A Constrained Optimum Adaptive Design for Dose Finding in Early Phase Clinical Trials

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Outline

Introduction

- Phase I is designed to assess safety, tolerability and pharmacokinetics (PK) of a drug.
- Phase II is designed to assess the efficacy of a drug.
- Recently, interest has grown in the development of dose finding methods incorporating both toxicity and efficacy as endpoints. Such trials are often seamless phase I-II trials.
- We introduce a new method which along with efficacy and toxicity as endpoints also considers PK information in dose-escalation.
- The goal is to develop an efficient dose finding method that exposes only a few patients to either sub-therapeutic or toxic doses.

Algorithm

Let k represent the stage in a trial and set it to 1 initially. Then the algorithm proceeds as follows:

Step 1: Treat a cohort of size c with the current best dose.
Step 2: Obtain the PK responses at the locally D-optimal sampling time points.
Step 3: Observe the dose-response outcomes.
Step 4: Estimate PK and dose-response parameters. Update the models.
Step 5: Select the best dose for the next cohort based on the chosen criterion and constraints.
Step 6: Do not skip more than one dose level at a time during the trials when the dose level is increased.
Step 7: Stop the trial if the stopping rule is met, otherwise set $k = k + 1$ and repeat Steps 1-6.
Step 8: Carry out a complete analysis of the data to recommend a dose for further studies.

PK Model: An Example

The one-compartment PK model with first-order absorption is

$$y_{il} = \frac{x k_{a_i}}{V_i(k_{a_i} - k_{e_i})} \left(e^{-k_{e_i} t_{il}} - e^{-k_{a_i} t_{il}}\right) + \epsilon_{il},$$

where $i = 1, \ldots, N$, $l = 1, \ldots, n_i$, y_{il} is the concentration of a drug in the blood for the ith individual observed at time t_{il} and x is the dose received.

- Assumptions:
  - $\boldsymbol{\beta}_i = \boldsymbol{\beta} + \boldsymbol{b}_i$, where $\boldsymbol{\beta} = (V, k_e, k_a)^T$ is the vector of mean population parameters and $\boldsymbol{b}_i = (b_{Vi}, b_{k_{e_i}}, b_{k_{a_i}})^T$ is the vector of random effects.
  - $\boldsymbol{b_i} \sim N_3(\mathbf{0}, \boldsymbol{\Omega})$, where $\boldsymbol{\Omega}$ is a diagonal matrix with σ_1^2, σ_2^2 and σ_3^2 on the diagonal.
  - $\boldsymbol{\epsilon_i} \sim N_{n_i}(\mathbf{0}, \sigma^2 \boldsymbol{I})$.
- The vector of population parameters to be estimated is $\boldsymbol{\Psi} = (V, k_e, k_a, \sigma_1^2, \sigma_2^2, \sigma_3^2, \sigma^2)^T$.
- The Fisher information matrix is derived to find the population D-optimal time points.

Dose-Response Model: An Example

- We consider binary outcomes for efficacy (Y) and toxicity (Z) and therefore, have four possible dose-response outcomes of the form (y, z).
- The Cox model (Cox, 1970) is employed to model the probabilities ψ_{yz} of the responses, where

$$\psi_{00}(x, \boldsymbol{\vartheta}) = \frac{1}{1 + e^{\vartheta_1 + \vartheta_2 x} + e^{\vartheta_3 + \vartheta_4 x} + e^{\vartheta_5 + \vartheta_6 x}},$$

$$\psi_{01}(x, \boldsymbol{\vartheta}) = \frac{e^{\vartheta_1 + \vartheta_2 x}}{1 + e^{\vartheta_1 + \vartheta_2 x} + e^{\vartheta_3 + \vartheta_4 x} + e^{\vartheta_5 + \vartheta_6 x}},$$

$$\psi_{10}(x, \boldsymbol{\vartheta}) = \frac{e^{\vartheta_3 + \vartheta_4 x}}{1 + e^{\vartheta_1 + \vartheta_2 x} + e^{\vartheta_3 + \vartheta_4 x} + e^{\vartheta_5 + \vartheta_6 x}}$$

and

$$\psi_{11}(x, \boldsymbol{\vartheta}) = \frac{e^{\vartheta_5 + \vartheta_6 x}}{1 + e^{\vartheta_1 + \vartheta_2 x} + e^{\vartheta_3 + \vartheta_4 x} + e^{\vartheta_5 + \vartheta_6 x}},$$

where $\boldsymbol{\vartheta} = (\vartheta_1, \vartheta_2, \vartheta_3, \vartheta_4, \vartheta_5, \vartheta_6)^T$ is the vector of parameters.

Dose Selection Criterion and Constraints

- Criterion:
  Select the dose x_{k+1} for the next cohort of patients so that

$$x_{k+1} = \arg\max_{x \in \mathcal{X}} \psi_{10}(x, \hat{\boldsymbol{\vartheta}}_k).$$

- Constraints:
  (a) toxicity constraint: $\psi_{\cdot 1}(x_{k+1}, \hat{\boldsymbol{\vartheta}}_k) \leq \gamma$.

  (b) constraint on the maximum concentration:

$$\frac{C_{\max}(x_{k+1}, \hat{\boldsymbol{\beta}}_k) - C_{\max(\text{target})}}{\hat{\text{SD}}(C_{\max_i} | x_k)} \leq \delta(x_k, \hat{\boldsymbol{\vartheta}}_k),$$

  where $\delta(x_k, \hat{\boldsymbol{\vartheta}}_k) = 1/\psi_{10}(x_k, \hat{\boldsymbol{\vartheta}}_k)$.

- Considered cases:
  - maximisation of ψ_{10}, constrained by (a).
  - maximisation of ψ_{10}, constrained by (a) and (b).

Stopping Rules

- We stop the trial when either of the following two happens
  - the same dose is repeated for r cohorts;
  - the trial reaches the maximum number of m cohorts.
- For early stopped trials, the optimum dose (OD) is defined as the dose that has been repeated r times.
- For trials that reach the maximum number of cohorts m, we carry out a complete analysis of the data, and take OD as the dose that would be allocated to cohort $(m+1)$ if that were in the trial.

Simulation Settings

- The available scaled doses are $\mathcal{X} = \{-3.0, -2.4, \ldots, 3.0\}$ and each trial starts with the lowest dose -3.0 mg/kg.
- Three plausible dose-response scenarios (Dragalin and Fedorov, 2006) are investigated assuming a single PK profile.

Table 1: Parameters for simulating PK responses (CV=20%)

V	k_e	k_a	σ_1^2	σ_2^2	σ_3^2	σ^2
2.0	0.05	0.50	0.16	0.0001	0.01	0.00005

- For the initial four cohorts in each of the trials, doses are selected based on an up-and-down design.
- The range of sampling time for PK responses is assumed to be from 0 to 50 hours.

Simulation Settings

- Blood samples are obtained from the ith patient in each cohort of size $c = 3$ at the $n_i = 4$ optimal time points. The time points are obtained using the software *PFIM 3.2* (Bazzoli et al., 2010).
- The accepted level for the probability of toxicity is $\gamma = 0.33$.
- $C_{\max(\text{target})}$ is set as the maximum concentration at the true OD in the scenario.
- We assume $r = 6$ and $m = 20$.
- We assume a joint uniform prior distribution for ϑ for Bayesian estimation.

Results

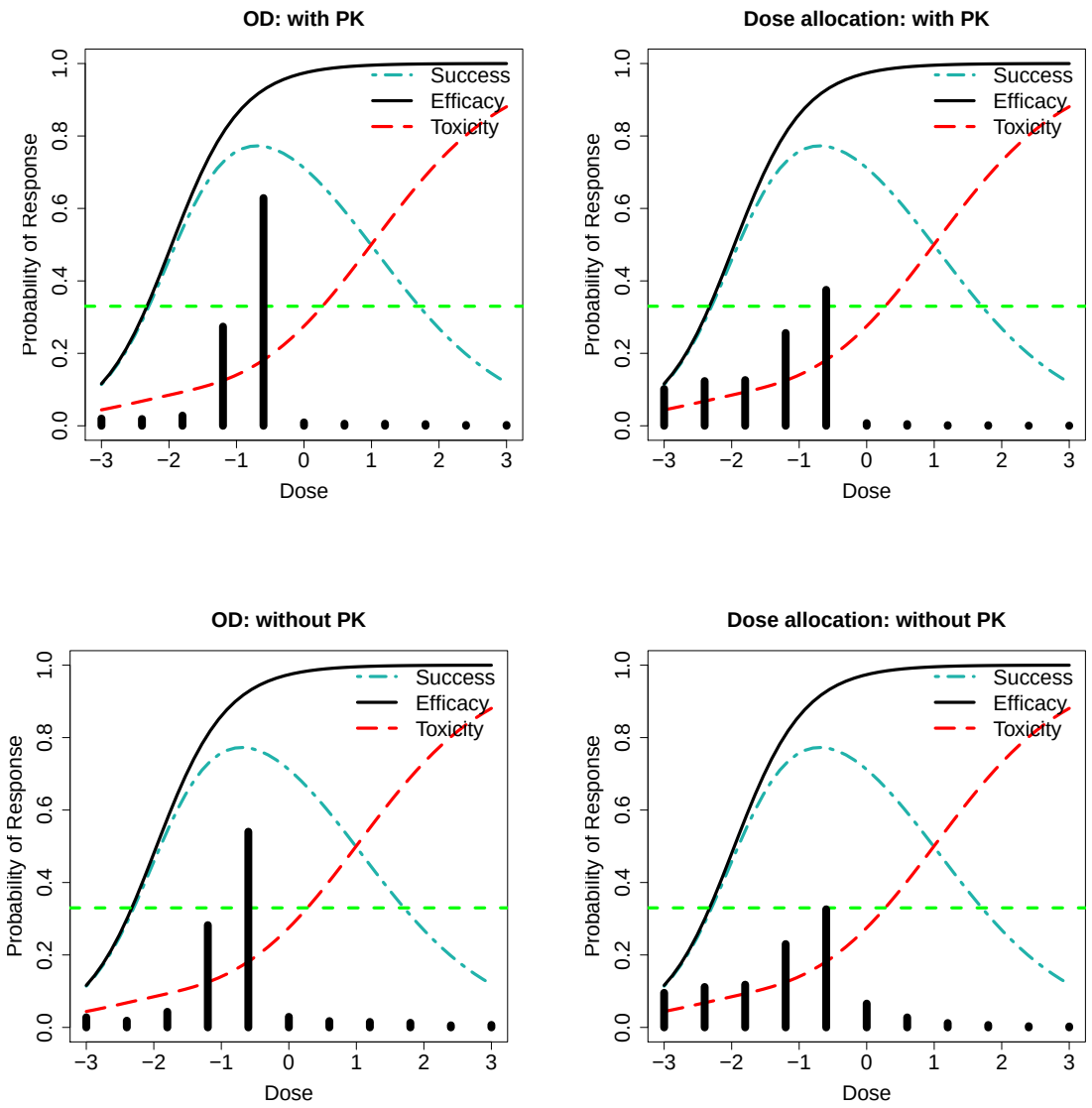

Figure 1: Scenario 1 with the OD as -0.6.

Results

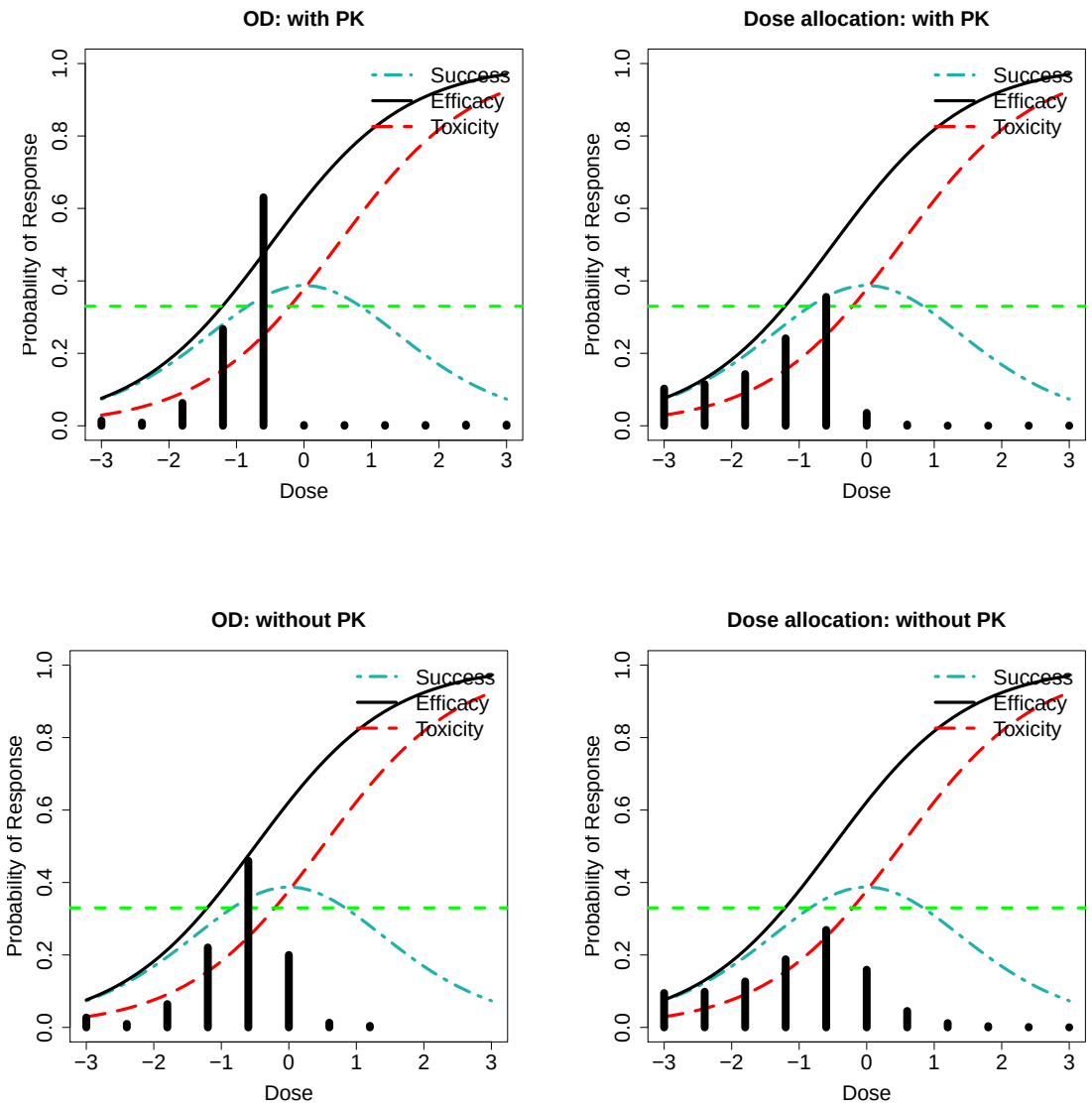

Figure 2: Scenario 2 with the OD as -0.6.

Results

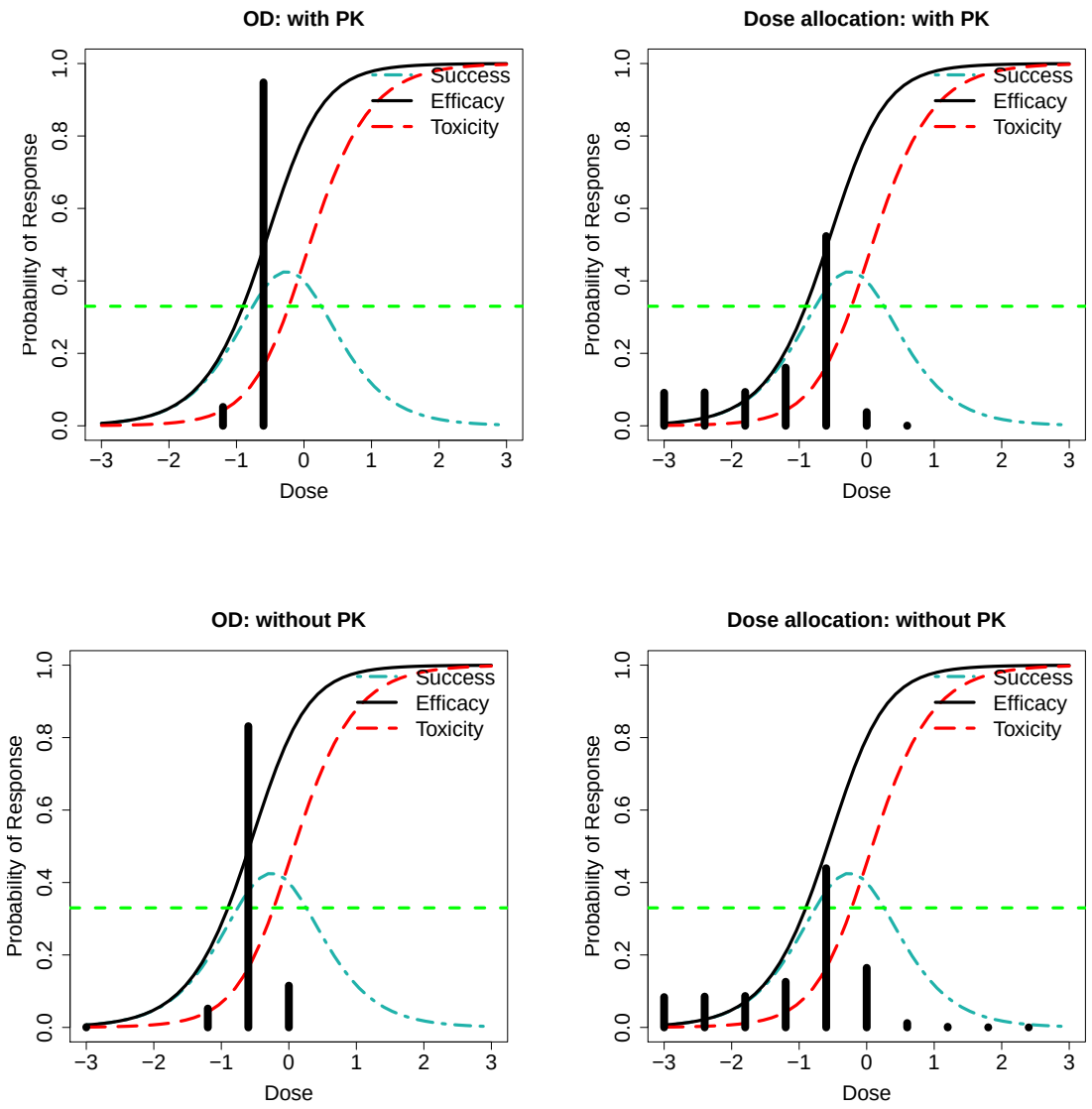

Figure 3: Scenario 3 with the OD as -0.6.

Results

Table 2: Percentage of best dose recommended as optimum for further studies (%OD), percentage of doses recommended as optimum, but carrying the probability of toxicity above the maximum allowed threshold (%TD), and percentage of cohorts treated at the best dose throughout the trials (%AD).

		%OD		%TD		%AD	
Scenario	Best Dose	PK	No PK	PK	No PK	PK	No PK
1	-0.6	62.9	54.0	2.0	5.6	37.5	32.6
2	-0.6	63.1	46.1	1.5	21.7	35.6	26.9
3	-0.6	94.8	83.1	0.0	11.5	52.4	43.9

Discussion

- The presented design is conceptually similar to that of Zhang et al. (2006), but their design does not incorporate PK responses.
- The OD has been identified more accurately in the scenarios.
- The new design has been found to limit overdosing by a considerable amount.
- The design also assigns patients to the most relevant doses throughout the trials.
- Small bias and mean square error of the PK parameter estimates have been found, as the D-criterion was used.
- The bias and mean square error of the dose-response parameter estimates obtained from the two approaches are very similar.
- The design is efficient and ethical.

References

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Thank you