Incorporating Patient Heterogeneity in Adaptive Phase I Trial Designs

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October 2, 2009

The CRM Design

- We have a Phase I study designed to determine which of J doses is the MTD
- Each of the doses is represented by a numeric value $D_j, j = 1, 2, \ldots, J$
- We enroll a maximum of N subjects
- We denote $D_{[i]}, i = 1, 2, \ldots, N$ as the dose assigned to subject i.

The CRM Design

- We observe each subject for a fixed period of time τ, and at any time $t_i \leq \tau$, we measure the binary outcome

$$Y(t_i) = \begin{cases} 0 & ; \quad \text{no DLT by time } t_i \\ 1 & ; \quad \text{DLT by time } t_i \end{cases}$$

- $Y(t_i)$ occurs with probability $F(t_i \mid D_{[i]}; \theta) = F_0(t_i \mid t_i \leq \tau) p(D_{[i]} \mid \theta)$
  - $F_0(t_i \mid t_i \leq \tau)$ is the conditional CDF of DLT in those experiencing DLT by τ
  - $p(D_{[i]} \mid \theta)$ is a function describing the association of dose and probability of DLT by time τ

- $F(t_i \mid D_{[i]}; \theta)$ is not a proper CDF, but results from what is commonly known as a mixture cure model

The CRM Design

- The likelihood for θ is:

$$\mathcal{L}_i(\theta|D_{[i]}, t_i, Y(t_i)) \quad \propto \quad p(D_{[i]} \mid \theta)^{Y(t_i)} [1 - F_0(t_i \mid t_i \leq \tau) p(D_{[i]} \mid \theta)]^{1-Y(t_i)}$$

- When a patient must be fully observed ($t_i \equiv \tau$) to be included in the likelihood:
  - $F_0(t_i \mid t_i \leq \tau) \equiv 1$
  - We have the Continual Reassessment Method (CRM) of O'Quigley, Pepe, & Fisher (1990)

- When each patient can be partially observed ($t_i \leq \tau$) to be included in the likelihood:
  - $F_0(t_i \mid t_i \leq \tau) \leq 1$
  - We have the Time-to-Event CRM (TITE-CRM) of Cheung & Chappell (2000)

The CRM Design

- We choose the dose-toxicity model

$$\begin{aligned} p(D_{[i]} \mid \theta) &= D_{[i]}^{\theta} \\ \log\{-\log\{p(D_{[i]} \mid \theta)\}\} &= \log(\theta) + \log\{-\log(D_{[i]})\}, \end{aligned}$$

  in which

$$\log(\theta) \sim \mathcal{N}(-0.5\sigma^2, \sigma^2)$$

  so that θ has mean 1.0

- We view the value of σ^2 as a "tuning" parameter that is determined through simulation rather than a value determined from prior beliefs and data

The Impact of Heterogeneity

- So far, we have assumed that the probability of DLT by τ is the same for every subject receiving the same dose.

- However, patients enrolled in Phase I trials vary greatly in:
  - current disease status
  - numbers and types of previous chemotherapy/radiation treatments
  - many other factors that would impact their likelihood of DLT beyond that explained by dose

- One might envision using an expanded dose-toxicity model $p(D_{[i]} \mid \boldsymbol{X}_i, \theta, \boldsymbol{\psi})$, where
  - $\boldsymbol{X}_i$ is the vector of characteristics for the i^{th} patient
  - $\boldsymbol{\psi}$ is the corresponding vector of regression parameters

The Impact of Heterogeneity

- Unfortunately, a regression model is impractical is most situations, as the small numbers of patients enrolled in most Phase I studies make accurate estimation of ψ nearly impossible

- As a alternative, one could envision treating all unmeasured patient characteristics as a "frailty", e.g.

$$p^*(D_{[i]} \mid V_i, \theta) = p(D_{[i]} \mid \theta)^{V_i} \quad (1)$$

$$or$$

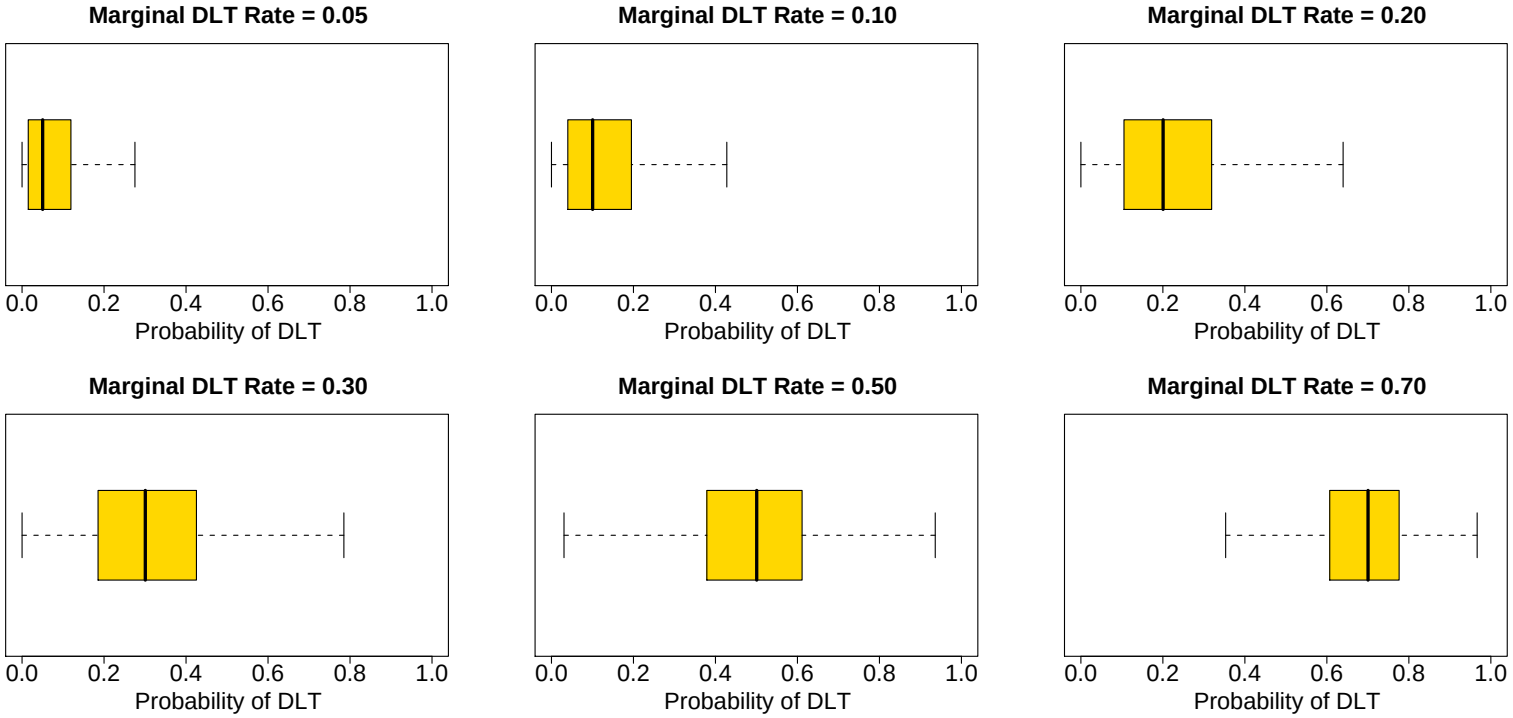
$$\text{logit}\{p^*(D_{[i]} \mid V_i, \theta)\} = \text{logit}\{p(D_{[i]} \mid \theta)\} + U_i \quad (2)$$

where

$$V_i = \exp\{U_i\};\ U_i \sim \mathcal{N}(0, \phi^2)$$

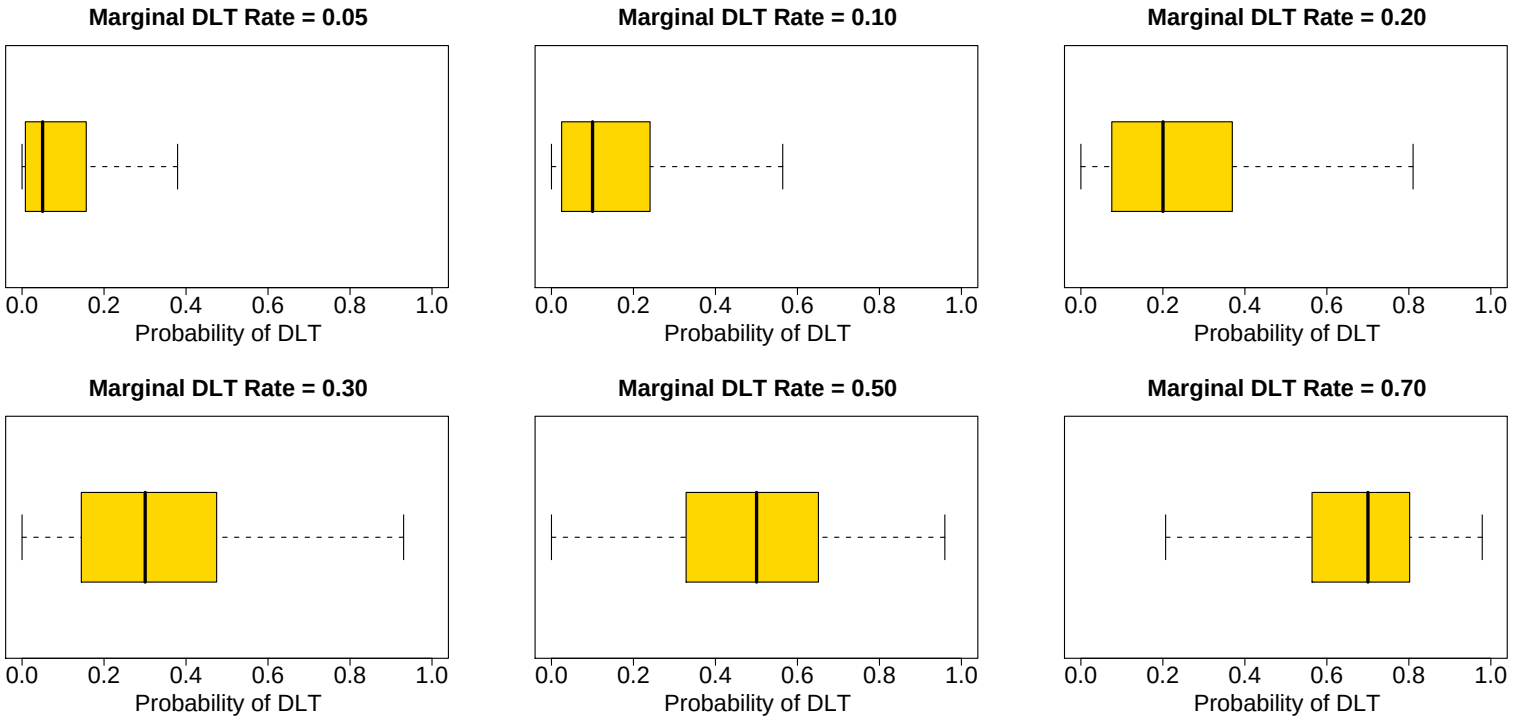
The Impact of Heterogeneity

- The amount of heterogeneity due to $\phi^2 = 0.25$ in the model $p^*(D_{[i]} \mid V_i, \theta) = p(D_{[i]} \mid \theta)^{V_i}$ can be seen below:



The Impact of Heterogeneity

- The amount of heterogeneity due to $\phi^2 = 0.50$ in the model $p^*(D_{[i]} \mid V_i, \theta) = p(D_{[i]} \mid \theta)^{V_i}$ can be seen below:



The Impact of Heterogeneity

- The importance of accounting for patient heterogeneity can be seen by examining the marginal mean of $p^*(D_{[i]} \mid \theta)$ in Model 1

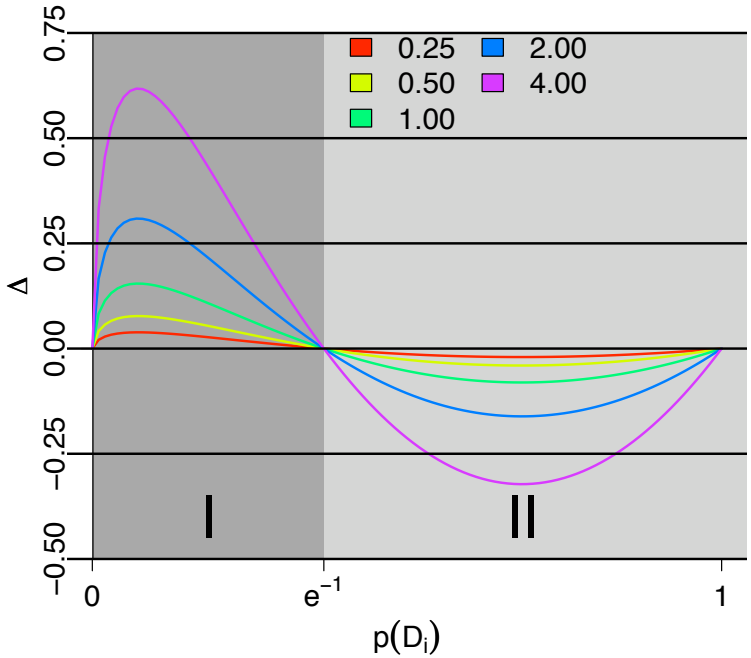
- Using a two-term Taylor series approximation of $g(u) = a^{exp(u)}$ around $E\{U_i\} = 0$, we find that

$$\begin{aligned} \Delta &= E\{p^*(D_{[i]} \mid \theta)\} - p(D_{[i]} \mid \theta) \\ &= \frac{1}{2}\sigma^2 p(D_{[i]} \mid \theta)\log\{p(D_{[i]} \mid \theta)\}[1 + \log\{p(D_{[i]} \mid \theta)\}] \end{aligned}$$

- Thus, $p(D_{[i]} \mid \theta)$ and $E\{p^*(D_{[i]} \mid \theta)\}$ are equivalent when $p(D_{[i]} \mid \theta) = e^{-1} \approx 0.37$

The Impact of Heterogeneity

- The plot below displays $p(D_{[i]} \mid \theta)$ versus Δ for five values of ϕ^2:



- Region I = overestimation of DLT probabilities & locating MTD at doses below the true MTD
- Region II = underestimation of DLT probabilities & locating MTD at doses above the true MTD

The Impact of Ignoring Heterogeneity

- This bias was also examined empirically via simulation in three hypothetical settings:
  - 1000 simulations in each setting
  - Study enrolled 30 patients
  - Goal: to determine which of six doses had a probability of DLT closest to 0.20
  - Skeleton values of $\{0.05, 0.10, 0.20, 0.30, 0.50, 0.70\}$ were assigned to the six doses
  - A $\mathcal{N}(-0.24, 0.48)$ prior was used for $log(\theta)$
- The following tables display number of simulations in which each dose was selected as the MTD when ignoring the heterogeneity

The Impact of Ignoring Heterogeneity

Setting 1:	0.05	0.10	0.20	0.30	0.50	0.70
ϕ^2	D_1	D_2	D_3	D_4	D_5	D_6
0.00	14	184	505	281	16	0
0.25	24	269	492	206	9	0
0.50	68	310	428	186	8	0
1.00	153	377	348	115	7	0

Setting 2:	0.06	0.08	0.12	0.18	0.40	0.71
ϕ^2	D_1	D_2	D_3	D_4	D_5	D_6
0.00	3	49	229	591	128	0
0.25	16	91	308	517	68	0
0.50	36	152	344	414	54	0
1.00	100	216	351	303	30	0

Setting 3:	0.05	0.06	0.08	0.11	0.19	0.34
ϕ^2	D_1	D_2	D_3	D_4	D_5	D_6
0.00	1	14	73	350	488	74
0.25	7	45	144	403	360	41
0.50	15	75	193	422	269	26
1.00	54	147	268	362	162	7

Incorporating Heterogeneity

- We consider two approaches for incorporating patient heterogeneity, still with $\log(\theta) \sim \mathcal{N}(-0.24, 0.48)$:
  1. Random-effects (frailty) model:

$$p^*(D_{[i]} \mid V_i, \theta) = \left(D_{[i]}{}^{\theta}\right)^{V_i}$$

where

$$V_i = \exp\{U_i\};\ U_i \sim \mathcal{N}(0, \nu^2)$$

  2. Hierarchical model:

$$\begin{aligned} p(D_{[i]} \mid \theta) &\sim Beta(a_{[i]}, b_{[i]}) \\ \log(a_{[i]}) &= \alpha_0 + \beta D_{[i]} \\ \log(b_{[i]}) &= \alpha_1 - \beta D_{[i]} \end{aligned}$$

where

$$\alpha_k \sim \mathcal{N}(\mu_k, \eta^2), k = 0, 1\ ;\ \beta \sim \mathcal{N}(\omega, \eta^2)$$

Incorporating Heterogeneity

- Utility of both approaches examined empirically via simulation under same settings as before:
  - 1000 simulations in each setting
  - Study enrolled 30 patients
  - Goal: to determine which of six doses had a probability of DLT closest to 0.20
  - Skeleton values of $\{0.05, 0.10, 0.20, 0.30, 0.50, 0.70\}$ were assigned to the six doses
  - A $\mathcal{N}(-0.24, 0.48)$ prior was used for $log(\theta)$
  - Heterogeneity simulated from frailty Model 1 with $\phi^2 = 0.5$

Simulation Results

Setting 1:	0.05	0.10	0.20	0.30	0.50	0.70
$\phi^2 = 0.0$	(14)	184	(505)	281	16	0
$\phi^2 = 0.5$	(68)	(310)	(428)	(186)	(8)	(0)

Frailty Model Approach

ν^2	D_1	D_2	D_3	D_4	D_5	D_6
0.10	65	317	460	155	3	0
0.25	38	297	451	208	6	0
0.50	43	215	469	263	10	0
1.00	9	131	445	390	25	0
2.00	2	84	356	483	75	0

Hierarchical Model Approach

η^2	D_1	D_2	D_3	D_4	D_5	D_6
0.05	0	7	353	511	112	17
0.10	1	114	553	275	51	6
0.20	32	251	420	220	52	25
0.50	140	334	313	132	51	30
1.00	176	339	270	136	40	39

Simulation Results

Setting 2:	0.06	0.08	0.12	0.18	0.40	0.71
$\phi^2 = 0.0$	(3)	(49)	(229)	(591)	(128)	(0)
$\phi^2 = 0.5$	(36)	(152)	(344)	(414)	(54)	(0)

Frailty Model Approach

ν^2	D_1	D_2	D_3	D_4	D_5	D_6
0.10	52	141	331	432	44	0
0.25	33	129	301	479	57	1
0.50	16	87	265	535	97	0
1.00	9	53	212	563	163	0
2.00	0	22	113	565	299	1

Hierarchical Model Approach

η^2	D_1	D_2	D_3	D_4	D_5	D_6
0.05	0	0	155	596	222	27
0.10	1	23	336	484	127	29
0.20	19	114	376	349	96	46
0.50	93	202	305	249	94	57
1.00	189	210	273	200	69	59

Simulation Results

Setting 3:	0.05	0.06	0.08	0.11	0.19	0.34
$\phi^2 = 0.0$	(1)	(14)	(73)	(350)	(488)	(74)
$\phi^2 = 0.5$	(15)	(75)	(193)	(422)	(269)	(26)

Frailty Model Approach

ν^2	D_1	D_2	D_3	D_4	D_5	D_6
0.10	25	87	202	407	266	13
0.25	10	62	185	421	298	24
0.50	5	40	119	407	408	21
1.00	3	14	87	345	500	51
2.00	0	4	36	247	611	102

Hierarchical Model Approach

η^2	D_1	D_2	D_3	D_4	D_5	D_6
0.05	19	0	7	167	357	450
0.10	33	3	54	226	338	346
0.20	69	31	112	251	254	283
0.50	174	81	140	213	186	206
1.00	303	95	117	154	133	198

Summary of Findings

- Ignoring patient heterogeneity appears to lead to conservative MTD estimates, assuming majority of doses have “relatively low” DLT probabilities
- Accounting for patient heterogeneity can lead to improved estimation of the MTD
- Accounting for patient heterogeneity can lead to increased exposure to DLT, especially if level of heterogeneity used is higher than what exists
  - Perhaps include additional hierarchy for variance parameter?
  - Perhaps use entire posterior distribution and not just posterior mean (*ala* EWOC) to identify MTD?