Supplementary Material to Monitoring Late Onset in Toxicities Phase I Trials Using Predicted Risks

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Appendix A

To carry out an assessment of the asymptotic behavior of our method, we must drop rules (3) and (6.1) of our method, since otherwise the sample size at each dose cannot grow large without limit.

Proposition 1 *Let β_{jk}^0 be the true value of the parameter β_{jk}. For any $\epsilon > 0$, any $j = 1, \ldots, C-1$ and dose k, $Pr(|\beta_{jk} - \beta_{jk}^0| < \epsilon | D_n) \to 1 \quad a.s.$ as $n_k \to \infty$.*

The proof of Proposition 1 follows from the Bayesian Central Limit Theorem (Carlin and Louis, 2000, P. 122), the Cramér-Wold Device (Sen and Singer, 1993, P. 106), and the consistency of the posterior mode under suitable regularity conditions (Gelman et al., 1995, P. 106). Since $\pi(\boldsymbol{\beta}, d_k) \equiv 1 - \prod_{j=1}^{C-1}\{1 - \Phi(\beta_{jk})\}$ is a monotone, continuous function of each β_{jk}, an immediate consequence of Proposition 1 is the following consistency result.

Proposition 2 *Let $\pi^0(\boldsymbol{\beta}, d_k) \equiv 1 - \prod_{j=1}^{C-1}\{1 - \Phi(\beta_{jk}^0)\}$ be the true toxicity probability at dose k. For any $\epsilon > 0$ and dose k, $Pr(|\pi(\boldsymbol{\beta}, d_k) - \pi^0(\boldsymbol{\beta}, d_k)| < \epsilon | D_n) \to 1 \quad a.s.$ as $n_k \to \infty$.*

Remark 1 Proposition 2 implies that, for n_k and n_{k+1} sufficiently large, the transformed posterior toxicity probabilities $\tilde{\pi}(\boldsymbol{\beta}, d_k)$ and $\tilde{\pi}(\boldsymbol{\beta}, d_{k+1})$, obtained via isotonic regression, will be the same as the untransformed quantities $\pi(\boldsymbol{\beta}, d_k)$ and $\pi(\boldsymbol{\beta}, d_{k+1})$, since these converge to the true values $\pi^0(\boldsymbol{\beta}, d_k)$ and $\pi^0(\boldsymbol{\beta}, d_{k+1}))$, which obey the order constraint.

Remark 2 Proposition 2 also implies that if n_k is large enough the predicted risks defined in (4.1) and (4.2)

equal 1 or 0, depending on whether or not $\pi^0(\boldsymbol{\beta}, d_k) > \pi^*$. Specifically, for each dose k and sufficiently large n_k,

$$PN_k(D_n) = \begin{cases} 0 & \text{if } \pi^0(\boldsymbol{\beta}, d_k) \geq \pi^* \\ 1 & \text{if } \pi^0(\boldsymbol{\beta}, d_k) < \pi^* \end{cases}$$

and

$$PE_k(D_n) = \begin{cases} 1 & \text{if } \pi^0(\boldsymbol{\beta}, d_k) \geq \pi^* \\ 0 & \text{if } \pi^0(\boldsymbol{\beta}, d_k) < \pi^*. \end{cases}$$

These results follow from the observations that 1) the first two moments of the posterior distribution of $\pi(\boldsymbol{\beta}, d_k)$ are matched with those of a beta distribution and 2) the first moment of the posterior converges to the true value $\pi^0(\boldsymbol{\beta}, d_k)$ by proposition 2, while the variance converges to zero.

Collectively, the above results imply that, as the number of patients treated at dose k gets large enough, the predictive probabilities used in the dose-assignment rules in (5.2), (6.3) and (6.4) will all equal 0 or 1, and hence accrual will not be suspended. Intuitively, for a sufficiently large sample the posterior probabilities become so informative that the predictive probabilities no longer add any useful additional information that will change the decision rules. Proposition 2 implies that, unless $\pi^0(\boldsymbol{\beta}, d_k) = \pi^*$ for some k, with an arbitrarily large sample and no early stopping, for dose k such that $\pi^0(\boldsymbol{\beta}, d_k) < \pi^* < \pi^0(\boldsymbol{\beta}, d_{k+1})$ the design would endlessly move back and forth between doses k and $k+1$. In practice, the trial will stop with the final dose assigned by rule (7).

Appendix B

For each dose d_k, we define a piecewise exponential distribution with $M+1$ hazards $\boldsymbol{\lambda}_k = (\lambda_{k1}, ..., \lambda_{kM}, \lambda_{k,M+1})$ over $M+2$ equally spaced timepoints $(0 \equiv t_0, t_1, ..., t_M = t^*, t_{M+1} \equiv \infty)$ where $A_s = t_s - t_{s-1}$ for $s = 1, ..., M+1$. We define this distribution so that the cumulative probability of toxicity at time t_s for dose k is p_{ks} and the cumulative probability of toxicity at the assessment time, $t_M = t^*$, is p_{kM}. The CDF for this distribution takes form $G(t_{s'}|\lambda_k) = p_{ks'} = 1 - \exp(-\sum_{s=1}^{s'} \lambda_{ks} A_s)$. To define λ_{ks}, we let $x_1, ..., x_M$ be M equally spaced points in $[0, 1]$, define the beta pdf kernel $f(x_s|\alpha, \beta) = x_s^{\alpha-1}(1-x_s)^{\beta-1}$ for $s = 1, ..., M$, and then define

$$\lambda_{ks} = \frac{-\log(1 - p_{kM}) f(x_s|\alpha_k, \beta_k)}{\sum_{r=1}^{M} f(x_r|\alpha_k, \beta_k) A_r}.$$

To generate toxicity times for dose d_k, we first generate $U \sim uniform(0,1)$, and if $U \in (p_{ks-1}, p_{k,s})$ (where s=1,...,M+1) we generate $t_k^* = \lambda_{ks}^{-1} \sum_{r=1}^{s-1} \lambda_{kr} A_{kr} - \log(1-U) + t_{s-1}$.

Appendix C

In addition to the simulation studies presented in the paper we also performed simulation studies using constant, bathtub shaped, and various early onset hazard functions. We simulated a version of our method without the trial suspension procedures used in decision rules (5) and (6). In this case, we found that our method performs similarly to the TITE-CRM in the late onset/rapid accrual case.

Various simulation studies are tabulated in this section. Table C1 explores the case in which accrual is slow at the start of a study and then accelerates over time, using a non-homogeneous Poisson process with rate function:

$$\lambda(\tau) = \begin{cases} 1/(30 - \tau\{22.5/365\}) & \text{for } \tau \leq 365 \\ 1/7.5 & \text{otherwise} \end{cases}$$

The results of this simulation study are consistent with the simulations in Table 2 and Figure 3 of the paper. Table C2 explores the case in which patients are assigned to lower doses rather than suspending accrual. Although this method is very safe resulting in far fewer toxicities compared to both the PRT and TITE-CRM methods, it 'spends' quite a few patients at much lower doses compared to the other two methods. Table C3 explores the impact of relaxing the isotonic regression transformation on the operating characteristics of the method. In this simulation study we found that Bayesian Isotonic Regression has an important role in improving the correct selection probability for our model. Lastly, Table C4 provides results for the case in which toxicities occur quickly (within 3 days from the start of therapy).

Table C1. *Operating characteristics Comparing the PRT and TITE-CRM designs when accrual starts slow then accelerates.*

		True Prob($T < 3$ *months* $\mid d_k$)								
Scenario 1 (Late Onset)		0.25	0.35	0.5	0.6	0.68	0.73	None	Total	Duration
PRT	*Selected*	41	44	4	0	0	0	12		1.8
	Patients	14.0	14.0	4.2	0.6	0.1	0.0		33.0	
	Toxicities	3.4	4.8	2.1	0.4	0.0	0.0		10.8	
TITE-CRM	*Selected*	41	45	8	0	0	0	6		1.5
	Patients	12.4	12.3	7.3	2.6	0.2	0.0		34.7	
	Toxicities	3.1	4.3	3.5	1.6	0.1	0.0		12.6	

Scenario 2 (Late Onset)		0.03	0.05	0.10	0.30	0.50	0.60	None	Total	Duration
PRT	*Selected*	0	0	25	67	8	0	0		2.0
	Patients	3.3	4.6	9.6	13.1	4.5	0.9		36.0	
	Toxicities	0.1	0.2	0.9	4.0	2.3	0.6		8.1	
TITE-CRM	*Selected*	0	0	12	72	16	0	0		1.5
	Patients	3.1	3.2	4.9	13.7	9.4	1.6		36.0	
	Toxicities	0.1	0.2	0.4	4.2	4.7	1.0		10.6	

Scenario 3 (Late Onset)		0.50	0.60	0.68	0.73	0.76	0.78	None	Total	Duration
PRT	*Selected*	14	0	0	0	0	0	86		1.1
	Patients	13.4	3.9	0.5	0.0	0.0	0.0		17.8	
	Toxicities	5.8	2.2	0.3	0.0	0.0	0.0		8.4	
TITE-CRM	*Selected*	16	0	0	0	0	0	84		1.0
	Patients	17.1	4.0	1.0	0.1	0.0	0.0		22.3	
	Toxicities	6.9	2.3	0.7	0.1	0.0	0.0		10.1	

Table C1. *(Continued)*

		True Prob($T < 3$ *months* $\mid d_k$)								
Scenario 4 (Late Onset)		0.01	0.02	0.03	0.05	0.50	0.60	None	Total	Duration
PRT	*Selected*	0	0	0	67	31	1	0		2.0
	Patients	3.1	3.5	4.1	13.1	9.7	2.5		36.0	
	Toxicities	0.0	0.1	0.1	0.6	4.9	1.5		7.2	
TITE-CRM	*Selected*	0	0	0	46	53	1	0		1.5
	Patients	3.0	3.0	3.2	6.5	15.1	5.1		36.0	
	Toxicities	0.0	0.1	0.1	0.3	7.5	3.0		11.1	

Scenario 5 (Late Onset)		0.25	0.35	0.50	0.60	0.68	0.73	None	Total	Duration
PRT	*Selected*	46	40	3	0	0	0	10		1.5
	Patients	15.7	14.1	3.2	0.2	0.0	0.0		33.2	
	Toxicities	4.0	5.1	1.6	0.1	0.0	0.0		10.8	
TITE-CRM	*Selected*	39	45	6	0	0	0	10		1.5
	Patients	16.1	12.4	4.5	0.6	0.0	0.0		33.6	
	Toxicities	4.1	4.4	2.2	0.4	0.0	0.0		11.0	

Table C2. *Operating characteristics of the PRT model when patients are assigned to lower doses rather than suspending accrual. We label this method NS for "No Suspension".*

		True Prob($T < 3$ *months* $\mid d_k$)								
Scenario 1 (Late Onset)		0.25	0.35	0.5	0.6	0.68	0.73	None	Total	Duration
NS	*Selected*	52.2	33.7	3.1	0.2	0.0	0.0	10.8		0.97
	Patients	14.9	14.7	4.2	0.3	0.0	0.0		34.1	
	Toxicities	4.1	5.3	2.0	0.2	0.0	0.0		11.6	
Scenario 2 (Late Onset)		0.0	0.1	0.1	0.3	0.5	0.6	None	Total	Duration
NS	*Selected*	0.0	1.1	40.2	56.7	1.9	0.0	0.1		1.0
	Patients	4.5	10.7	12.5	7.2	1.2	0.0		36.0	
	Toxicities	0.1	0.7	1.8	2.3	0.6	0.0		5.5	
Scenario 3 (Late Onset)		0.50	0.60	0.68	0.73	0.76	0.78	None	Total	Duration
NS	*Selected*	15.3	0.0	0.0	0.0	0.0	0.0	84.7		0.6
	Patients	15.7	8.0	1.4	0.0	0.0	0.0		25.1	
	Toxicities	6.4	3.9	0.8	0.0	0.0	0.0		11.1	
Scenario 4 (Late Onset)		0.01	0.02	0.03	0.05	0.50	0.60	None	Total	Duration
NS	*Selected*	0.0	0.0	4.9	76.1	18.8	0.2	0.0		1.0
	Patients	4.3	8.9	10.2	8.7	3.8	0.2		36.0	
	Toxicities	0.0	0.2	0.3	0.6	1.9	0.1		3.2	
Scenario 5 (Early Onset)		0.25	0.35	0.50	0.60	0.68	0.73	None	Total	Duration
NS	*Selected*	47.2	39.0	2.0	0.0	0.0	0.0	11.8		0.9
	Patients	17.2	14.1	1.8	0.0	0.0	0.0		33.0	
	Toxicities	4.4	4.9	0.9	0.0	0.0	0.0		10.2	

Table C3. *Operating characteristics of the PRT design when Bayesian Isotonic Regression Transform is relaxed.*

		True Prob($T < 3$ *months* $\mid d_k$)								
Scenario 1		0.25	0.35	0.5	0.6	0.68	0.73	None	Total	Duration
PRT	*Selected*	49	34	3	0	0	0	13		1.5
	Patients	15.3	13.3	3.6	0.6	0.1	0.0	0.0	32.9	
	Toxicities	3.7	4.6	1.8	0.4	0.0	0.0	0.0	10.5	
Scenario 2		0.03	0.05	0.10	0.30	0.50	0.6	None	Total	Duration
PRT	*Selected*	3	7	28	53	8	1	0		1.8
	Patients	4.1	5.1	10.4	11.4	4.0	1.0	0.0	36.0	
	Toxicities	0.1	0.3	1.1	3.5	2.1	0.6	0.0	7.6	
Scenario 3		0.50	0.60	0.68	0.73	0.76	0.8	None	Total	Duration
PRT	*Selected*	11	1	0	0	0	0	88		0.8
	Patients	12.7	4.9	0.4	0.1	0.0	0.0	0.0	18.1	
	Toxicities	5.4	2.5	0.3	0.0	0.0	0.0	0.0	8.3	
Scenario 4		0.01	0.02	0.03	0.05	0.50	0.6	None	Total	Duration
PRT	*Selected*	1	6	18	41	29	6	0		1.9
	Patients	3.3	3.6	4.9	12.0	9.3	2.9	0.0	36.0	
	Toxicities	0.0	0.1	0.1	0.6	4.6	1.7	0.0	7.2	

Table C4. *Operating characteristics of the PRT and TITE-CRM designs when toxicities occur very early, within 3 days from the start of therapy.*

		True Prob($T < 3$ *months* $\mid d_k$)								
Scenario 1		0.25	0.35	0.5	0.6	0.68	0.73	None	Total	Duration
PRT	*Selected*	43	39	3	0	0	0	15		1.0
	Patients	17.0	12.3	2.4	0.1	0.0	0.0		31.9	
	Toxicities	4.2	4.4	1.2	0.1	0.0	0.0		9.8	
TITE-CRM	*Selected*	37	43	7	0	0	0	13		0.9
	Patients	16.9	11.8	3.3	0.3	0.0	0.0		32.3	
	Toxicities	4.2	4.1	1.7	0.2	0.0	0.0		10.2	

Scenario 2		0.03	0.05	0.10	0.30	0.50	0.6	None	Total	Duration
PRT	*Selected*	0	1	30	65	5	0	0		1.4
	Patients	4.1	5.6	11.8	12.4	2.2	0.1		36.0	
	Toxicities	0.1	0.3	1.2	3.7	1.1	0.0		6.5	
TITE-CRM	*Selected*	0	0	8	79	13	0	0		1.0
	Patients	3.6	3.5	6.7	17.9	4.3	0.1		36.0	
	Toxicities	0.1	0.2	0.7	5.4	2.1	0.0		8.6	

Scenario 3		0.50	0.60	0.68	0.73	0.76	0.8	None	Total	Duration
PRT	*Selected*	9	0	0	0	0	0	90		0.3
	Patients	11.8	1.1	0.0	0.0	0.0	0.0		12.9	
	Toxicities	5.8	0.7	0.0	0.0	0.0	0.0		6.4	
TITE-CRM	*Selected*	9	0	0	0	0	0	91		0.3
	Patients	12.3	0.8	0.1	0.0	0.0	0.0		13.3	
	Toxicities	6.1	0.5	0.1	0.0	0.0	0.0		6.7	

Table C4. *(Continued)*

		True Prob($T < 3$ *months* $\mid d_k$)								
Scenario 4		0.01	0.02	0.03	0.05	0.50	0.6	None	Total	Duration
PRT	*Selected*	0	0	1	65	34	0	0		1.5
	Patients	3.3	3.8	5.1	15.4	8.0	0.5		36.0	
	Toxicities	0.0	0.1	0.2	0.8	4.0	0.3		5.3	
TITE-CRM	*Selected*	0	0	0	26	73	0	0		1.0
	Patients	3.2	3.1	3.3	10.4	15.7	0.3		36.0	
	Toxicities	0.0	0.1	0.1	0.5	7.9	0.2		8.8	

Scenario 5		0.05	0.06	0.08	0.11	0.19	0.34	None	Total	Duration
PRT	*Selected*	0	1	8	24	44	22	0		1.4
	Patients	4.5	5.3	7.0	8.0	7.8	3.4		36.0	
	Toxicities	0.2	0.3	0.5	0.9	1.4	1.1		4.5	
TITE-CRM	*Selected*	0	0	2	18	60	20	0		1.0
	Patients	3.8	3.6	4.4	8.5	12.3	3.4		36.0	
	Toxicities	0.2	0.2	0.3	0.9	2.3	1.1		5.1	