Joint Survival and QOL Modeling of PARTNER Data

Jacob Spertus

Sections

- Background
- Notation and Model
- MCMC Fitting
- Model Checking
- Inference

Why Do Joint Modeling?

- Ibrahim, Chu, and Chen 2010 (Oncology):

1. More efficient treatment effect on survival estimates
2. More efficient effect on longitudinal QOL estimates
3. Reduced bias on "overall" treatment effect (survival and longitudinal)
4. Incorporating survival information into longitudinal estimates accounts for informative missing data due to death (Gould et al, 2015)

These qualities mean that an RCT has more power, so it can rely on a smaller sample size to achieve a given level of precision.

Past Focuses

- Much past research has focused on reducing bias and variance of the estimated effect on survival (Gould et al, 2015) (β_T)
- A few researchers have focused more on longitudinal component (McCardle et al, 2005) (γ_0 and γ_1)
- Interest has recently surrounded magnitude of association between longitudinal and survival components (θ_{0i}, θ_{1i}, β_θ)
- Much development has been in oncology and AIDS research, with past joint modeling practices and guidelines reflecting idiosyncracies of those fields.
- We would like to develop methods specifically with cardiological applications in mind.

A QOL and Survival Model

$i \in \{1, ..., I\}$ indexes subjects; $j \in \{1, .., J\}$ indexes time points. Y_{ij} gives the KCCQOS score at time j for subject i; T_i is treatment; S_i is survival time and is possibly right censored.

$$Y_{ij} = \mu_{\theta_0} + \theta_{0i} + \mu_{\theta_1} j + \theta_{1i} j + \gamma_0 T_i + \gamma_1 T_i j + \epsilon_{ij} \quad (1)$$

$$S_i \sim \text{Weibull}\{\alpha, \exp(-(\beta_0 + \beta_T \cdot T_i + \beta_{\theta_0} \cdot \theta_{0i} + \beta_{\theta_1} \cdot \theta_{1i}))\} \quad (2)$$

$$\epsilon_{ij} \sim \mathcal{N}(0, \sigma^2) \quad (3)$$

$$\theta_{0i} \sim \mathcal{N}(0, \sigma^2_{\theta_0}) \quad (4)$$

$$\theta_{1i} \sim \mathcal{N}(0, \sigma^2_{\theta_1}) \quad (5)$$

$$[\mu_{\theta_0}, \mu_{\theta_1}] \sim \mathcal{N}(0, 1) \quad (6)$$

$$[\gamma_0, \gamma_1] \sim \mathcal{N}(0, 1) \quad (7)$$

$$[\beta_{\theta_0}, \beta_{\theta_1}] \sim \mathcal{N}(0, 1) \quad (8)$$

$$[\beta_T, \beta_0] \sim \mathcal{N}(0, 10) \quad (9)$$

$$[\sigma, \sigma_{\theta_0}, \sigma_{\theta_1}] \sim t_3^+(0, 1) \quad (10)$$

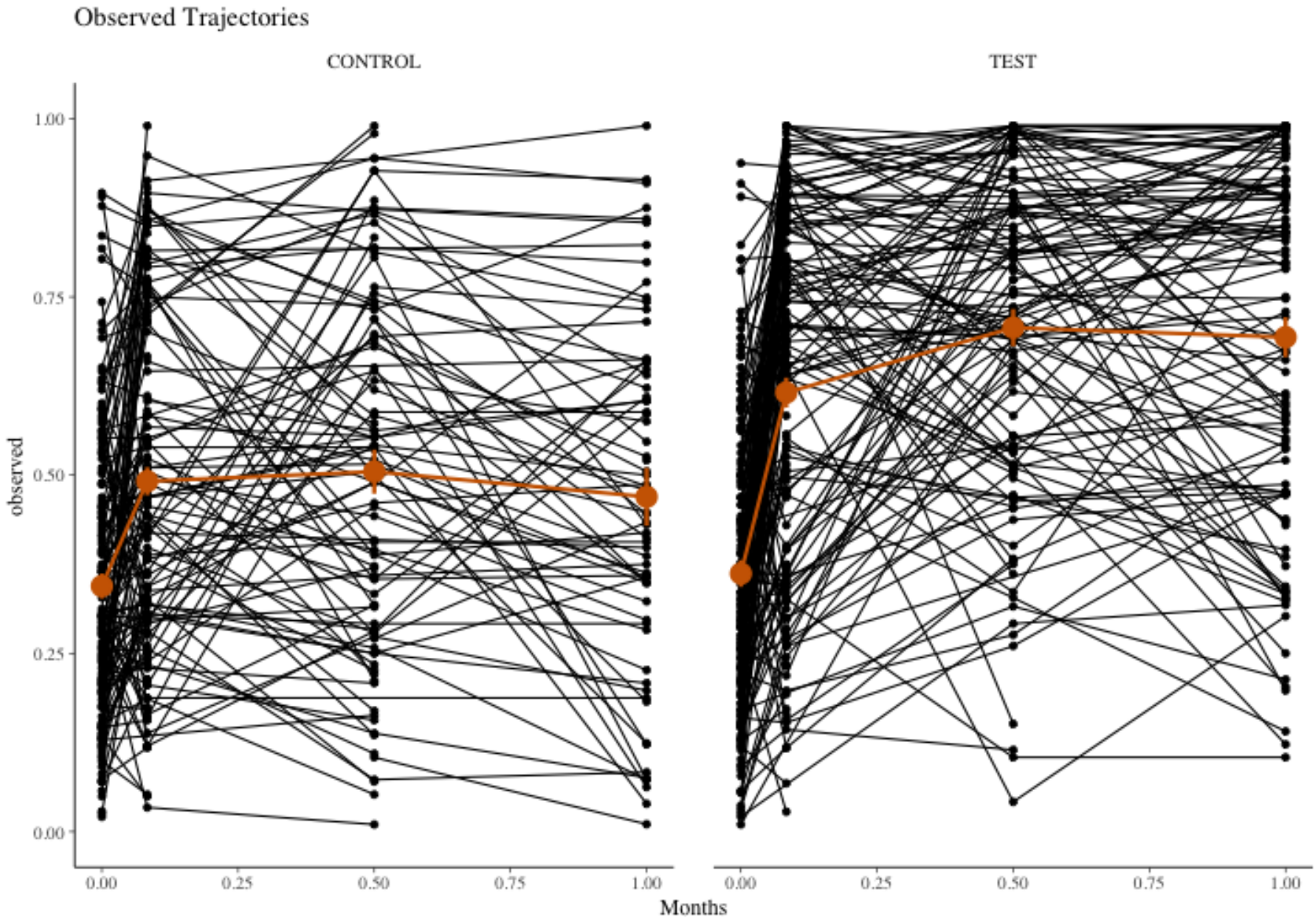
$$\alpha \sim \mathcal{N}^+(0, 10) \quad (11)$$

PARTNER Data

- Transcatheter aortic valve replacement (TAVR) in patients not eligible for surgical valve replacement
- $n_1 = 179$ were randomized to TAVR and $n_0 = 179$ were randomized to standard therapy
- Quality-of-life (QOL) data collected using Kansas City Cardiomyopathy Questionnaire (KCCQ) at 0, 1, 6, and 12 months
- Survival data was also recorded, and all subjects were followed for at least 1-year after implantation
- Initial analyses showed substantially improved QOL and reduction in mortality due to treatment (Reynolds et al 2011, Leon et al 2010).
- Hazard ratio: 0.55 (95% CI, 0.40-0.74)
- 6-month KCCQ summary difference: 21 points (95% CI, 15-27)

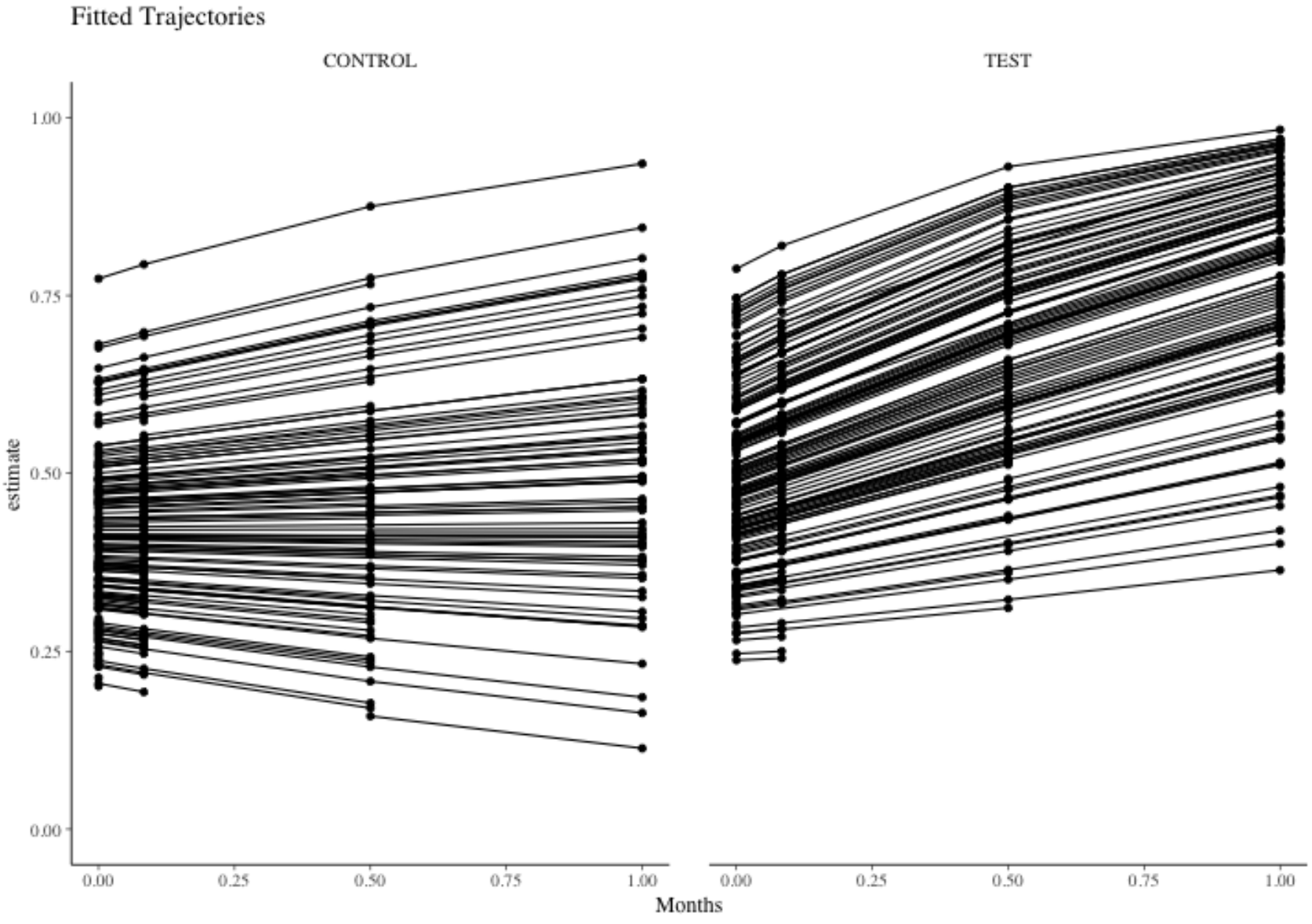
Observed Trajectories

The trajectories observed in the data. Monthly averages are overlayed in orange.



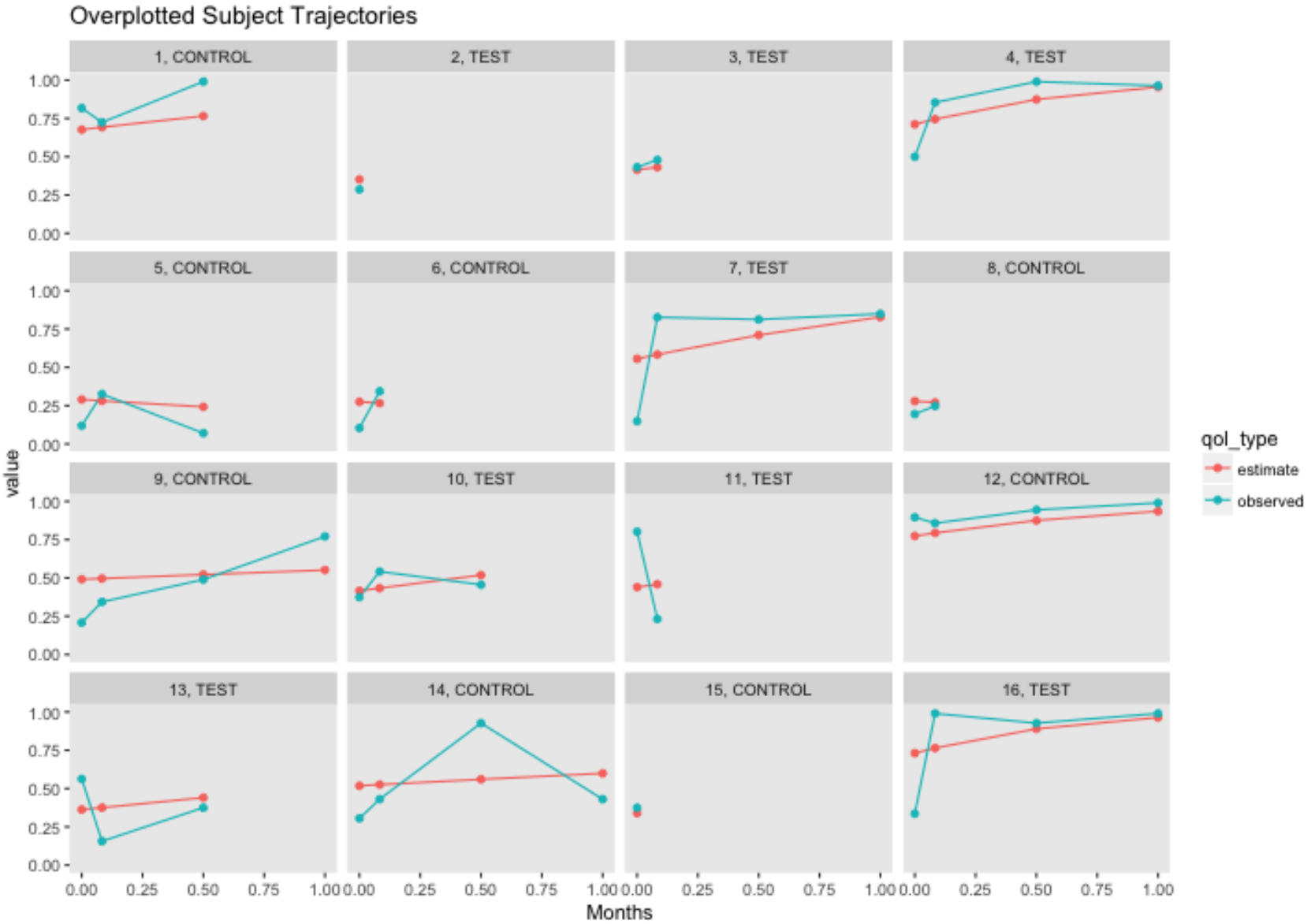
Linear Predictors

Predicted trajectories for individuals estimated from the model.



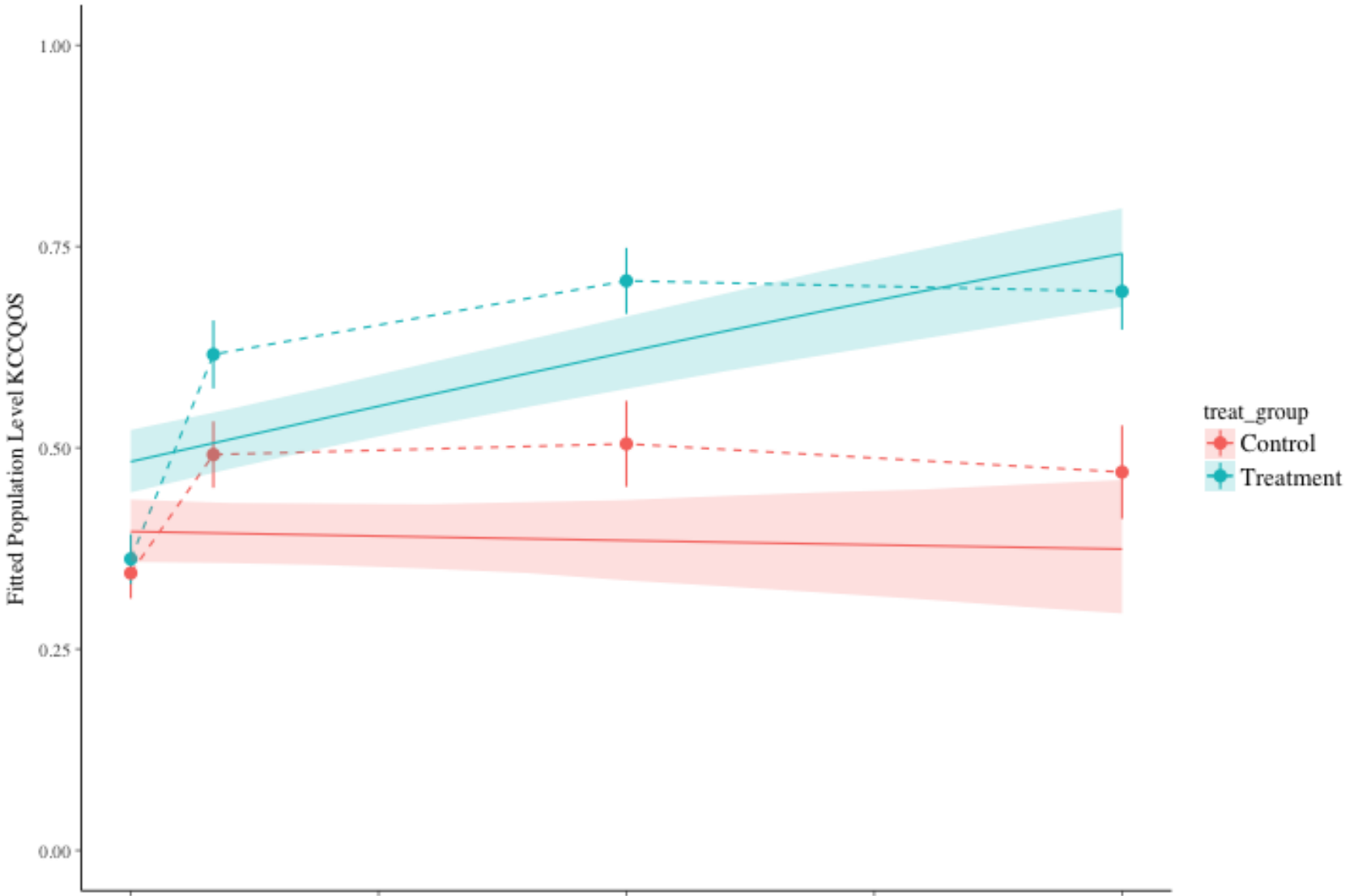
Individual Trajectories

Predicted trajectories overlayed with observed trajectories for 16 individual subjects.



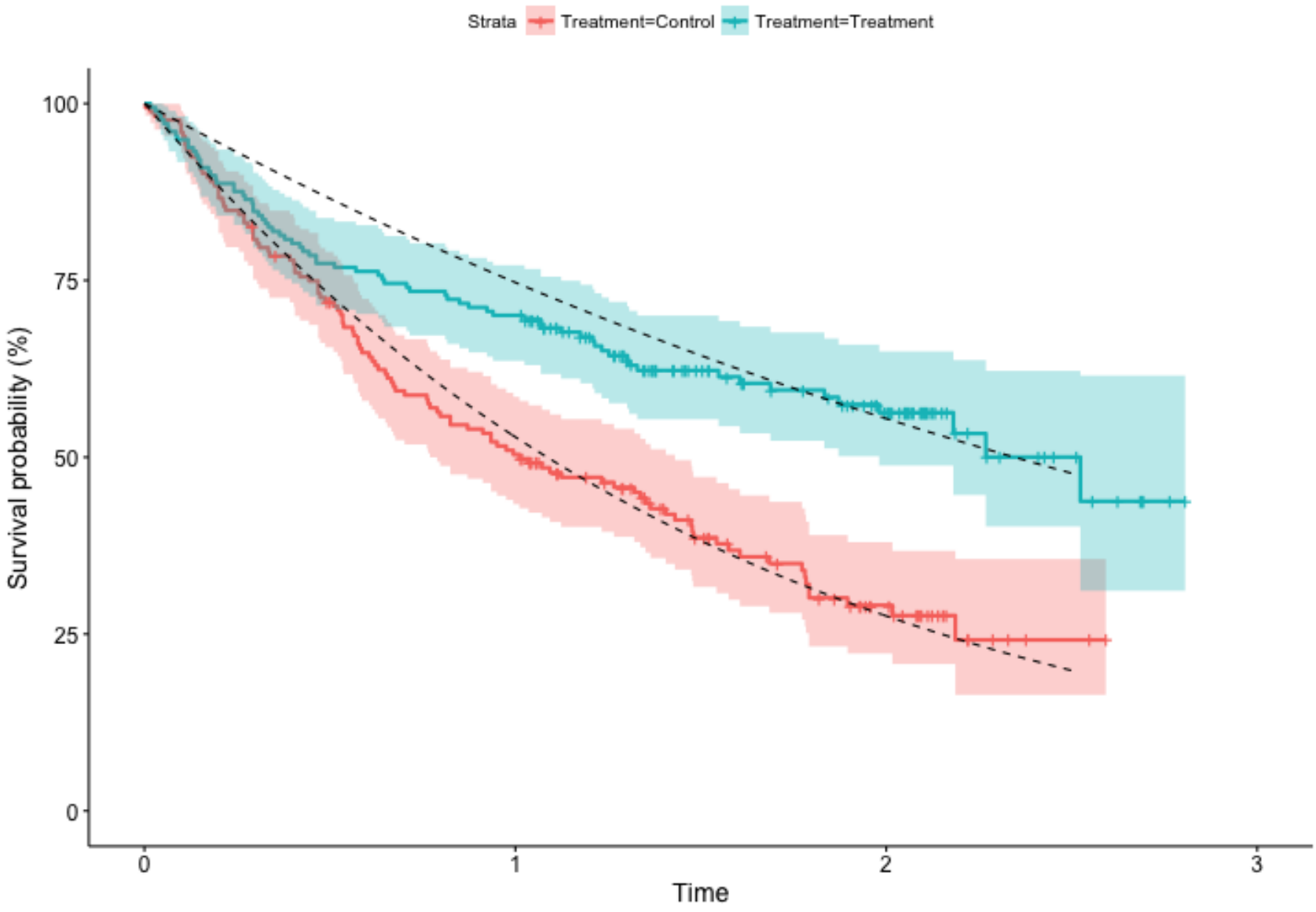
Population Level QOL Curves

The dotted lines and points with error bars are average observed KCCQOS values with 95% credible intervals. Solid lines are model estimates with 95% credible intervals.



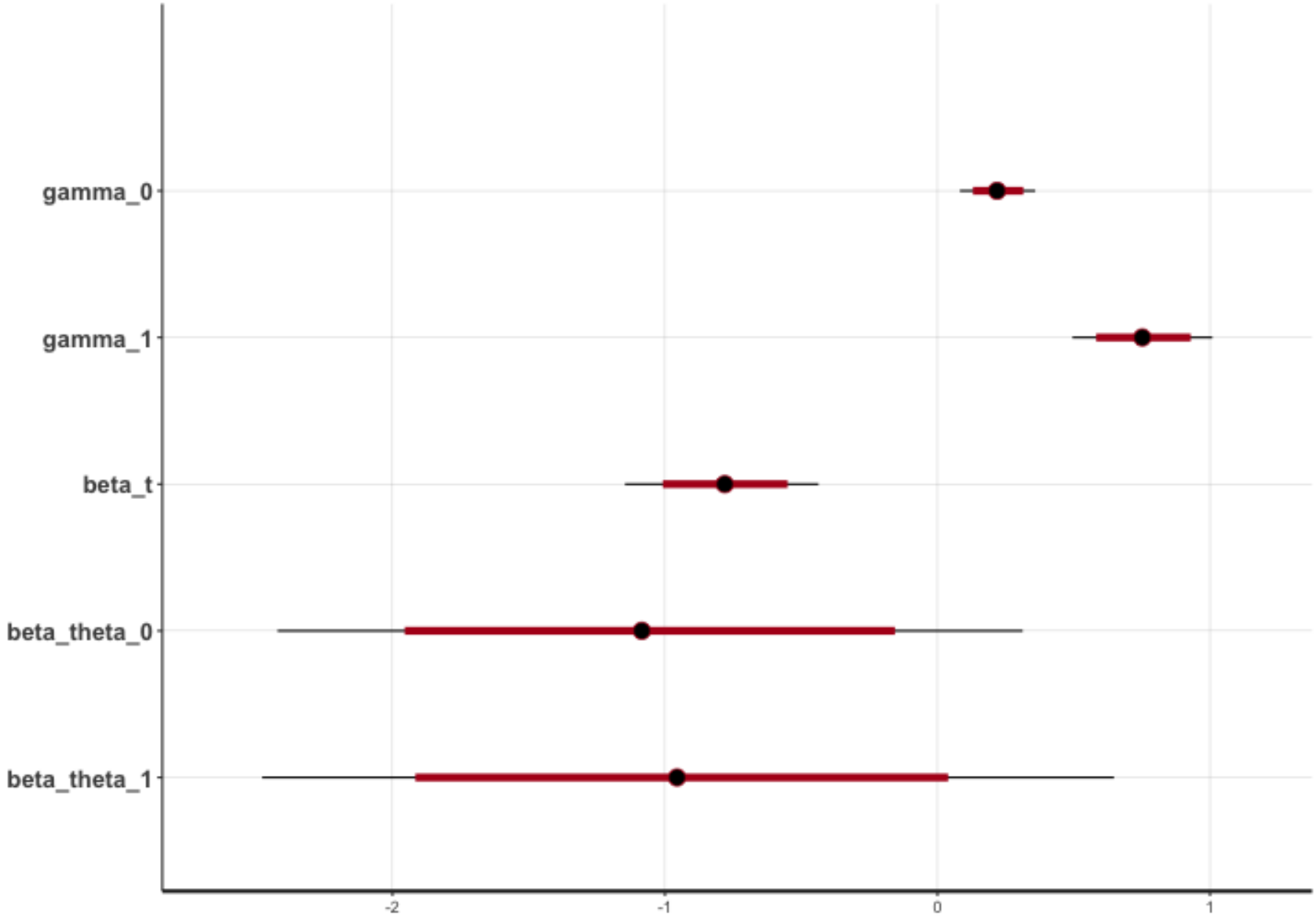
Survival Curves

Observed Kaplan-Meier and estimated Weibull survival curves, for each treatment group.



Forest Plots for Key Parameters

Treatment parameters γ_0, γ_1 and β_T are of key interest.



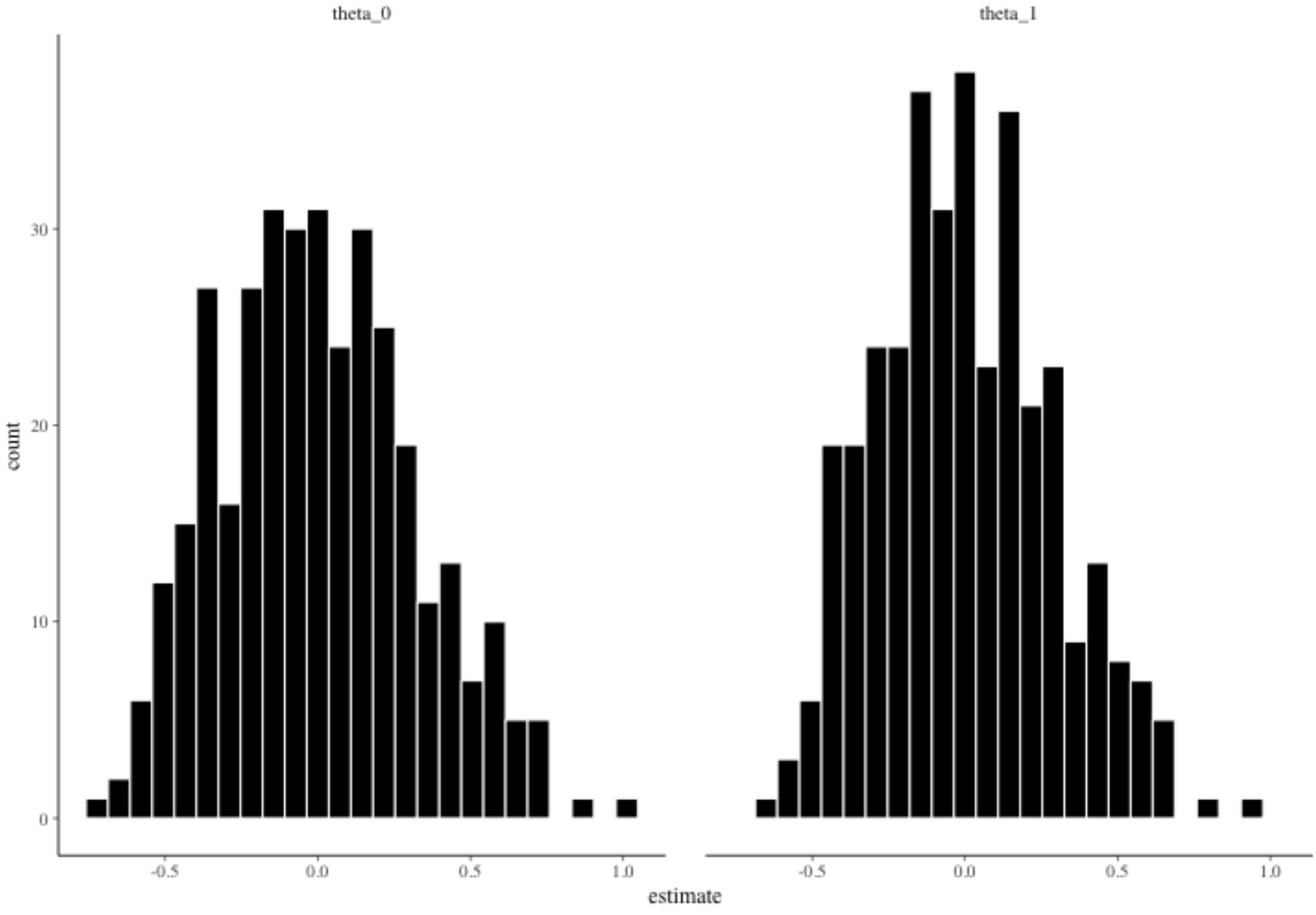
Key Parameters

The posterior mean for γ_0 is 0.22 (95% CI: 0.08, 0.36). Under the model, subjects in the treatment group have an average 6-month QOL of 0.62 compared to 0.38 in the control group, a difference of 0.25.

On the hazard ratio scale, the posterior mean for β_T is 0.46 (95% CI: 0.32, 0.65). The posterior mean for β_{θ_0} is 0.35 (95% CI: 0.09, 1.37), and for β_{θ_1} is 0.39 (95% CI: 0.08, 1.91). Ths although the estimated hazard for β_{θ_0} is low, it is important to note that there is considerable uncertainty in this estimate. The estimate for β_{θ_1} is even more uncertain, and the credible intervals are almost completely uninformative.

Posterior Mean Thetas

The distributions of θ_0 and θ_1 appear below:



Inferential Conclusions

A (relatively very healthy) subject with a θ_{0i} value of 1, which puts them at a mean predicted baseline QOL of 0.77 in the control group or 0.83 in the treatment group, multiplies their hazard by 0.35 (95% CI: 0.09, 1.37). In other words, due to their high baseline QOL, these patients have under half the risk of mortality as a patient with average QOL (with considerable uncertainty however).

β_T tells us how treatment impacts survival. The hazard ratio for treatment of 0.46 (95% CrI: 0.32,0.65) tells us that treatment basically halves the risk of mortality over time. In the original partner trial reported in NEJM, analysis indicated a hazard (at 1 year) of .55 (95% CI: .40, .74).

Further Questions

1. R packages for fitting and inference (`rstan`, `JMBayes`, etc)
2. Other specifications: Cox survival, joint trajectory, covariates