Subgroup-specific dose finding in phase I clinical trials based on time to toxicity allowing adaptive subgroup combination

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In this web based appendix, we provide additional details that are discussed but not included in the manuscript. In section A, we detail the sampling methods used in the Markov Chain Monte Carlo (MCMC) sampler to produce the posterior optimal doses. In section B, we give supplementary tables mentioned for the simulation study in section 4.

A Sampling details for the MCMC

In this section, we describe the sampling procedure used to obtain posterior estimates for $\boldsymbol{\theta}$ and $\boldsymbol{\zeta}$ which are used to determine what dose to give the next patient, and the subgroups that should have accrual suspended. We found that 2000 iterations were sufficient for both exploring the sample space and MCMC convergence, where we burned the first 1000 iterations before making any trial decisions. We make the following moves in our MCMC scheme, with details describing how each is conducted.

1. Metropolis Hastings move on (α, β) and on (α_g, β_g) for all g such that $\rho_g = 1$ given current values of $\boldsymbol{\rho}, \boldsymbol{\zeta}$. For a move on any parameter θ_j in the linear term for the baseline group or any other subgroup, we draw a proposal value $\theta_j^* \sim N(\theta_j, c_j)$ where c_j starts at a value of 1 for intercept parameters and .5 for slope parameters. This proposal variance is adaptively adjusted every 100 iterations for the first half of the MCMC to have a move specific acceptance probability between .2 and .5. We accept θ_j^* over θ_j for the $j = 1, ..., 2G + 1$ linear terms with probability

$$\min \left[\frac{L\left(\mathcal{D}_{n_t} | \boldsymbol{x}, \boldsymbol{Z}, \theta_j^*, \boldsymbol{\theta}_{-j}\right) N\left(\theta_j^* | \tilde{\theta}_j, \sigma_j^2\right)}{L\left(\mathcal{D}_{n_t} | \boldsymbol{x}, \boldsymbol{Z}, \theta_j^*, \boldsymbol{\theta}_{-j}\right) N\left(\theta_j | \tilde{\theta}_j, \sigma_j^2\right)}, 1 \right],$$

   where θ_{-j} is the subvector of $\boldsymbol{\theta}$ without entry j and σ_j^2 is the prior variance of θ_j. The likelihood used here is also a function of the followup times of patients who have not experienced a toxicity or have been followed past the reference time T. We do not adaptively adjust c_j for any j after 1000 iterations so that the posterior used in trial decision making is proper.

2. Metropolis Hastings move on $\boldsymbol{\rho}, \boldsymbol{\zeta}, \boldsymbol{\theta}$ to change the clustering of latent patient subgroups. We do three different types of moves here, each occuring with probability 1/3.

   - **Cluster or uncluster all subgroups:** This move proposes setting all $\rho_g^* = 0$ or $\rho_g^* = 1$ with equal probability to either collapse all subgroups or uncluster all subgroups. If we propose to uncluster all subgroups, we set all $\zeta_g^* = g$ and $\rho_g^* = 1$ which produces the new latent subgroup proposal vector $\boldsymbol{Z}^*$. We draw proposals for the subgroup specific parameters α_g^*, β_g^* for all g such that $\rho_g = 0$, i.e. all subgroups that were clustered with other subgroups. We accept the new latent subgroup vector $\boldsymbol{Z}^*$ and the new parameter vector $\boldsymbol{\theta}^*$ with probability

$$\min\left[\frac{L\left(\mathcal{D}_{n_t}|\boldsymbol{x},\boldsymbol{Z}^*,\boldsymbol{\theta}^*\right)\prod_{g=1}^{G-1}9N(\alpha_g^*|\tilde{\alpha}_g,\sigma_\alpha)N(\beta_g^*|\tilde{\beta}_g,\sigma_\beta)I[\rho_g=0]}{L\left(\mathcal{D}_{n_t}|\boldsymbol{x},\boldsymbol{Z},\boldsymbol{\theta}\right)},1\right],$$

For a move that proposes clustering all subgroups, we propose setting all $\rho_g^* = 0$ and all $\zeta_g^* = 0$, creating a new proposed latent subgroup vector $\boldsymbol{Z}^*$. We accept the new latent subgroup vector with probability

$$\min\left[\frac{L\left(\mathcal{D}_{n_t}|\boldsymbol{x},\boldsymbol{Z}^*,\boldsymbol{\theta}\right)}{L\left(\mathcal{D}_{n_t}|\boldsymbol{x},\boldsymbol{Z},\boldsymbol{\theta}\right)\prod_{g=1}^{G-1}9N(\alpha_g|\tilde{\alpha}_g,\sigma_\alpha)N(\beta_g^|\tilde{\beta}_g,\sigma_\beta)I[\rho_g=0]},1\right],$$

These two moves help the trial be driven by ignoring patient heterogeneity when none is present and also perform subgroup specific dose finding when no subgroups have similar dose toxicity curves.

- **Cluster or uncluster a subgroup:** This move picks a $g = 1, ..., G-1$ at random and if $\rho_g = 1$, we propose clustering subgroup g with some other latent subgroup, otherwise we propose removing subgroup g from the cluster it's currently a member of. If we sample a g such that $\rho_g = 0$, we propose $\rho_g^* = 1$ and additionally propose new values of α_g^*, β_g^*, which are generated from normal distributions with mean 0 and variances 1 and 1/10, respectively. These proposals give good mixing and acceptance rates within our MCMC. We set $\zeta_g^* = g$, which forms a new latent subgroup vector $\boldsymbol{Z}^*$. This move to remove subgroup g from it's cluster and form a new cluster accepted with probability

$$\min\left[\frac{9L\left(\mathcal{D}_{n_t}|\boldsymbol{x},\boldsymbol{Z}^*,\alpha_g^*,\beta_g^*,\boldsymbol{\theta}_{-(g)}\right)N(\alpha_g^*|\tilde{\alpha}_g,\sigma_\alpha)N(\beta_g^*|\tilde{\beta}_g,\sigma_\beta)\sum_{g=1}^{G-1}\rho_g}{L\left(\mathcal{D}_{n_t}|\boldsymbol{x},\boldsymbol{Z},\boldsymbol{\theta}\right)},1\right],$$

where here $\boldsymbol{\theta}_{-(g)}$ denotes sub-parameter vector without entries corresponding to group g. If we randomly select a g such that $\rho_g = 1$, then we propose collapsing subgroup g into one of the latent subgroups present at the current iteration. We set $\rho_g^* = 0$ and ζ_g^* is proposed from the set of current latent subgroups $S^* = \{0\} \cup \{\boldsymbol{\zeta} : \boldsymbol{\rho}^* = 1\}$ which results in a new latent subgroup vector $\boldsymbol{Z}^*$. This move is accepted with probability

$$\min \left[\frac{L\left(\mathcal{D}_{n_t} | \boldsymbol{x}, \boldsymbol{Z}^*, \boldsymbol{\theta}\right)}{9L\left(\mathcal{D}_{n_t} | \boldsymbol{x}, \boldsymbol{Z}, \boldsymbol{\theta}\right) N(\alpha_g | \tilde{\alpha}_g, \sigma_\alpha) N(\beta_g | \tilde{\beta}_g, \sigma_\beta) \sum_{g=1}^{G-1} \rho_g}, 1 \right],$$

- **Swap** This move selects one subgroup such that $\rho_g = 0$ and one such that $\rho_k = 1$ for $k \neq g$ and swaps their values. We set $\rho_g^* = 1$, $\zeta_g^* = g$ and set $\rho_k^* = 0$. Then we draw ζ_k^* from the set $S^* = \{0\} \cup \{\zeta_g : \boldsymbol{\rho}^* = 1\}$. The prior ratio here is a combination of the add and delete moves discussed above.

3. Metropolis Hastings move on $\boldsymbol{\zeta}|\boldsymbol{\rho}$. For this we take some g such that $\rho_g = 0$ and draw ζ_g^* from the set $S = \{0\} \cup \{\zeta_g : \rho_g = 1\}$. After proposing $\boldsymbol{\zeta}^*$, we obtain $\boldsymbol{Z}^*$ that will be used in the likelihood ratio, which is equivalent to the acceptance ratio for this type of move.

This sampler is implemented in C++ to improve computational speed.

B Web Based tables

In this section, we present 3 tables referred to in the manuscript that contains the elicited prior toxicity probability matrix used in the simulations in Web Table 1, the four dose-toxicity vectors for each scenario in Web Table 2, and the results of the robustness study in Web Table 3.

Table 1: True Dose-Toxicity vectors for simulation scenarios. The homogeneous scenario 4 is not shown, but the subgroup specific dose-toxicity vector is $(.05, .10, .15, .30, .50)$. The third and fourth subgroups for scenario 5 are not shown since we did not include this in the four group sensitivity study.

Scenario	Subgroup Toxicity Probabilities	Scenario	Subgroup Toxicity Probabilities
1	(.18, .25, .45, .66, .74)	2	(.25, .58, .70, .78, .84)
	(.10, .15, .30, .50, .60)		(.10, .20, .30, .40, .50)
	(.08, .12, .20, .30, .50)		(.10, .20, .30, .40, .50)
	(.05, .10, .15, .20, .30)		(.05, .10, .15, .30, .50)
3	(.05, .08, .13, .33, .57)	5	(.50, .67, .75, .86, .88)
	(.02, .03, .05, .15, .32)		(.30, .52, .61, .76, .80)
	(.05, .08, .13, .33, .57)		———
	(.05, .08, .13, .33, .57)		——-

Table 2: Evaluation of the Sub-TITE design's robustness to the true time-to-toxicity distribution. For subgroup g, Δ_g is the average absolute distance between the optimal dose toxicity probability and the selected dose's true toxicity probability, $Psel_g$ is the probability of selecting the optimal dose, and $Ntox_g$ is the average number of toxicities. $Pstop_g = P[\text{Stop Subgroup } g]$ and Dur is the average length of the trial, in years. Weibull $\downarrow$ has a decreasing hazard.

Scen	Dist	Δ_0	Δ_1	$Psel_0$	$Psel_1$	$Ntox_0$	$Ntox_1$	$Pstop_0$	$Pstop_1$	Dur
1	Exponential	.08	.05	.54	.70	9.7	8.3	$< .01$	0	2.96
	Uniform	.08	.05	.54	.70	10.0	8.6	$< .01$	0	2.96
	Lognormal	.07	.05	.55	.69	10.3	8.9	$< .01$	0	2.96
	Weibull $\downarrow$	.07	.06	.53	.64	11.7	10.6	$< .01$	0	2.96
2	Exponential	.06	.05	.81	.50	11.2	7.8	.02	0	2.98
	Uniform	.06	.05	.81	.50	11.5	8.0	.02	0	2.98
	Lognormal	.05	.05	.83	.51	11.6	8.3	.02	0	2.98
	Weibull $\downarrow$	.05	.06	.86	.44	13.1	9.5	.02	0	2.97
3	Exponential	.05	.06	.74	.66	8.5	6.1	0	0	2.96
	Uniform	.06	.06	.74	.65	8.7	6.1	0	0	2.95
	Lognormal	.05	.05	.76	.69	9.2	6.6	0	0	2.96
	Weibull $\downarrow$	.05	.05	.75	.69	9.0	6.7	0	0	2.96
4	Exponential	.05	.05	.68	.68	7.4	7.9	0	0	2.97
	Uniform	.05	.05	.68	.69	7.6	8.0	0	0	2.96
	Lognormal	.05	.05	.72	.72	8.1	8.7	0	0	2.96
	Weibull $\downarrow$	.04	.04	.72	.72	9.2	9.8	0	0	2.96
5	Exponential	—	.04	—	.83	11.3	13.5	.70	.06	3.57
	Uniform	—	.05	—	.82	11.1	13.6	.71	.06	3.58
	Lognormal	—	.04	—	.83	11.3	13.6	.69	.05	3.58
	Weibull $\downarrow$	—	.04	—	.84	13.5	14.6	.72	.04	3.42

Table 3: Evaluation of the Sep-TITE design's robustness to the true time-to-toxicity distribution. For subgroup g, Δ_g is the average absolute distance between the optimal dose toxicity probability and the selected dose's true toxicity probability, $Psel_g$ is the probability of selecting the optimal dose, and $Ntox_g$ is the average number of toxicities. $Pstop_g = P[\text{Stop Subgroup } g]$ and Dur is the average length of the trial, in years. Weibull $\downarrow$ has a decreasing hazard.

Scen	Dist	Δ_0	Δ_1	$Psel_0$	$Psel_1$	$Ntox_0$	$Ntox_1$	$Pstop_0$	$Pstop_1$	Dur
1	Exponential	.07	.08	.55	.52	9.2	8.8	$< .01$	0	2.97
	Uniform	.06	.08	.57	.52	9.5	9.0	$< .01$	0	2.95
	Lognormal	.06	.09	.57	.50	9.6	9.2	$< .01$	0	2.96
	Weibull $\downarrow$	.05	.09	.61	.47	10.8	10.2	$< .01$	0	2.96
2	Exponential	.05	.07	.84	.40	10.4	8.9	.04	0	2.99
	Uniform	.05	.07	.85	.39		10.6	9.0	.03	0 2.99
	Lognormal	.04	.07	.86	.38	10.7	9.3	.03	0	2.98
	Weibull $\downarrow$	.04	.07	.88	.38	12.2	10.0	.02	0	2.97
3	Exponential	.07	.04	.66	.78	8.3	7.1	0	0	2.96
	Uniform	.08	.04	.65	.78	8.4	7.2	0	0	2.95
	Lognormal	.08	.04	.64	.76	8.7	7.4	0	0	2.96
	Weibull $\downarrow$	.09	.05	.60	.73	9.3	7.6	0	0	2.96
4	Exponential	.06	.07	.63	.58	8.2	8.4	0	0	2.95
	Uniform	.07	.07	.62	.60	8.2	8.5	0	0	2.96
	Lognormal	.07	.08	.62	.57	8.5	8.8	0	0	2.95
	Weibull $\downarrow$	.07	.08	.61	.54	9.2	9.4	0	0	2.95
5	Exponential	—	.05	—	.82	11.4	13.2	.74	.11	3.53
	Uniform	—	.05	—	.82	12.0	13.1	.72	.11	3.49
	Lognormal	—	.05	—	.83	11.9	13.4	.74	.10	3.51
	Weibull $\downarrow$	—	.04	—	.85	14.2	14.0	.69	.08	3.32

Table 4: Evaluation of the TITE design's robustness to the true time-to-toxicity distribution. For subgroup g, Δ_g is the average absolute distance between the optimal dose toxicity probability and the selected dose's true toxicity probability, $Psel_g$ is the probability of selecting the optimal dose, and $Ntox_g$ is the average number of toxicities. $Pstop_g = P[\text{Stop Subgroup } g]$ and Dur is the average length of the trial, in years. Weibull ↓ has a decreasing hazard.

Scen	Dist	Δ_0	Δ_1	$Psel_0$	$Psel_1$	$Ntox_0$	$Ntox_1$	$Pstop_0$	$Pstop_1$	Dur
1	Exponential	.11	.08	.48	.49	10.1	6.9	$< .01$	$< .01$	2.96
	Uniform	.10	.08	.49	.49	10.4	7.0	$< .01$	$< .01$	2.96
	Lognormal	.10	.08	.49	.49	10.8	7.2	$< .01$	$< .01$	2.95
	Weibull ↓	.09	.09	.57	.40	12.0	8.5	0	0	2.96
2	Exponential	.21	.14	.37	.01	13.4	5.4	$< .01$	$< .01$	2.95
	Uniform	.21	.14	.38	.02	13.7	5.5	$< .01$	$< .01$	2.95
	Lognormal	.21	.14	.37	.02	14.0	5.7	$< .01$	$< .01$	2.95
	Weibull ↓	.19	.14	.42	.02	15.7	6.7	$< .01$	$< .01$	2.96
3	Exponential	.07	.13	.71	.28	11.0	5.5	0	0	2.96
	Uniform	.07	.13	.72	.27	11.1	5.6	0	0	29.6
	Lognormal	.07	.13	.73	.25	11.5	5.8	0	0	2.96
	Weibull ↓	.05	.14	.79	.19	12.3	6.5	0	0	2.96
4	Exponential	.04	.04	.78	.78	8.0	8.0	0	0	2.96
	Uniform	.04	.04	.79	.79	8.1	8.1	0	0	2.96
	Lognormal	.04	.04	.79	.79	8.4	8.5	0	0	2.96
	Weibull ↓	.04	.04	.78	.78	9.2	9.3	0	0	2.96
5	Exponential	—	.20	—	.35	13.7	8.7	.65	.65	1.91
	Uniform	—	.19	—	.37	13.9	9.1	.63	.63	1.99
	Lognormal	—	.18	—	.39	14.0	9.1	.61	.61	2.05
	Weibull ↓	—	.17	—	.43	15.6	10.6	.57	.57	2.35

Table 5: Evaluation of the SOCA-TITE design's robustness to the true time-to-toxicity distribution. For subgroup g, Δ_g is the average absolute distance between the optimal dose toxicity probability and the selected dose's true toxicity probability, $Psel_g$ is the probability of selecting the optimal dose, and $Ntox_g$ is the average number of toxicities. $Pstop_g = P[\text{Stop Subgroup } g]$ and Dur is the average length of the trial, in years. Weibull ↓ has a decreasing hazard.

Scen	Dist	Δ_0	Δ_1	$Psel_0$	$Psel_1$	$Ntox_0$	$Ntox_1$	$Pstop_0$	$Pstop_1$	Dur
1	Exponential	.07	.09	.56	.49	9.2	9.2	0	0	2.95
	Uniform	.06	.09	.56	.51	9.4	9.3	0	0	2.96
	Lognormal	.06	.09	.56	.49	9.6	9.5	0	0	2.96
	Weibull ↓	.08	.09	.54	.51	8.7	8.6	0	0	2.96
2	Exponential	.05	.07	.85	.41	10.5	9.1	0	0	2.95
	Uniform	.05	.07	.86	.39	10.8	9.2	0	0	2.96
	Lognormal	.05	.07	.86	.38	10.8	9.5	0	0	2.96
	Weibull ↓	.07	.07	.80	.39	9.9	8.6	0	0	2.96
3	Exponential	.11	.03	.48	.82	8.6	7.3	0	0	2.96
	Uniform	.12	.03	.46	.81	8.7	7.4	0	0	2.96
	Lognormal	.12	.04	.44	.80	8.9	7.5	0	0	2.96
	Weibull ↓	.11	.03	.52	.85	8.1	7.1	0	0	2.96
4	Exponential	.10	.09	.43	.48	8.6	8.7	0	0	2.96
	Uniform	.10	.09	.45	.49	8.6	8.8	0	0	2.96
	Lognormal	.10	.09	.43	.46	8.8	9.0	0	0	2.95
	Weibull ↓	.10	.09	.47	.49	8.1	8.3	0	0	2.96
5	Exponential	—	.02	—	.89	15.7	11.3	0	0	2.97
	Uniform	—	.03	—	.88	15.9	11.6	0	0	2.96
	Lognormal	—	.03	—	.89	15.8	11.6	0	0	2.97
	Weibull ↓	—	.03	—	.88	15.5	10.8	0	0	2.95