Modified isotonic regression based design for phase I/II clinical trials

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Introduction

- Conventional phase I/II clinical trial design often uses complex parametric models to characterize dose-response relationships and conduct trials.
- Parametric models are difficult to justify in practice, and model misspecification can lead to substantially undesirable performance in phase I/II clinical trials.
- A transparent and efficient phase I/II clinical trial design (mISO) is proposed without parametric assumptions to identify the optimal biological dose (OBD) for molecularly targeted agents and immunotherapy.

Probability model

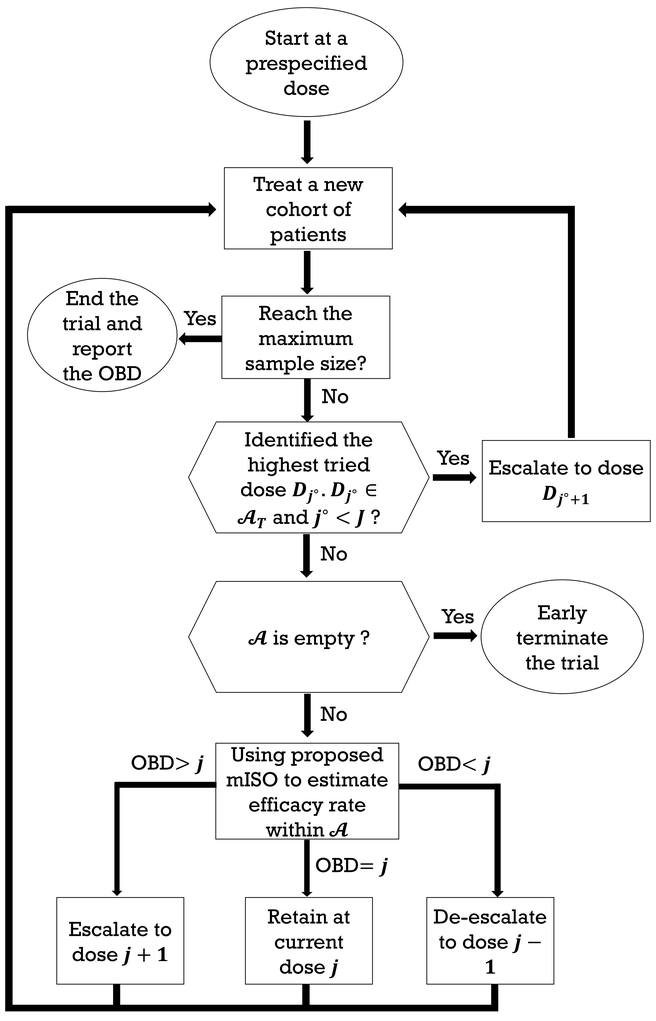
- Prespecified increasing doses: $\boldsymbol{D} = (\boldsymbol{d_1}, \dots, \boldsymbol{d_J})$
- Binary dose-limiting toxicity (DLT) endpoint: $\boldsymbol{T} = \mathbf{0}, \mathbf{1}$
- Binary efficacy endpoint: $\boldsymbol{E} = \mathbf{0}, \mathbf{1}$
- DLT rate: $\boldsymbol{p_{T,j}} = \boldsymbol{Pr}(\boldsymbol{T} = \mathbf{1} | \boldsymbol{D} = \boldsymbol{d_j})$
- Efficacy rate: $\boldsymbol{p_{E,j}} = \boldsymbol{Pr}(\boldsymbol{E} = \mathbf{1} | \boldsymbol{D} = \boldsymbol{d_j})$
- The general dose-toxicity relationship:
$$\boldsymbol{p_{T,1}} < \cdots < \boldsymbol{p_{T,J}}$$
- The plateaued dose-efficacy relationship:
$$\boldsymbol{p_{E,1}} < \cdots < \boldsymbol{p_{E,j^\dagger}} = \boldsymbol{p_{E,j^\dagger+1}} = \cdots = \boldsymbol{p_{EJ}}$$
- Denote $\boldsymbol{r_{T,j}}$ and $\boldsymbol{r_{E,j}}$ as number of patients experiencing $\boldsymbol{T} = \mathbf{1}$ and $\boldsymbol{E} = \mathbf{1}$ among $\boldsymbol{n_j}$ patients at dose $\boldsymbol{j}$.
- Let $\mathcal{O}$ be the observed data, beta-binomial model for each dose independently is proposed to construct admissible set.
- $\boldsymbol{p_{T,j}} | \mathcal{O} \sim \boldsymbol{Beta}\,(\boldsymbol{\alpha_T} + \boldsymbol{r_{T,j}}, \boldsymbol{\beta_T} + \boldsymbol{n_j} - \boldsymbol{r_{T,j}})$
- $\boldsymbol{p_{E,j}} | \mathcal{O} \sim \boldsymbol{Beta}\,(\boldsymbol{\alpha_E} + \boldsymbol{r_{E,j}}, \boldsymbol{\beta_E} + \boldsymbol{n_j} - \boldsymbol{r_{E,j}})$
- Admissible set of toxicity: $\mathcal{A}_T = \{\mathbf{1}: \boldsymbol{D_{jT-1}}\}$
$$\boldsymbol{D_{jT}} = \mathbf{argmin}_{D_j}(\boldsymbol{Pr}(\boldsymbol{p_{T,j}} > \boldsymbol{\phi_T} | \mathcal{O}) > \boldsymbol{\mu_T})$$
- Admissible set of efficacy: $\mathcal{A}_E = \{\boldsymbol{D_{jE+1}}: \boldsymbol{D_J}\}$
$$\boldsymbol{D_{jE}} = \mathbf{argmax}_{D_j}(\boldsymbol{Pr}(\boldsymbol{p_{E,j}} < \boldsymbol{\phi_E} | \mathcal{O}) > \boldsymbol{\mu_E})$$
- Overall admissible set: $\mathcal{A} = \mathcal{A}_T \cap \mathcal{A}_E$
- "Collapse-then-split" method:

  1. Set $\widehat{\boldsymbol{p}}_{\boldsymbol{E,1}} = {}^{\boldsymbol{r_{E,1}}}/_{\boldsymbol{n_1}}, \dots, \widehat{\boldsymbol{p}}_{\boldsymbol{E,j^\triangle}} = \sum_{\boldsymbol{j=j^\dagger}}^{\boldsymbol{J}} \boldsymbol{r_{E,j}} / \sum_{\boldsymbol{j=j^\dagger}}^{\boldsymbol{J}} \boldsymbol{n_j}$

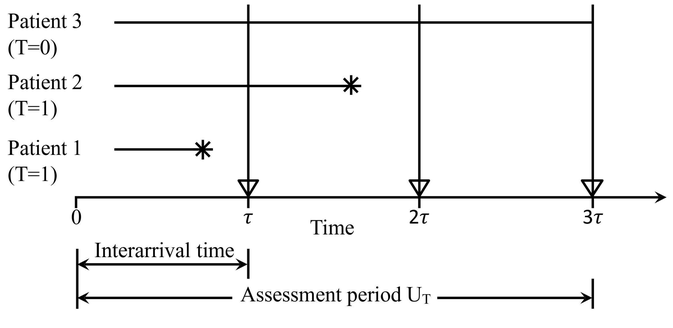
  2. Apply the pooled-adjacent-violators algorithm (PAVA) to $\{\widehat{\boldsymbol{p}}_{\boldsymbol{E,1}}, \dots, \widehat{\boldsymbol{p}}_{\boldsymbol{E,j^\triangle}}\}$ and get the isotonic estimates $\{\widetilde{\boldsymbol{p}}_{\boldsymbol{E,1}}, \dots, \widetilde{\boldsymbol{p}}_{\boldsymbol{E,j^\triangle}}\}$

  3. Re-define the isotonic estimates in plateau as $\widetilde{\boldsymbol{p}}_{\boldsymbol{E,j^\dagger}} = \cdots = \widetilde{\boldsymbol{p}}_{\boldsymbol{EJ}} = \widetilde{\boldsymbol{p}}_{\boldsymbol{E,j^\triangle}}$
- Enumerate all the possible locations for $\boldsymbol{j^\dagger}$ and derive the corresponding isotonic estimates and associated AIC using "Collapse-then-split" method.
- Select the best location and the corresponding estimates based on statistical model-fitting criterion AIC.

Dose-finding design



Delayed outcomes

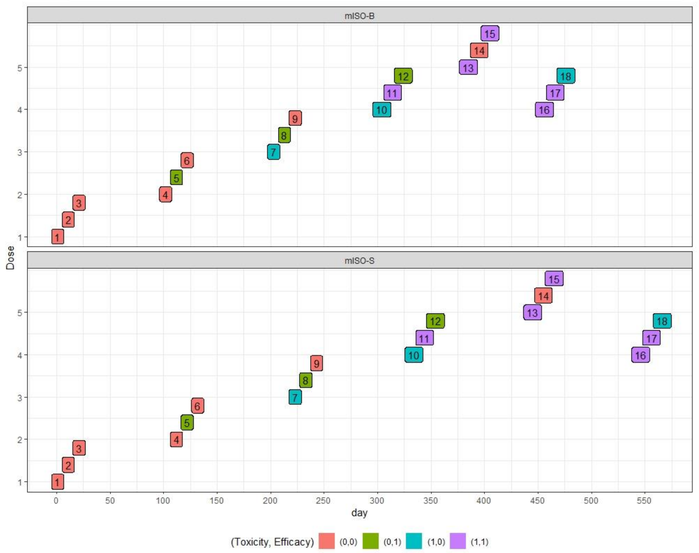


- The horizontal line segment represents the follow-up. The toxicity outcome is indicated by an asterisk and triangles represent the arrival time of a new cohort.

Delayed outcomes

- Toxicity & Efficacy fixed follow-up time: $[\mathbf{0}, \boldsymbol{U_T}]$ & $[\mathbf{0}, \boldsymbol{U_E}]$.
- Delayed outcome: patient interarrival time $\boldsymbol{\tau} < \boldsymbol{U_T}$, or $\boldsymbol{\tau} < \boldsymbol{U_E}$.
- $\boldsymbol{V_T}$ and $\boldsymbol{V_E}$: actual follow-up time of toxicity and efficacy.
- $\boldsymbol{X_T}$ and $\boldsymbol{X_E}$: time to toxicity and efficacy
- $\boldsymbol{Pr}(\boldsymbol{X_T} > \boldsymbol{V_T} | \boldsymbol{D_j}) = \boldsymbol{Pr}(\boldsymbol{X_T} > \boldsymbol{V_T}, \boldsymbol{X_T} > \boldsymbol{U_T} | \boldsymbol{D_j}) + \boldsymbol{Pr}(\boldsymbol{X_T} > \boldsymbol{V_T}, \boldsymbol{X_T} \le \boldsymbol{U_T} | \boldsymbol{D_j}) \approx \mathbf{1} - \boldsymbol{p_{T,j}} + \boldsymbol{p_{T,j}} \frac{\boldsymbol{U_T} - \boldsymbol{V_T}}{\boldsymbol{U_T}} = \mathbf{1} - \frac{\boldsymbol{V_T}}{\boldsymbol{U_T}} \boldsymbol{p_{T,j}} \approx (\mathbf{1} - \boldsymbol{p_{T,j}})^{\boldsymbol{V_T}/\boldsymbol{U_T}}$
- Assume $\boldsymbol{n_{1j}}$ patients being completely followed at dose $\boldsymbol{D_j}$.
- $\boldsymbol{r_{1j}}$ patients among $\boldsymbol{n_{1,j}}$ patients reported DLT.
- $\boldsymbol{n_{2j}}$ pending patients at dose $\boldsymbol{D_j}$ with actual follow-up time for toxicity $\{\boldsymbol{v_{j,1}}, \dots, \boldsymbol{v_{j,n_{2j}}}\}$.
- Likelihood for toxicity:
$$\boldsymbol{L_T} = \prod_{\boldsymbol{j=1}}^{\boldsymbol{J}} (\boldsymbol{p_{T,j}})^{\boldsymbol{r_{1,j}}} (\mathbf{1} - \boldsymbol{p_{T,j}})^{\boldsymbol{n_{1j}} - \boldsymbol{r_{1j}} + \sum_{\boldsymbol{l=1}}^{\boldsymbol{n_{2j}}} \boldsymbol{v_{j,l}} / \boldsymbol{U_T}}$$

Trial implementation



- The mISO-B design incorporates the binomial approximation approach while the mISO-S suspends the trial and defers the interim analysis if any pending patients exist.
- The mISO-B greatly shortens trial duration while having similar decisions to mISO-S.

Simulation studies

Design		Dose level 0	1	2	3	4	5	6	# of sample
Scenario 1									
	True efficacy		0.2	0.4	0.6	0.6	0.6	0.6	
	True toxicity		0.03	0.1	0.15	0.3	0.4	0.5	
mISO	Selection (%)	19.9	0.3	15.7	**54.7**	7.6	1.6	0.1	52.7
	Patient (%)		11.5	26.5	36.7	13.4	8.4	3.5	
ISO	Selection (%)	0.0	11.9	14.2	**44.0**	22.8	6.5	0.5	60.0
	Patient (%)		16.4	18.6	34.5	19.6	8.4	2.5	
MTA-RA	Selection (%)	9.1	1.1	8.3	**43.1**	28.8	8.4	1.2	57.7
	Patient (%)		10.5	17.4	29.3	25.5	12.8	4.5	
Scenario 2									
	True efficacy		0.1	0.2	0.4	0.6	0.6	0.6	
	True toxicity		0.03	0.1	0.15	0.18	0.4	0.5	
mISO	Selection (%)	26.7	0.0	0.2	17.5	**51.8**	3.5	0.3	49.9
	Patient (%)		9.8	13.1	27.7	34.8	10.6	4.1	
ISO	Selection (%)	0.0	15.6	13.8	17.5	**39.2**	13.4	0.5	60.0
	Patient (%)		18.2	14.0	12.4	34.5	15.9	5.0	
MTA-RA	Selection (%)	19.1	1.4	1.6	7.2	**43.4**	23.6	3.7	54.6
	Patient (%)		8.4	9.6	18.7	32.4	23.0	7.7	

Design		Dose level 0	1	2	3	4	5	6	# of sample	Duration (in months)
Scenario 1										
	True efficacy		0.2	0.4	0.6	0.6	0.6	0.6		
	True toxicity		0.03	0.1	0.15	0.3	0.4	0.5		
mISO-B	Selection (%)	20.7	0.5	18.2	**51.8**	7.1	1.6	0.1	52.7	38.3
	Patient (%)		11.8	28.3	34.3	13.5	8.6	3.5		
mISO-S	Selection (%)	19.4	0.3	16.3	**54.6**	7.8	1.4	0.1	52.8	67.8
	Patient (%)		11.6	27.3	36.4	13.2	8.3	3.3		
Scenario 2										
	True efficacy		0.1	0.2	0.4	0.6	0.6	0.6		
	True toxicity		0.03	0.1	0.15	0.18	0.4	0.5		
mISO-B	Selection (%)	27.7	0.0	0.2	18.8	**49.8**	3.0	0.4	49.9	36.7
	Patient (%)		9.9	13.2	28.5	33.1	10.9	4.4		
mISO-S	Selection (%)	27.9	0.1	0.3	16.4	**51.5**	3.4	0.4	49.5	63.6
	Patient (%)		10.0	13.2	27.3	34.6	10.7	4.2		

Conclusion

- Under the setting where the toxicity and efficacy outcomes can be immediately ascertained, the mISO yielded the best performances in terms of OBD selection and percentage of patients treated at OBD under clinically meaningful dose-response curves.
- Under the delayed outcomes setting, the mISO-B yielded slightly lower true OBD selection and patients' allocation percentages than the conventional mISO-S design, but almost halved the trial duration.
- The proposed mISO-B is preferable to the mISO-S design by considering all the design metrics including OBD selection, patients allocation and trial duration.
- The concise, clinically interpretable model expression and dose-finding algorithm make the proposed designs highly translational from the statistical community to the clinical community.