Supplementary Materials for "Bayesian Phase I/II Biomarker-based Dose Finding for Precision Medicine with Molecularly Targeted Agents"

Table 1: True model parameters for the eight scenarios

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
$\beta_{T,0,1}$	-0.2	1.5	1.8	0.56
$\beta_{T,0,2}$	2.3	3.5	3.5	3.06
$\beta_{T,1}$	1	-3.18	-3.18	-0.4
$\boldsymbol{\beta}_{T,2}$	-0.2, 0, 0, 0, -0.2	0, 0, 0, 0, 0	1, 0, 1, 0, 0	0, 0, 0, -0.3, 0
$\boldsymbol{\beta}_{T,3}$	-0.7, -0.6, 0, -1, -2	0, 0, 2, 0, 0	-1, 0, 0, 0, 0	0, 0, 0, 0, -2.5
$\beta_{E,0,1}$	-0.4	-1.5	-1.5	0
$\beta_{E,0,2}$	0.9	0.5	0.5	1.5
$\beta_{E,1}$	1.4	-2	-2	-1.5
$\boldsymbol{\beta}_{E,2}$	-0.6, 0, -1, 0, 0	2, -0.2, 1, 1, 0	1.5, 0, 1.5, 0, 0	0.4, -0.44, 0.2, 0, -0.5
$\boldsymbol{\beta}_{E,3}$	-1, 0, 0, -2, 0	-3, -0.2, 3, 0.1, -0.2	-2.4, 0, 2.7, 0, 0	-2, 0, 0.5, -0.6, -0.7
τ	-1	2	2	-3
σ^2	0.5	0.5	0.2	1

	Scenario 5	Scenario 6	Scenario 7	Scenario 8
$\beta_{T,0,1}$	-0.2	0.4	1.8	0.28
$\beta_{T,0,2}$	2.3	2.9	3.5	1.48
$\beta_{T,1}$	1	-0.4	-3.18	1.2
$\boldsymbol{\beta}_{T,2}$	0.5, -0.45, 0.1, 0, 0.1	0, 0, 0, -0.3, 0	1, 0, 1, 0, 0	0.45, -0.4, 0.05, 0, 0.15
$\boldsymbol{\beta}_{T,3}$	-0.7, -0.6, 0, -0.1, -1	0, 0, 0, 0, -1.5	-1, 0, 0, 0, 0	0, 0, 0, 0, 0
$\beta_{E,0,1}$	-0.4	0.1	21.3	4.5
$\beta_{E,0,2}$	0.9	1.6	22.8	5.7
$\beta_{E,1}$	1.4	-1.5	1.8	-1.4
$\boldsymbol{\beta}_{E,2}$	-0.6, 0.2, -1, -0.3, 0.2	0, 0, 0.2, 0, -0.5	-7.5, -8, -7.5, 0, 0	-4[a], 0, 0, 3, 0
$\boldsymbol{\beta}_{E,3}$	1.1, -1, 0, -2, -0.1	0, 0, 0, 0, 2	-2, 3.5, 3, -1, 0	0, 0, 0, 0, 0
τ	-1	-3	2	0
σ^2	0.5	1	0.2	0.4

[a] -4 is the coefficient of the indicator of whether there is any alteration in the first 3 biomarkers

Figure 1: Probability of efficacy category 3 of the five doses for 16 biomarker patterns under the eight scenarios. Each sub-figure is for one biomarker pattern, which is listed on top. The eight curves represent the eight scenarios.

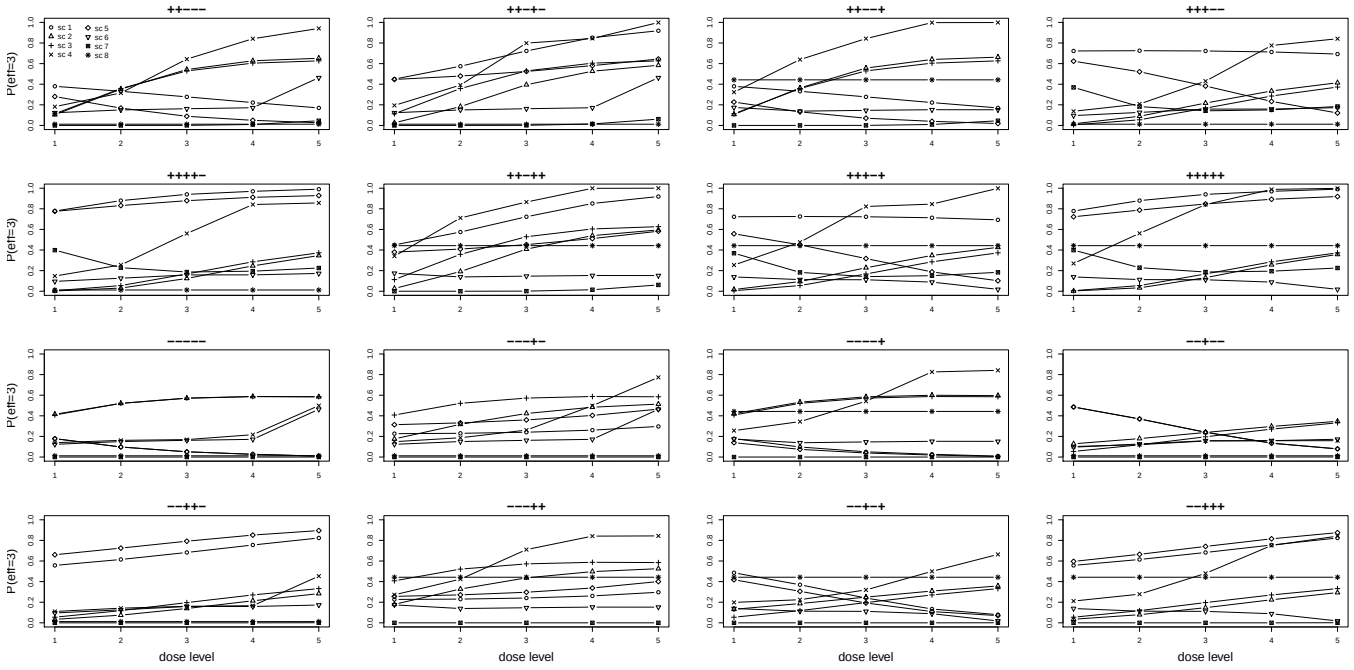


Figure 2: Probability of efficacy category 2 of the five doses for 16 biomarker patterns under the eight scenarios. Each sub-figure is for one biomarker pattern, which is listed on top. The eight curves represent the eight scenarios.

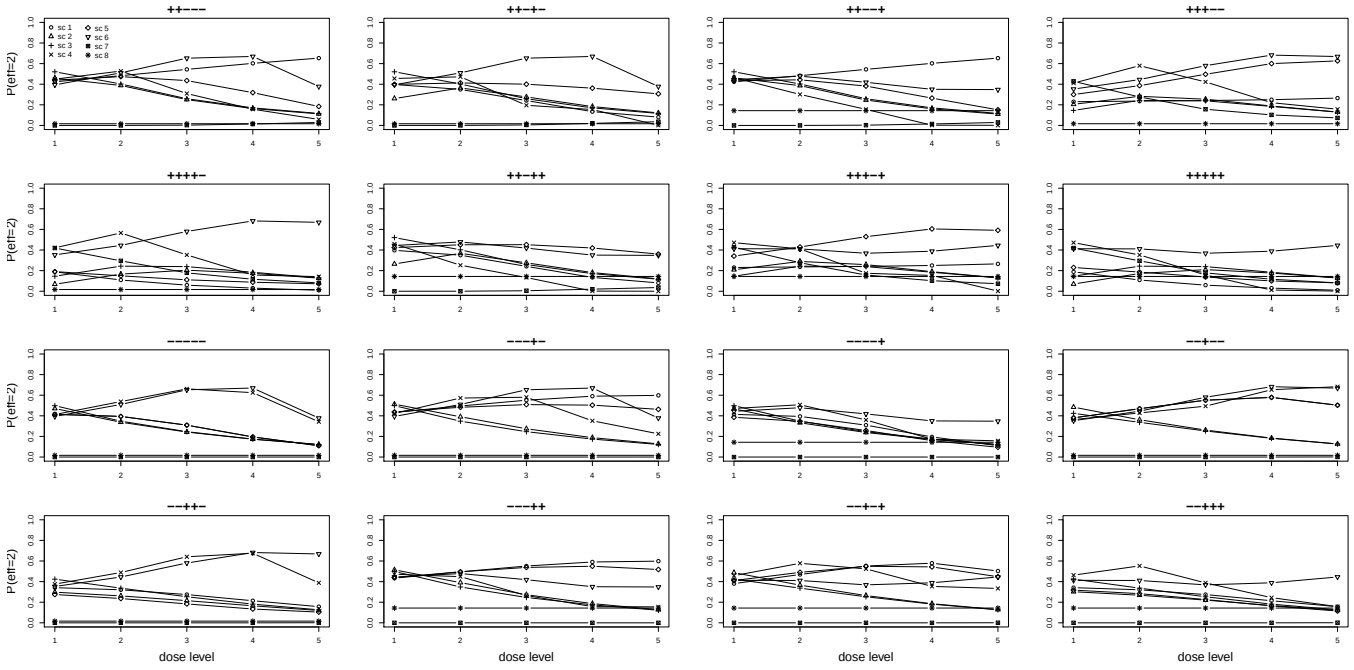


Figure 3: Probability of toxicity category 3 of the five doses for 16 biomarker patterns under the eight scenarios. Each sub-figure is for one biomarker pattern, which is listed on top. The eight curves represent the eight scenarios.

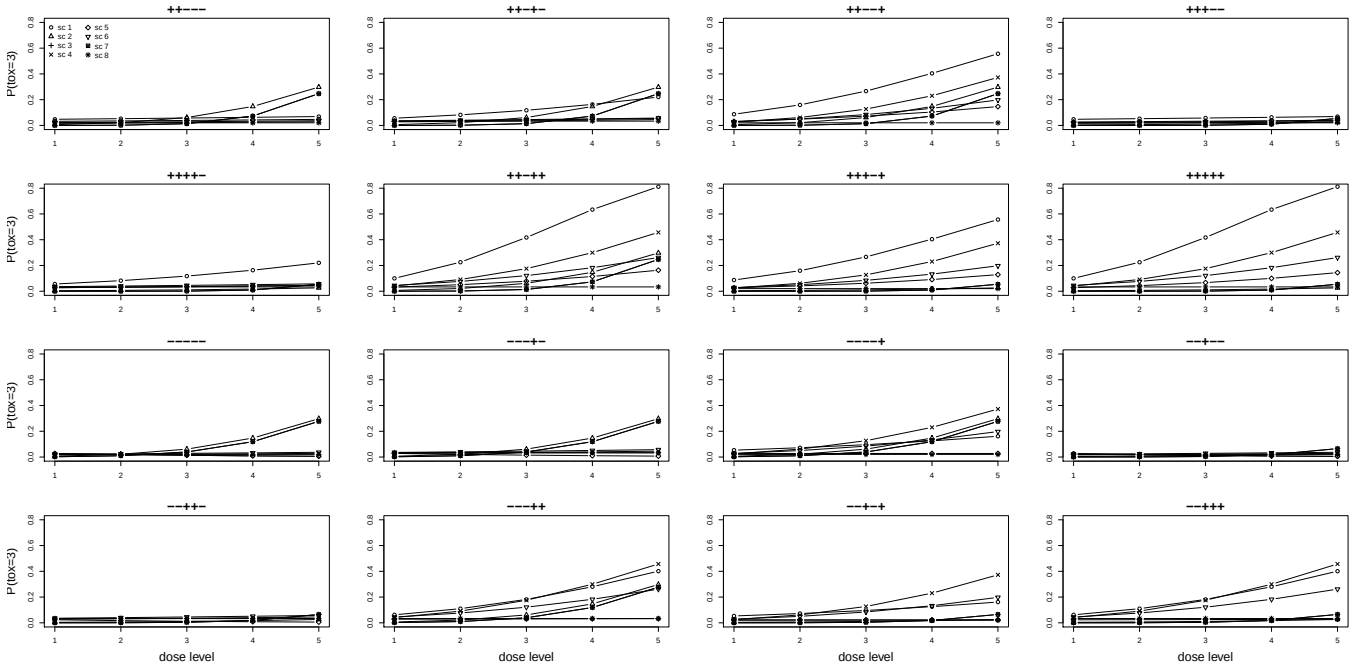


Figure 4: Bias of toxicity and efficacy probabilities for scenarios 1 to 4

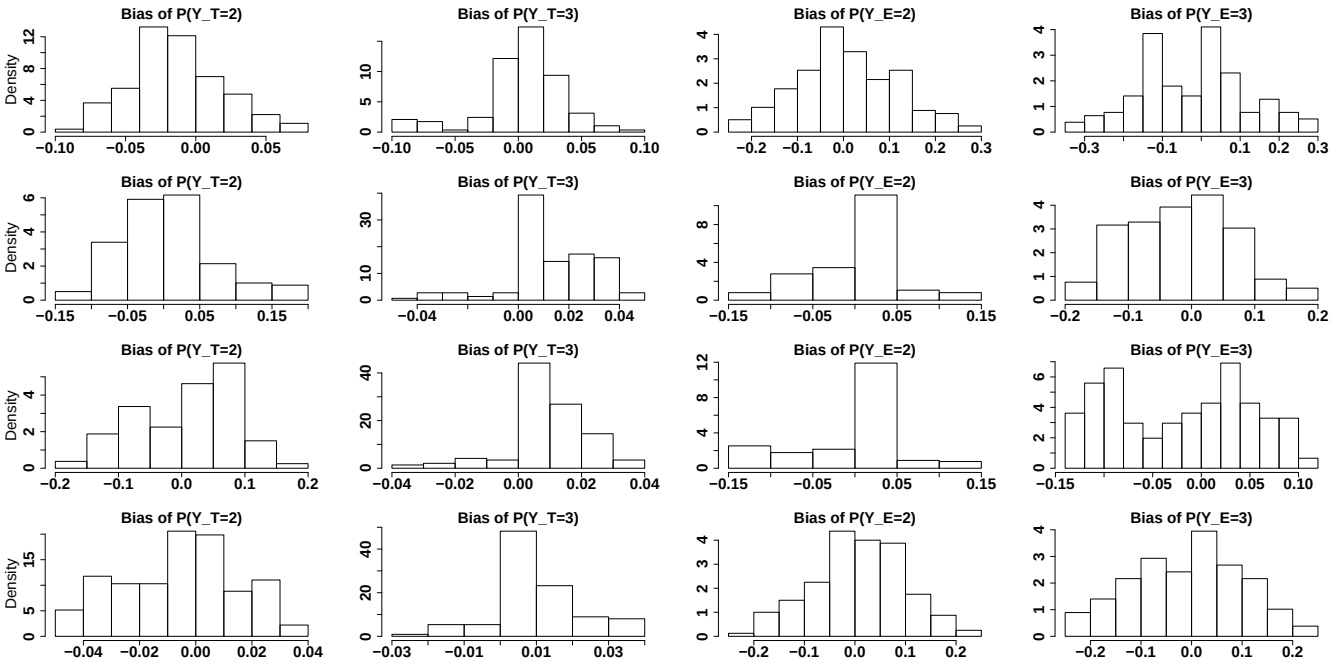
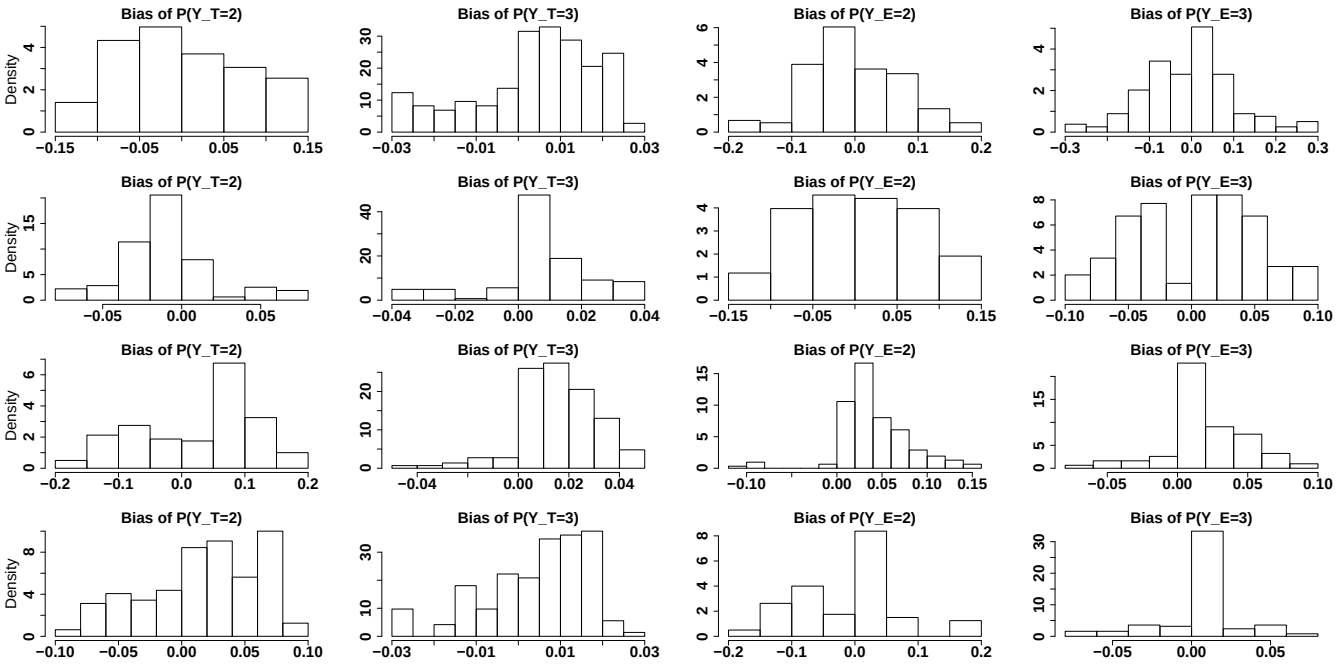


Figure 5: Bias of toxicity and efficacy probabilities for scenarios 5 to 8



Evaluation of the robustness of the CPLS components

We examined the robustness of the CPLS components at the end of the trial across 1000 simulated trials. Since a CPLS score is a linear combination of the covariates weighted by the CPLS loading weights, this is equivalent to evaluating the robustness (or similarity) of the 1000 loading weight vectors obtained from 1000 simulated trials. In order to do that, we used the idea of permutation test in cluster analysis. Specifically, we first calculated the mean Euclidean distance from the 1000 loading weight vectors to their centroid (the average of the 1000 loading weight vectors). We denote this observed mean distance as $\bar{D}_{obs}$. Next, we randomly permuted the loading weights within each vector and calculated the mean Euclidean distance from the permuted loading weight vectors to the centroid of the original loading weight vectors, denoted as $\bar{D}_{per}$. We conducted this permutation 1000 times and obtained the empirical distribution of $\bar{D}_{per}$. Under the null that there is no similarity among the loading weight vectors across simulations, the observed mean distance $\bar{D}_{obs}$ should be located in the central area of the distribution of $\bar{D}_{per}$. The further $\bar{D}_{obs}$ is away from the central area of the distribution of $\bar{D}_{per}$, the stronger the evidence that the loading weight vectors are similar across simulations. The Figure S6 below shows $\bar{D}_{obs}$ versus the empirical distribution of $\bar{D}_{per}$ for efficacy and toxicity in scenario 1. We can see that $\bar{D}_{obs}$ is extremely unlikely under the empirical distribution of $\bar{D}_{per}$, suggesting the robustness of the loading weights across simulated trials. The patterns of the loading weights are similar for the other scenarios (results not shown).

Figure 6: Observed mean distance (indicated by solid lines) versus the distribution of mean distance from randomly permuted loading weights (depicted by dashed curves).

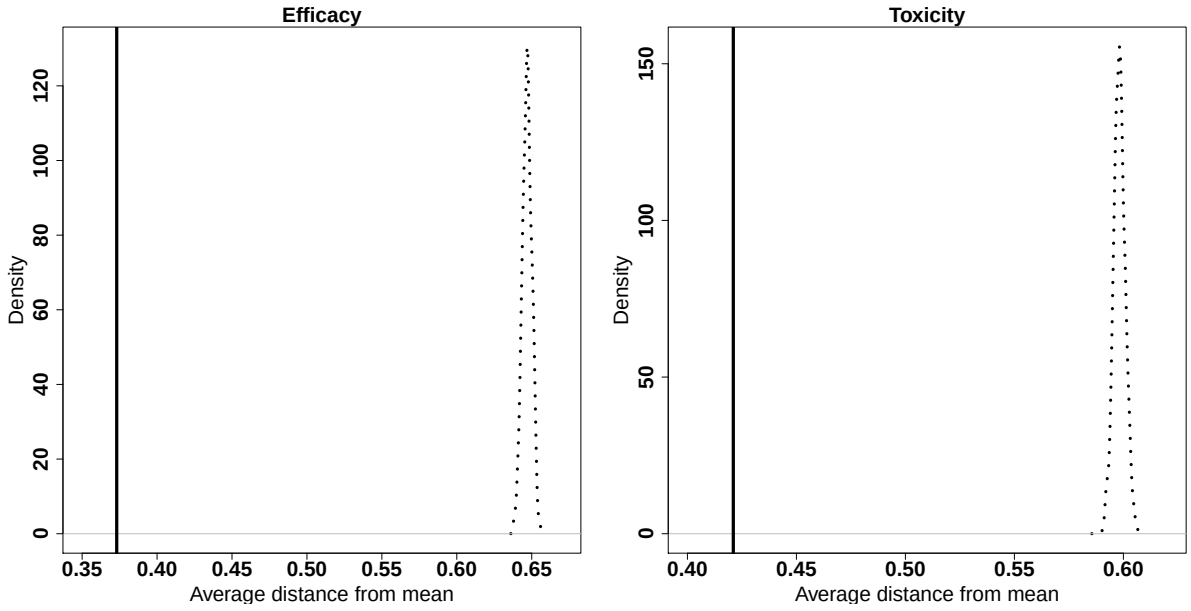


Table 2: Utility

	y_E=1	y_E=2	y_E=3
y_T=1	0	50	100
y_T=2	0	20	60
y_T=3	0	10	20

Table 3: The average and standard deviation (SD) of the percentage of correct selection (PCS) of target doses across 32 possible biomarker patterns with the above utility.

	Scenario							
PCS	1	2	3	4	5	6	7	8
Mean	0.661	0.704	0.722	0.772	0.714	0.652	0.680	0.823
SD	0.20	0.24	0.16	0.30	0.23	0.19	0.27	0.17

Table 4: Utility

	y_E=1	y_E=2	y_E=3
y_T=1	0	65	100
y_T=2	0	35	75
y_T=3	0	25	35

Table 5: The average and standard deviation (SD) of the percentage of correct selection (PCS) of target doses across 32 possible biomarker patterns with the above utility.

	Scenario							
PCS	1	2	3	4	5	6	7	8
Mean	0.630	0.686	0.755	0.841	0.719	0.642	0.670	0.815
SD	0.23	0.25	0.18	0.26	0.26	0.19	0.28	0.17

Table 6: The average and standard deviation (SD) of the percentage of correct selection (PCS) of target doses across all possible biomarker patterns under the proposed design and the direct approach with 2 biomarkers.

		Scenario		
Method	PCS	1	2	3
Proposed	Mean	0.802	0.752	0.93
	SD	0.08	0.17	0.11
Direct approach	Mean	0.82	0.787	0.941
	SD	0.07	0.19	0.05

Table 7: The average and standard deviation (SD) of the percentage of correct selection (PCS) of target doses across all possible biomarker patterns under the proposed design with 3 biomarkers.

	Scenario		
	1	2	3
Mean PCS	0.74	0.722	0.659
SD PCS	0.20	0.15	0.13

The direct approach broke down in this case with 3 biomarkers.

Table 8: The average and standard deviation (SD) of the percentage of correct selection (PCS) of target doses across 32 possible biomarker patterns under the proposed designs using CRM in Stage I.

	Scenario							
PCS	1	2	3	4	5	6	7	8
Mean	0.717	0.711	0.696	0.772	0.719	0.721	0.685	0.824
SD	0.17	0.23	0.16	0.31	0.24	0.11	0.26	0.17

Posterior Inference

In our model, with standardized variables, the prior distributions for β_T and β_E are $N(\xi_T, \Sigma_{T,0})$, $N(\xi_E, \Sigma_{E,0})$, respectively. As described above, ξ_T and ξ_E are vectors of 0's of lengths q_1 and q_2, respectively, and $\Sigma_{T,0}$ and $\Sigma_{E,0}$ are $q_1 \times q_1$ and $q_2 \times q_2$ diagonal matrices with $\sigma_0^2 = 1.25^2$ on the diagonal. Denote $Z = (z_1, \cdots, z_n)'$, $\boldsymbol{\theta} = (\theta_1, \cdots, \theta_n)'$, $\mathbf{Y}_T^* = (Y_{T,1}^*, \cdots, Y_{T,n}^*)'$, $\mathbf{Y}_E^* = (Y_{E,1}^*, \cdots, Y_{E,n}^*)'$. Let X_T and X_E be the design matrices for toxicity and efficacy models, respectively, and Σ_{Y*} be the diagonal matrix with the ith diagonal element $\exp(2\tau z_i)$. The posterior full conditionals are below.

1. $[\boldsymbol{\beta}_T|D, \theta] \sim N\Big((\Sigma_{T,0}{}^{-1} + X_T'X_T)^{-1}(\Sigma_{T,0}{}^{-1}\boldsymbol{\beta}_{T,0} - X_T'(\mathbf{Y}_T^* + \boldsymbol{\theta})), (\Sigma_{T,0}{}^{-1} + X_T'X_T)^{-1}\Big)$

2. $[Y_{T,i}^*|D, \theta, Y_{T,i} = j] \sim N(-\theta_i - \beta_{T,1}\omega_{T,1,i} - \beta_{T,2}\omega_{T,2,i}, 1)I(\beta_{T,0,j-1} < Y_{T,i}^* \leq \beta_{T,0,j})$

3. $[\beta_{T,0,j}|D, \theta] \sim N(0, \sigma_0^2)I\Big(\max\{\max\{Y_{T,i}^* : Y_{T,i} = j\}, \beta_{T,0,j-1}\} < \beta_{T,0,j} \leq \min\{\min\{Y_{T,i}^* : Y_{T,i} = j+1\}, \beta_{T,0,j+1}\}\Big), j = 1, 2$

4. $[\boldsymbol{\beta}_E|D, \theta] \sim N\Big((\Sigma_{E,0}{}^{-1} + X_E'\Sigma_{Y*}{}^{-1}X_E)^{-1}(\Sigma_{E,0}{}^{-1}\boldsymbol{\beta}_{E,0} - X_E'\Sigma_{Y*}{}^{-1}(\mathbf{Y}_E^* + \boldsymbol{\theta})), (\Sigma_{E,0}{}^{-1} + X_E'\Sigma_{Y*}{}^{-1}X_E)^{-1}\Big)$

5. $[Y_{E,i}^*|D, \theta, Y_{E,i} = j] \sim N(-\theta_i - \beta_{E,1}\omega_{E,1,i} - \beta_{E,2}\omega_{E,2,i}, \exp(2\tau \mathrm{z_i}))I(\beta_{E,0,j-1} < Y_{E,i}^* \leq \beta_{E,0,j})$

6. $[\beta_{E,0,j}|D, \theta] \sim N(0, \sigma_0^2)I\Big(\max\{\max\{Y_{E,i}^* : Y_{E,i} = j\}, \beta_{E,0,j-1}\} < \beta_{E,0,j} \leq \min\{\min\{Y_{E,i}^* : Y_{E,i} = j+1\}, \beta_{E,0,j+1}\}\Big), j = 1, 2$

7. $[\theta_i|D, \theta] \sim N(\mu_{\theta_i}, \sigma_{\theta_i}^2)$, where $\sigma_{\theta_i}^2 = \frac{1}{1+1/\exp(2\tau z_i)+1/\sigma^2}$ and

$$\mu_{\theta_i} = -\Big(Y_{T,i}^* + \beta_{T,1}\omega_{T,1,i} + \beta_{T,2}\omega_{T,2,i} + \frac{Y_{E,i}^* + \beta_{E,1}\omega_{E,1,i} + \beta_{E,2}\omega_{E,2,i}}{\exp(2\tau z_i)}\Big)\sigma_{\theta_i}^2$$

8. $[\tau|D, \theta] \propto \prod_{i=1}^n \frac{1}{\exp(\tau z_i)}\exp\big(-(Y_{E,i}^* + \theta_i + \beta_{E,1}\omega_{E,1,i} + \beta_{E,2}\omega_{E,2,i})^2/(2\exp(2\tau z_i))\big)[-c, c]$

9. $[\sigma^2|D, \theta] \sim \text{InvGamma}(a + n/2, b + \sum \theta_i^2/2)$