Bayesian models for cost-effectiveness analysis in the presence of structural zero costs

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

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Health economic evaluations

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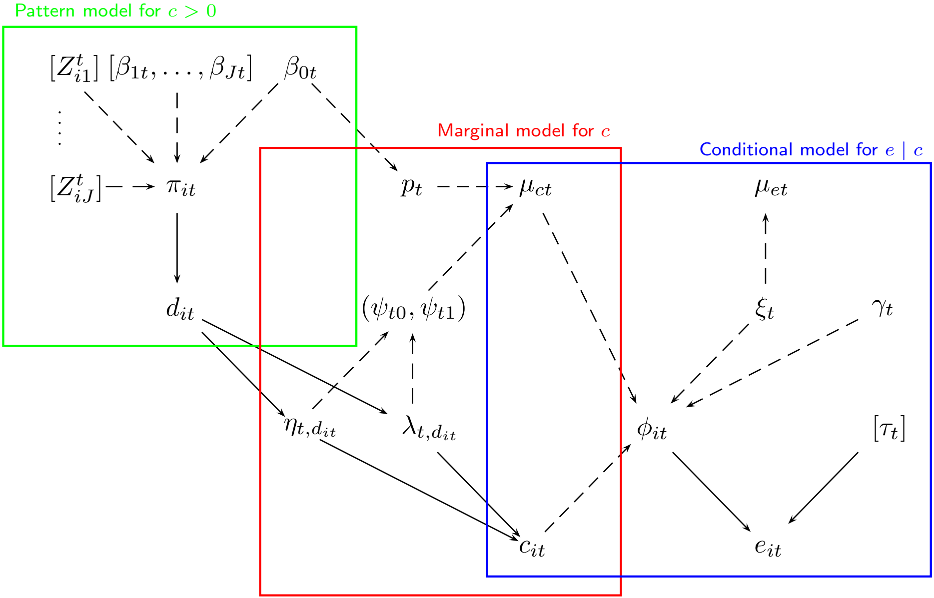
- **Structural zeros**
  - For a proportion of subjects, the observed cost is equal to zero — but Gamma or log-Normal are defined for strictly positive arguments!

  Solutions/limitations
  - Add a small constant ε to all cost (all sorts of problems)
  - Hurdle models (not been extended to a full health economic evaluation)

Modelling framework



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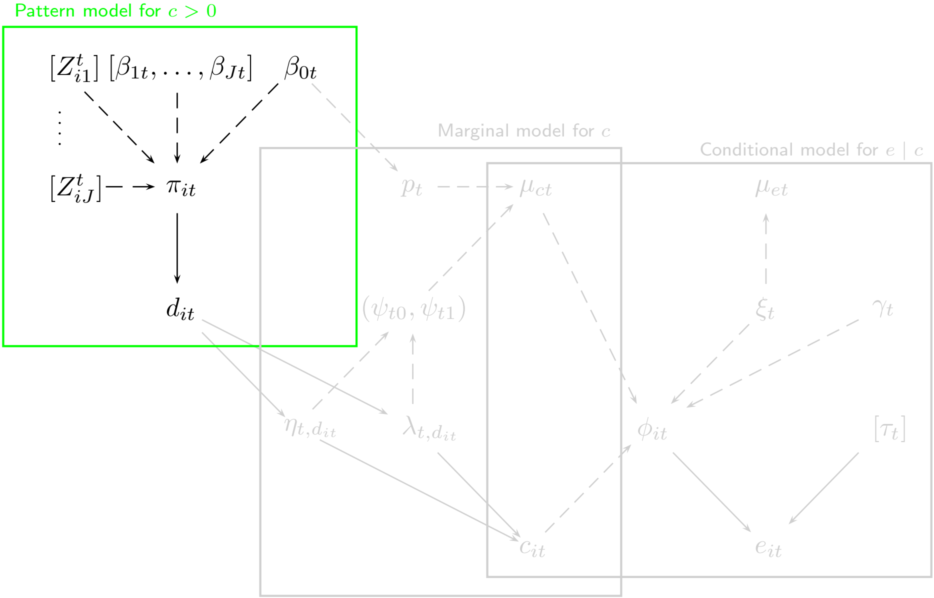

1. (Basic) Pattern model for $c = 0$

- For individual i and treatment t, define a zero cost indicator d_{it} and model

$$d_{it} \sim \text{Bernoulli}(\pi_{it}), \qquad \text{logit}(\pi_{it}) = \beta_{0t} + \sum_{j=1}^{J} \beta_{jt} Z_{ij}^{t}$$

  - π_{it} indicates the individual probability of structural zero
  - $Z_{ij}^t = X_{ij}^t - \text{E}[\boldsymbol{X}_j^t]$ are the **centered** version of some relevant covariates X_{ij}^t

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- Define a prior for the parameters $\boldsymbol\beta_t = (\beta_{0t}, \beta_{1t}, \ldots, \beta_{Jt})$
  - Typically use independent minimally informative Normal
  - If **separation** is a potential issue, can model $\boldsymbol\beta_t \stackrel{iid}{\sim} \text{Cauchy}(0, \kappa)$, where κ is a small scale parameter $\Rightarrow$ more stable estimates

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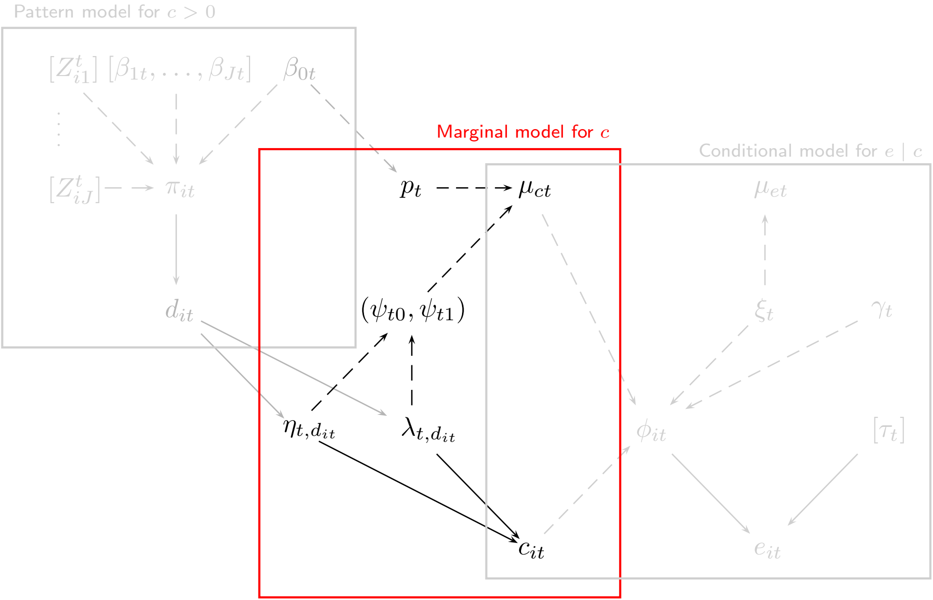
- The **"average"** probability of zero cost is

$$p_t = \frac{\exp(\beta_{0t})}{1 + \exp(\beta_{0t})}$$

  - Can use sub-groups or extend the model (e.g. include "random" effects or more complex structures)

Modelling framework



2. Marginal model for the costs

- For $s = d_{it} = 0, 1$, specify a single distribution indexed by $\boldsymbol\theta_t = (\boldsymbol\theta_t^{\rm pos}, \boldsymbol\theta_t^{\rm null})$

$$c_{it} \mid d_{it} \quad \sim \quad \begin{cases} p(c_{it} \mid d_{it} = 0) = p(c_{it} \mid \boldsymbol\theta_t^{\rm pos}) & \text{skewed, positive} \\ p(c_{it} \mid d_{it} = 1) = p(c_{it} \mid \boldsymbol\theta_t^{\rm null}) & \text{degenerate at 0} \end{cases}$$

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- **Original-scale** vs **natural-scale** parameters
  - $\boldsymbol\theta_t = (\eta_{ts}, \lambda_{ts})$: specific to the chosen density
  - $\boldsymbol\omega_t = h(\boldsymbol\theta_t) = (\psi_{ts}, \zeta_{ts})$ = mean and sd of the costs

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- Gamma model
  - $(\eta_{ts}, \lambda_{ts})$ = shape and rate
  - $\psi_{ts} = \dfrac{\eta_{ts}}{\lambda_{ts}}$ and $\zeta_{ts} = \sqrt{\dfrac{\eta_{ts}}{\lambda_{ts}^2}}$
- log-Normal model
  - $(\eta_{ts}, \lambda_{ts})$ = log-mean and log-sd
  - $\psi_{ts} = \exp\left(\eta_{ts} + \dfrac{\lambda_{ts}^2}{2}\right)$ and $\zeta_{ts} = \sqrt{(\exp(\lambda_{ts}^2) - 1)\exp(2\eta_{ts} + \lambda_{ts}^2)}$

- Much more intuitive to set the priors on $\boldsymbol\omega_t$, e.g.
  - $\psi_{t0} \sim \text{Uniform}(0, H_\psi)$ and $\zeta_{t0} \sim \text{Uniform}(0, H_\zeta)$
  - $\psi_{t1} = w$ and $\zeta_{t1} = W$, $(w, W) \to 0$ — **NB**: this implies $p(c \mid \boldsymbol\theta_t^{\text{null}}) := 0$

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- Since $\boldsymbol\theta_t = h^{-1}(\boldsymbol\omega_t)$, the prior on $\boldsymbol\omega_t$ will automatically induce one for $\boldsymbol\theta_t$
- **NB**: Even if $p(\boldsymbol\omega_t)$ is very vague, the induced $p(\boldsymbol\theta_t)$ may be very informative. But that's OK — however informative, $p(\boldsymbol\theta_t)$ will by necessity be consistent with the substantive knowledge (or lack thereof) we are assuming on $\boldsymbol\omega_t$!

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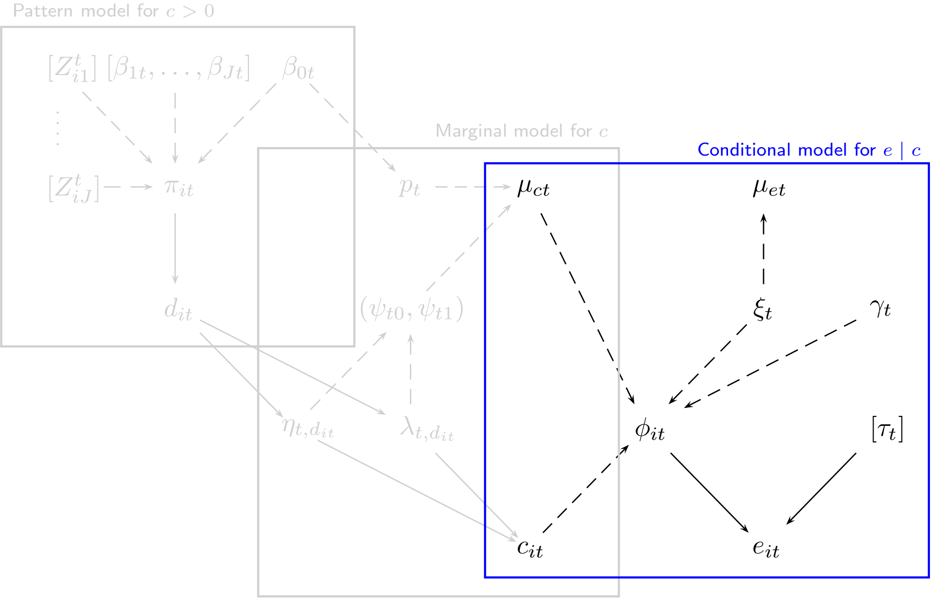
- The overall average cost in the population is

$$\mu_{ct} = (1 - p_t)\psi_{t0} + p_t\psi_{t1} = (1 - p_t)\psi_{t0}$$

where the weights are given by the estimated probability associated with each of the two classes

Modelling framework



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$$g(\phi_{it}) = \xi_t + \gamma_t (c_{it} - \mu_{ct})$$

where

  - ϕ_{it} is the conditional average effectiveness for individual i in arm t
  - $g(\cdot)$ is the link function, depending on the scale in which ϕ_{it} is defined
  - μ_{ct} is the population average cost obtained in the marginal model
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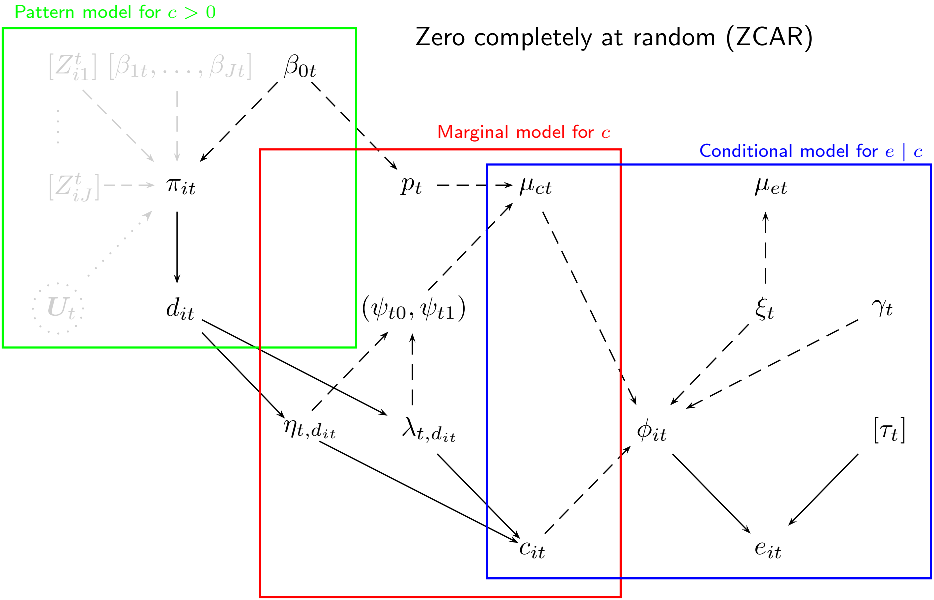
- **NB**: The **marginal** average effectiveness **on the natural scale** is

$$\mu_{et} = g^{-1}(\xi_t)$$

Links with the missing data framework

Zero completely at random (ZCAR)



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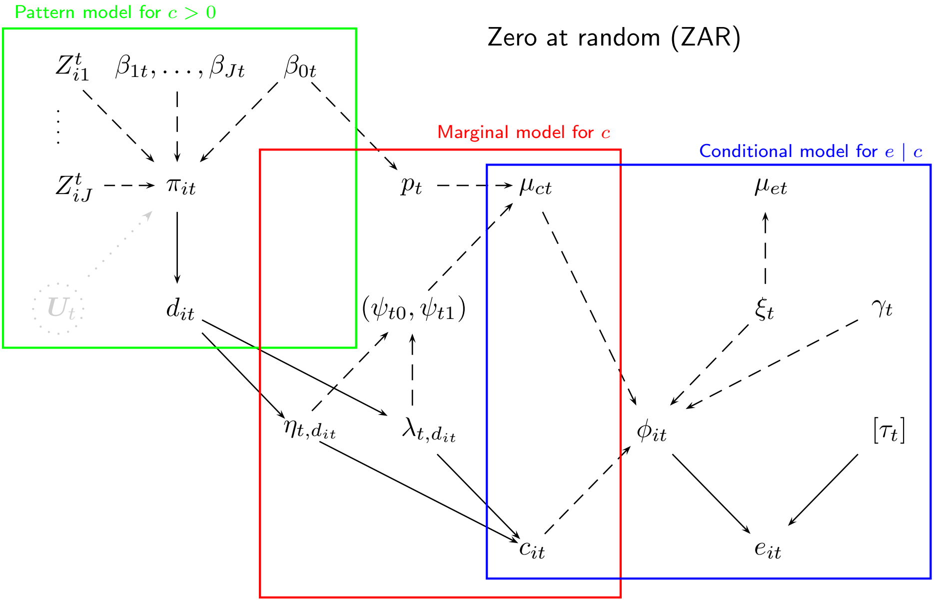

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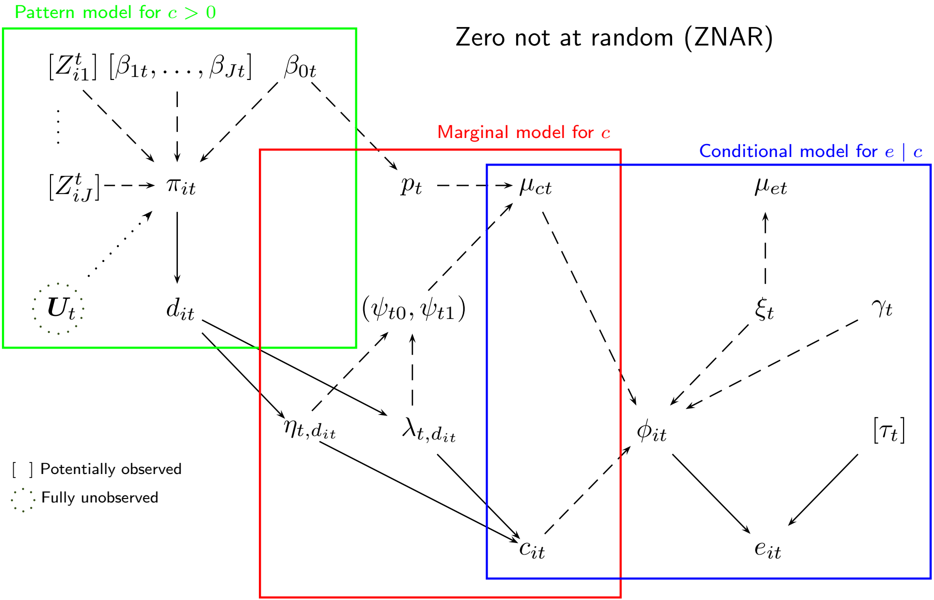

Example: the TOPICAL trial

- Double blind, multicenter, phase III RCT on non-small lung cancer patients
- Data available on a subsample of 228 patients
  - 120 with placebo ($t = 0$)
  - 108 with erlotinib 150mg/day ($t = 1$)
- Measure of effectiveness: total QALYs gained
  - **NB**: Annual time-horizon $\Rightarrow$ QALYs $\in [0; 1]$
- Overall cost calculated adding up several resources
- Additional information available on
  - $\boldsymbol{X}_1^t$ = age
  - $\boldsymbol{X}_2^t$ = sex (female = 0, male = 1)
  - $\boldsymbol{X}_3^t$ = baseline stage of disease (IIIb = 0, IV = 1)
  - $\boldsymbol{X}_4^t$ = pre-progression quality of life
- Run the model under both ZCAR and ZAR

Model specification

Pattern model for $c = 0$

- $d_{it} \sim \text{Bernoulli}(\pi_{it})$
- $\text{logit}(\pi_{it}) = \beta_{0t} \left[+ \sum_{j=1}^{4} \beta_{jt} Z_{ij}^{t} \right], \qquad \boldsymbol{\beta}_t \sim \text{Cauchy}(0, 2.5)$
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- For both the Gamma and logNormal model
  - $w = W = 0.000001$ + sensitivity analysis
  - $H_\psi = 50\,000$ and $H_\zeta = 15\,000$

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Conditional model for the QALYs

- Beta regression
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  - $\text{logit}(\phi_{it}) = \xi_t + \gamma_t(c_{it} - \mu_{ct})$
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  - $\xi_t, \gamma_t, \log(\tau_t) \stackrel{iid}{\sim} \text{Normal}(0, 10\,000)$

Results — model estimation

ZCAR mechanism	Gamma/Beta model				log-Normal/Beta model			
Parameter	Mean	SD	95% interval		Mean	SD	95% interval	
p_0	0.17	0.04	0.11	0.24	0.17	0.03	0.11	0.24
ψ_{00}	4 069.95	512.85	3 190.65	5 166.28	4 312.52	461.62	3 358.93	5 176.79
μ_{c0}	3 373.55	444.88	2 571.21	4 315.12	3 583.45	411.49	2 770.08	4 385.66
μ_{e0}	0.21	0.02	0.18	0.25	0.22	0.02	0.18	0.25
p_1	0.04	0.02	0.01	0.09	0.04	0.02	0.01	0.08
ψ_{10}	10 356.47	1 060.49	8 463.40	12 653.51	9 321.01	717.66	7 884.13	10 681.00
μ_{c1}	9 930.72	1 032.05	8 082.63	12 155.24	8 939.05	707.12	7 551.40	10 284.65
μ_{e1}	0.23	0.02	0.19	0.27	0.22	0.02	0.19	0.25

ZAR mechanism	Gamma/Beta model				log-Normal/Beta model			
Parameter	Mean	SD	95% interval		Mean	SD	95% interval	
β_{00} (intercept)	–2.70	0.53	–3.88	–1.78	–2.68	0.53	–3.86	–1.78
β_{10} (age)	–0.03	0.04	–0.10	0.05	–0.03	0.04	–0.10	0.05
β_{20} (sex)	0.63	0.57	–0.47	1.8	0.62	0.60	–0.48	1.88
β_{30} (stage)	0.09	0.61	–1.15	1.20	0.06	0.59	–1.05	1.26
β_{40} (QALY)	–1.61	0.50	–2.70	–0.73	–1.58	0.51	–2.72	–0.72
p_0	0.07	0.03	0.02	0.14	0.07	0.03	0.02	0.14
ψ_{00}	4 104.42	556.05	3 159.00	5 370.27	4 322.24	467.200	3 342.10	5 193.25
μ_{c0}	3 817.95	537.16	2 905.75	4 989.01	4 014.76	467.52	3 068.24	4 903.59
μ_{e0}	0.21	0.02	0.12	0.25	0.21	0.02	0.18	0.25
β_{01} (intercept)	–3.86	0.66	–5.34	–2.73	–3.85	0.67	–5.31	–2.73
β_{11} (age)	–0.09	0.09	–0.28	0.12	–0.09	0.10	–0.27	0.10
β_{21} (sex)	–0.35	0.99	–2.23	1.63	–0.27	0.94	–2.16	1.73
β_{31} (stage)	0.61	1.13	–1.43	3.21	0.63	1.12	–1.24	3.15
β_{41} (QALY)	–0.12	0.31	–0.81	0.39	–0.14	0.31	–0.88	0.37
p_1	0.02	0.01	0.00	0.06	0.02	0.01	0.00	0.06
ψ_{10}	10 376.91	1 035.29	8 550.78	12 571.45	9 320.26	710.00	7 777.58	10 659.33
μ_{c1}	10 119.80	1 022.73	8 367.69	12 329.24	9 086.38	701.03	7 594.49	10 362.48
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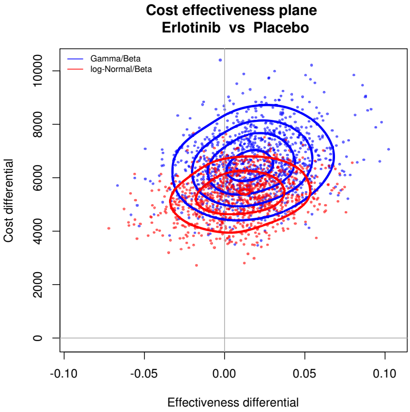
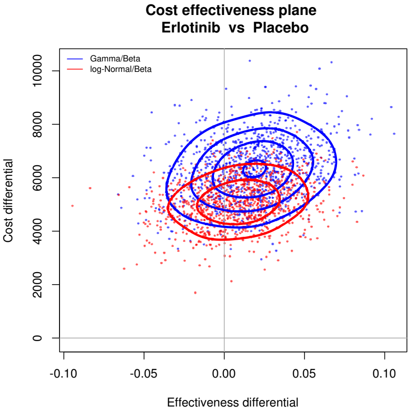
μ_{e0}	0.21	0.02	0.18	0.25	0.22	0.02	0.18	0.25
p_1	0.04	0.02	0.01	0.09	0.04	0.02	0.01	0.08
ψ_{10}	10 356.47	1 060.49	8 463.40	12 653.51	9 321.01	717.66	7 884.13	10 681.00
μ_{c1}	9 930.72	1 032.05	8 082.63	12 155.24	8 939.05	707.12	7 551.40	10 284.65
μ_{e1}	0.23	0.02	0.19	0.27	0.22	0.02	0.19	0.25

ZAR mechanism	Gamma/Beta model				log-Normal/Beta model			
Parameter	Mean	SD	95% interval		Mean	SD	95% interval	
β_{00} (intercept)	–2.70	0.53	–3.88	–1.78	–2.68	0.53	–3.86	–1.78
β_{10} (age)	–0.03	0.04	–0.10	0.05	–0.03	0.04	–0.10	0.05
β_{20} (sex)	0.63	0.57	–0.47	1.8	0.62	0.60	–0.48	1.88
β_{30} (stage)	0.09	0.61	–1.15	1.20	0.06	0.59	–1.05	1.26
β_{40} (QALY)	–1.61	0.50	–2.70	–0.73	–1.58	0.51	–2.72	–0.72
p_0	0.07	0.03	0.02	0.14	0.07	0.03	0.02	0.14
ψ_{00}	4 104.42	556.05	3 159.00	5 370.27	4 322.24	467.200	3 342.10	5 193.25
μ_{c0}	3 817.95	537.16	2 905.75	4 989.01	4 014.76	467.52	3 068.24	4 903.59
μ_{e0}	0.21	0.02	0.12	0.25	0.21	0.02	0.18	0.25
β_{01} (intercept)	–3.86	0.66	–5.34	–2.73	–3.85	0.67	–5.31	–2.73
β_{11} (age)	–0.09	0.09	–0.28	0.12	–0.09	0.10	–0.27	0.10
β_{21} (sex)	–0.35	0.99	–2.23	1.63	–0.27	0.94	–2.16	1.73
β_{31} (stage)	0.61	1.13	–1.43	3.21	0.63	1.12	–1.24	3.15
β_{41} (QALY)	–0.12	0.31	–0.81	0.39	–0.14	0.31	–0.88	0.37
p_1	0.02	0.01	0.00	0.06	0.02	0.01	0.00	0.06
ψ_{10}	10 376.91	1 035.29	8 550.78	12 571.45	9 320.26	710.00	7 777.58	10 659.33
μ_{c1}	10 119.80	1 022.73	8 367.69	12 329.24	9 086.38	701.03	7 594.49	10 362.48
μ_{e1}	0.23	0.02	0.19	0.27	0.22	0.02	0.19	0.26

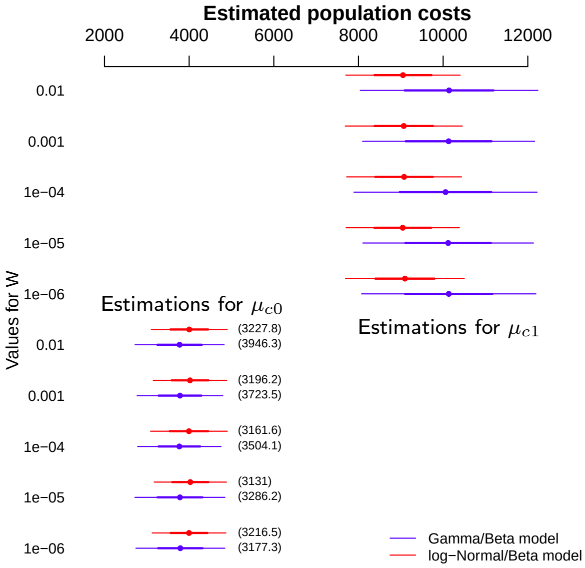
ZCAR mechanism



ZAR mechanism



Sensitivity to the specification for (ψ_{t1}, ζ_{t1})



The BCEs0 package for R

- The package BCEs0 implements the general framework
  - Freely available from CRAN
  - Documentation at www.statistica.it/gianluca/BCEs0
- The user needs to specify some basic options
  - Distributional assumption for the costs (Gamma, logNormal, Normal)
  - Distributional assumption for the benefits (Gamma, Beta, Binomial, Normal)
  - A list of data
  - ...
- BECs0 then writes a .txt file with the resulting JAGS/BUGS code needed to run the model
- This can be used as a template
  - To develop more complex analyses
  - To encode more suitable assumptions (eg random effects)

Thank you!