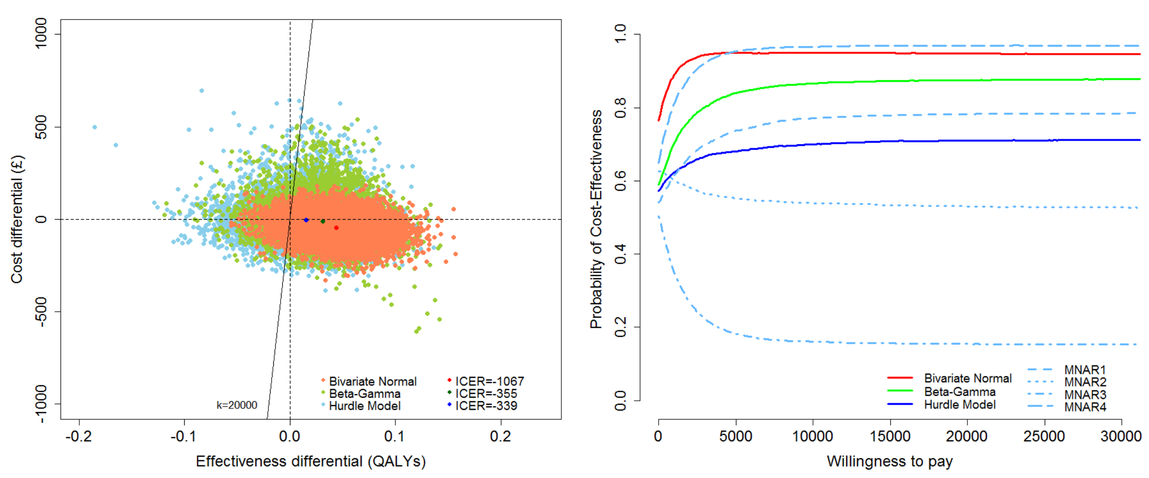
6 Sensitivity Analysis – MNAR



(a) Probability of structural one ($\bar{\pi}_e$) (b) Mean QALYs (μ_e)

Figure 3: Posterior density strips for π_e and μ_e in both arms under MAR and four MNAR scenarios

7 Economic Evaluation



(a) Cost-Effectiveness Plane) (b) Cost-Effectiveness Acceptability Curve)

Figure 4: CEP and CEAC associated with the three models under MAR and four MNAR scenarios

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