Adaptive Dose Finding in Early Phase Clinical Trials Incorporating Pharmacokinetic Information

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Outline

Clinical Trials

Clinical trials are commonly classified into four phases:

- Phase I is the first stage of testing in humans and designed to assess safety, tolerability and pharmacokinetics (PK) of a drug.
- Phase II is designed to assess how well the drug works and it also monitors safety in a large group of patients.
- Phase III assesses the effectiveness of the drug in comparison with the current standard treatments.
- Phase IV, also known as post-marketing surveillance, aims to detect any rare or long-term adverse effects over a large population.

Goals

- 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.

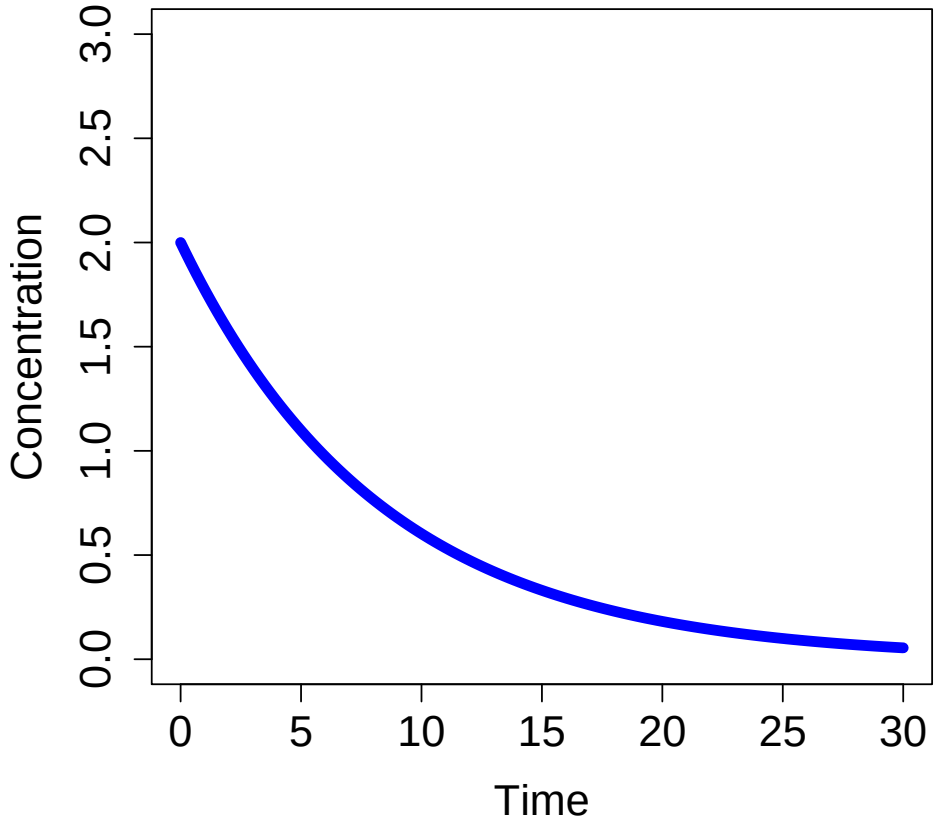

Figure 1: Concentration profile for an individual.

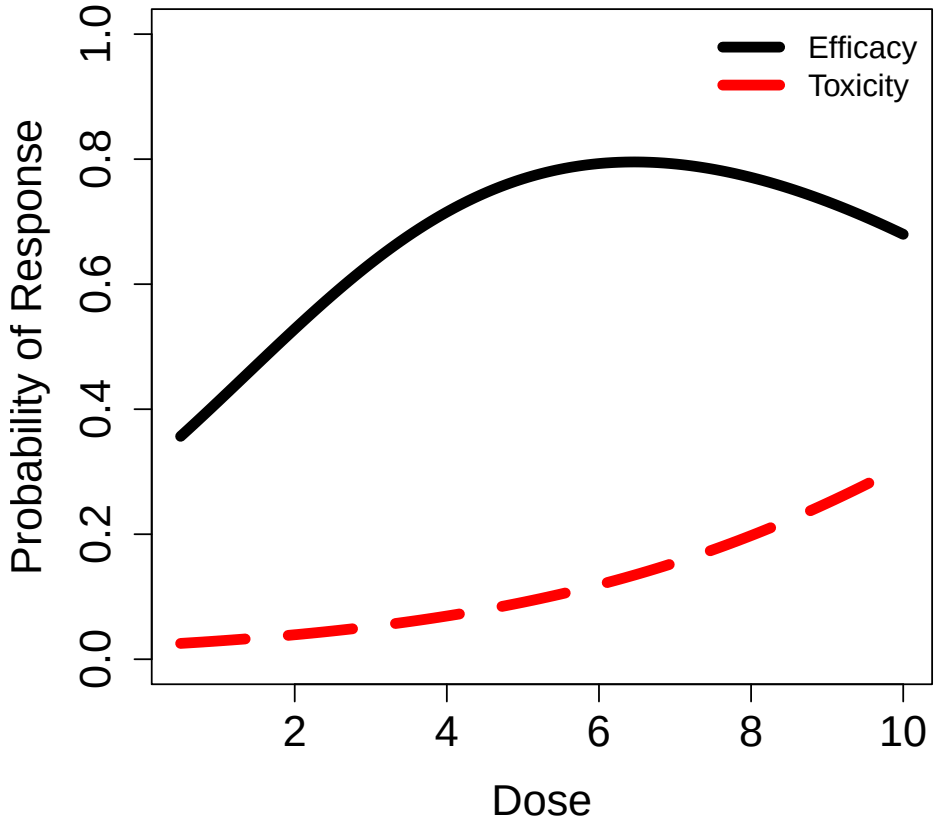

Figure 2: Dose-response curves.

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 dose-response curves.
Step 5: Select the best dose for the next cohort based on the chosen criteria.
Step 6: Stop the trial if the stopping rule is met, otherwise set $k = k + 1$ and repeat Steps 1-5.
Step 7: Carry out a complete analysis of the data to recommend a dose for further studies.

PK Model

The one-compartment PK model with bolus input and first-order elimination is

$$y_{il} = f(\boldsymbol{\theta}_i, t_{il}) + \epsilon_{il} = \frac{x}{V_i}\exp\left(-\frac{Cl_i}{V_i}\, t_{il}\right) + \epsilon_{il},$$

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}, x is the dose received and $\boldsymbol{\theta}_i = (V_i, Cl_i)^T$ is the vector of parameters: volume of distribution and clearance.

- Assumptions:
  - $\boldsymbol{\theta}_i = \boldsymbol{\beta} + \boldsymbol{b}_i$, where $\boldsymbol{\beta} = (V, Cl)^T$ is the vector of mean population parameters and $\boldsymbol{b}_i = (b_{Vi}, b_{Cli})^T$ is the vector of random effects.
  - $\boldsymbol{b_i} \sim N_2(\mathbf{0}, \boldsymbol{\Omega})$, where $\boldsymbol{\Omega}$ is a diagonal matrix with σ_1^2 and σ_2^2 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 $\boldsymbol{\Psi} = (V, Cl, \sigma_1^2, \sigma_2^2, \sigma^2)^T$.
- The Fisher information matrix is derived to find the population D-optimal time points.

Dose-Response Model

- We consider a trinomial response $\boldsymbol{Y} = (Y_0, Y_1, Y_2)^T$ for each patient, where Y_0 is a neutral response, Y_1 is an efficacious response and Y_2 is a toxic response.
- The corresponding probabilities are $\psi_0(x, \boldsymbol{\vartheta}), \psi_1(x, \boldsymbol{\vartheta})$ and $\psi_2(x, \boldsymbol{\vartheta})$ so that $\psi_0(x, \boldsymbol{\vartheta}) + \psi_1(x, \boldsymbol{\vartheta}) + \psi_2(x, \boldsymbol{\vartheta}) = 1$, where $\boldsymbol{\vartheta}$ is the vector of dose-response parameters.
- The continuation ratio model of Fan and Chaloner (2004) is employed to model the responses, and is given as

$$\log\left(\frac{\psi_1(x, \boldsymbol{\vartheta})}{\psi_0(x, \boldsymbol{\vartheta})}\right) = \vartheta_1 + \vartheta_2 x$$

and

$$\log\left(\frac{\psi_2(x, \boldsymbol{\vartheta})}{1 - \psi_2(x, \boldsymbol{\vartheta})}\right) = \vartheta_3 + \vartheta_4 x,$$

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

Dose Selection Criteria

Denote $\hat{\boldsymbol{\vartheta}}_k = (\hat{\vartheta}_{k1}, \hat{\vartheta}_{k2}, \hat{\vartheta}_{k3}, \hat{\vartheta}_{k4})^T$. We select the dose x_{k+1} for the next cohort of patients so that

$$x_{k+1} = \arg\max_{x \in \mathcal{X}} \psi_1(x, \hat{\boldsymbol{\vartheta}}_k),$$

subject to the conditions that

$$\psi_2(x_{k+1}, \hat{\boldsymbol{\vartheta}}_k) \leq \gamma$$

and

$$\frac{h(x_{k+1}, \hat{\boldsymbol{\beta}}_k) - AUC_{\text{target}}}{\hat{\text{SD}}(C_i|x_k)} \leq \delta,$$

where γ is the accepted level for the probability of toxicity and $\delta = 1/\psi_1(x_k, \hat{\boldsymbol{\vartheta}}_k)$. The vector of estimates of the mean population PK parameters is $\hat{\boldsymbol{\beta}}_k$ and $h(x, \hat{\boldsymbol{\beta}}_k)$ is the estimate of the approximated AUC at stage k. The estimate of the approximated standard deviation of AUC is denoted by $\hat{\text{SD}}(C_i|x_k)$.

Stopping Rules

- 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. However, for trials that reach the maximum number of cohorts m, we carry out a complete analysis of the data, and define OD as the dose that would be allocated to cohort $(m+1)$ if that cohort were in the trial.

Simulation Settings

- The available doses are $\mathcal{X} = \{0.5, 1.0, \ldots, 10.0\}$ and each trial starts with the lowest dose 0.5 mg/kg.
- Four hypothetical dose-response scenarios are investigated assuming a single PK profile.

Table 1: Parameters for simulating PK responses

V	Cl	σ_1^2	σ_2^2	σ^2
0.5	0.06	0.004	0.00005	0.000225

- For the initial four cohorts in each of the trials, doses are selected based on an up-and-down design.
- The sampling time for PK responses is assumed to be from 0 to 30 hours.
- Blood samples are obtained from the ith patient in each cohort of size $c = 3$ at the $n_i = 3$ optimal time points, obtained using the software *PFIM 3.2* (Bazzoli et al., 2010).

Simulation Settings

- The accepted level for probability of toxicity is $\gamma = 0.20$.
- AUC_{target} is set as the AUC at true OD in the scenario.
- Assume $r = 6$ and $m = 20$.
- We employ a joint uniform prior distribution for ϑ for Bayesian estimation.
- The design is not allowed to skip more than one dose level at a time during the trials when the dose level is increased.

OD and Dose Allocation

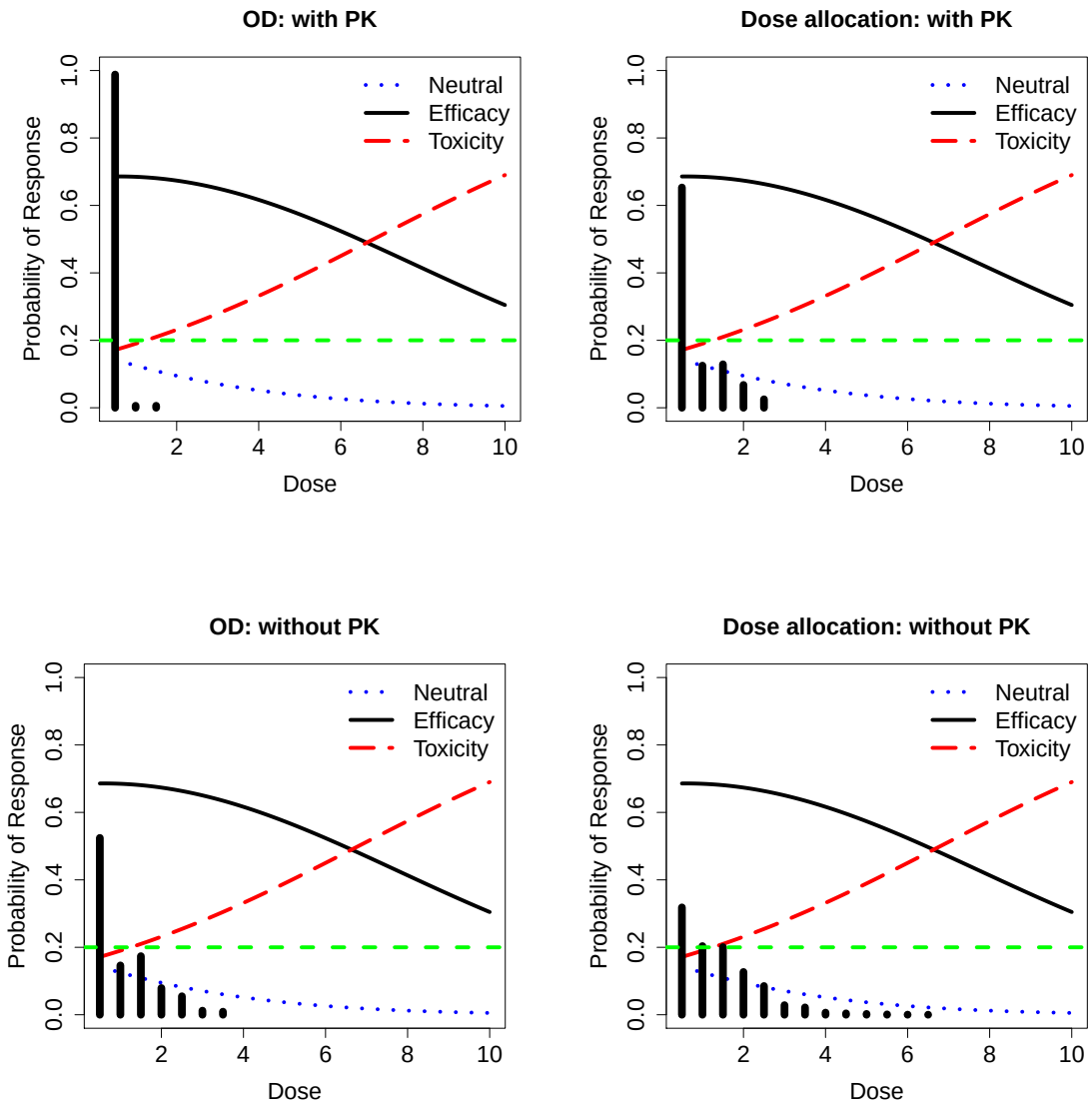

Figure 3: Scenario 1 with the OD as 0.5.

OD and Dose Allocation

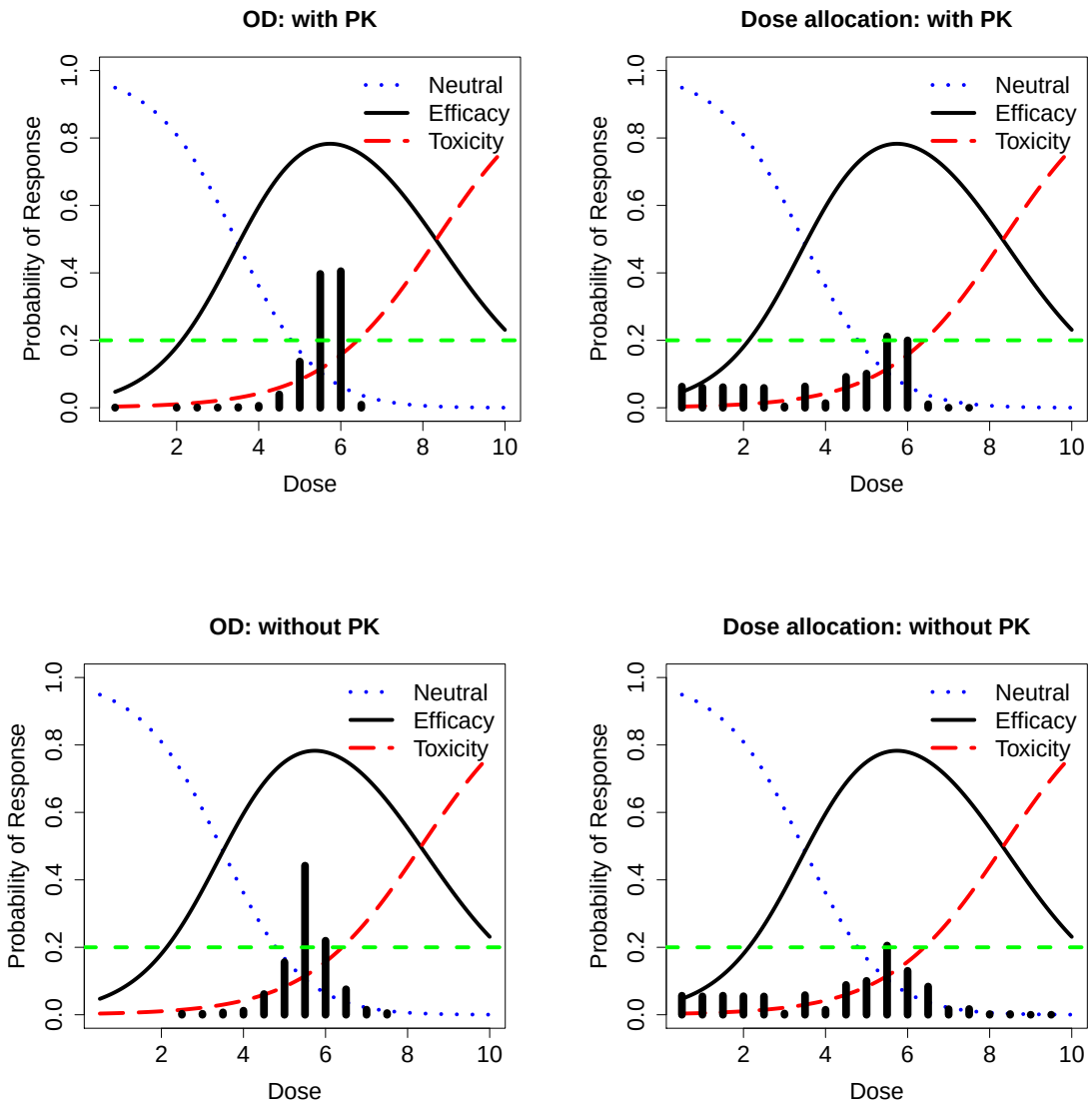

Figure 4: Scenario 2 with the OD as 5.5.

OD and Dose Allocation

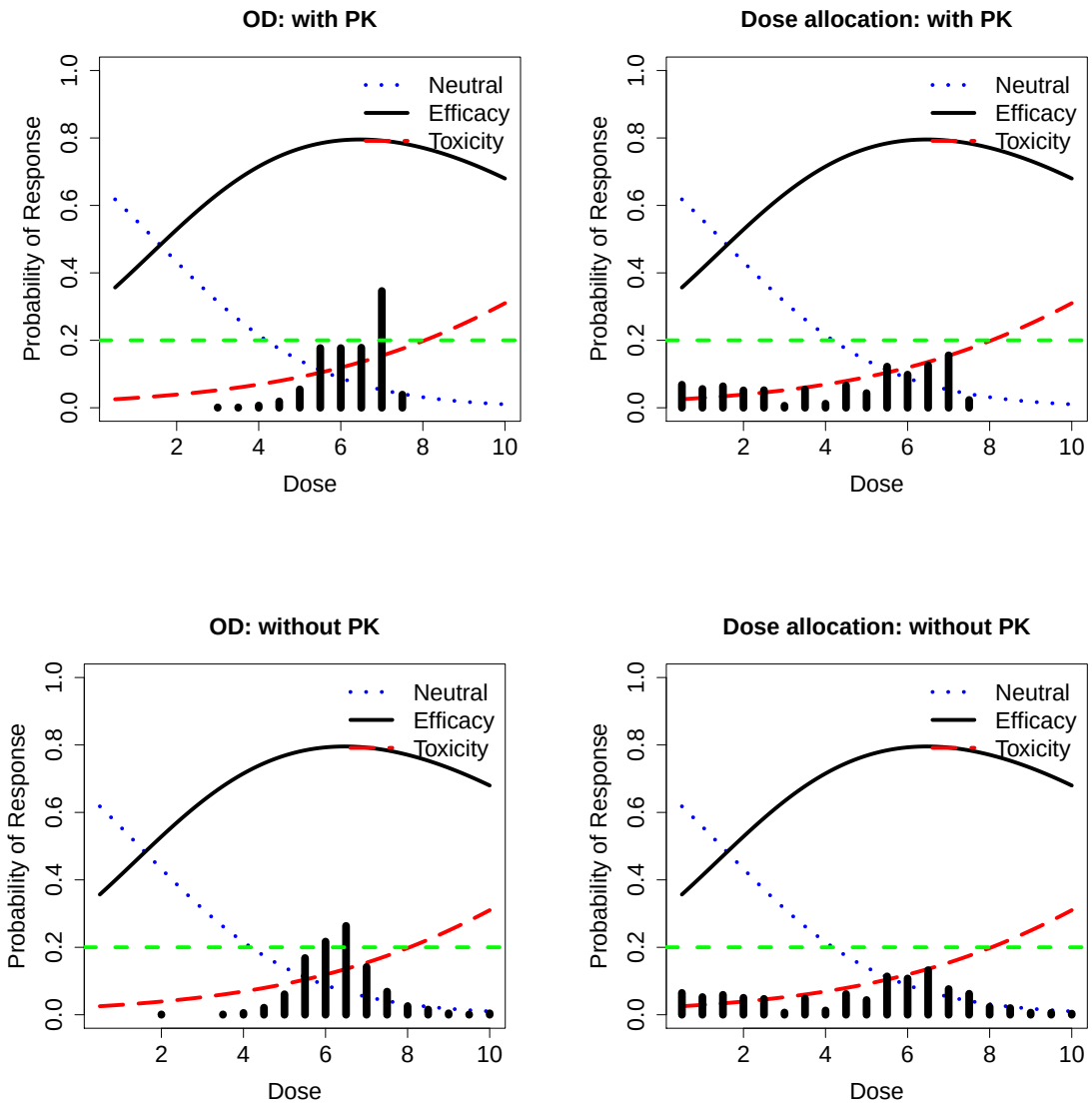

Figure 5: Scenario 3 with the OD as 6.5.

OD and Dose Allocation

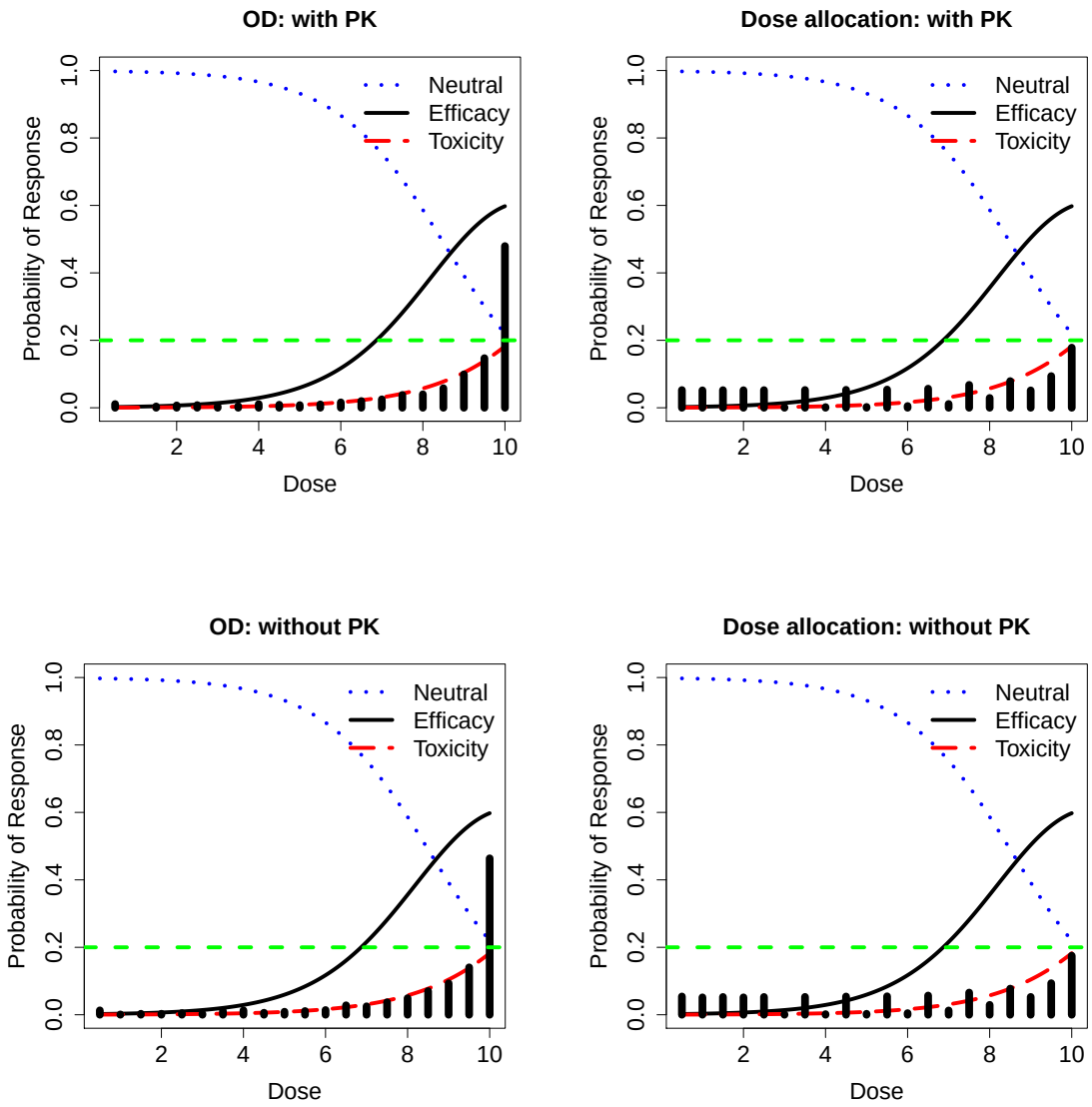

Figure 6: Scenario 4 with the OD as 10.0.

Dose-Response Parameter Estimates

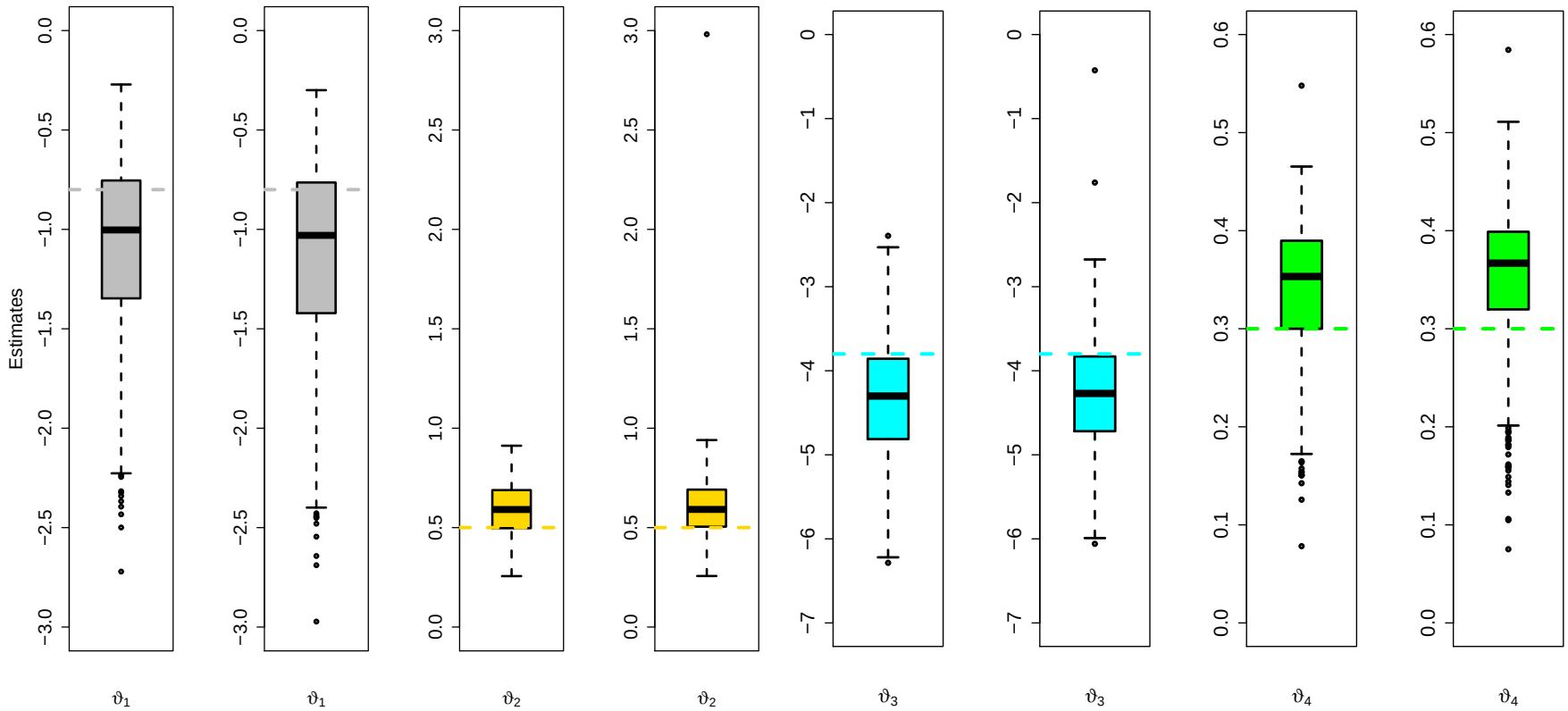

Figure 7: Box plots of the dose-response parameter estimates for scenario 3 obtained from simulations. The dotted horizontal lines indicate the respective true parameter values used in the simulations.

PK Parameter Estimates

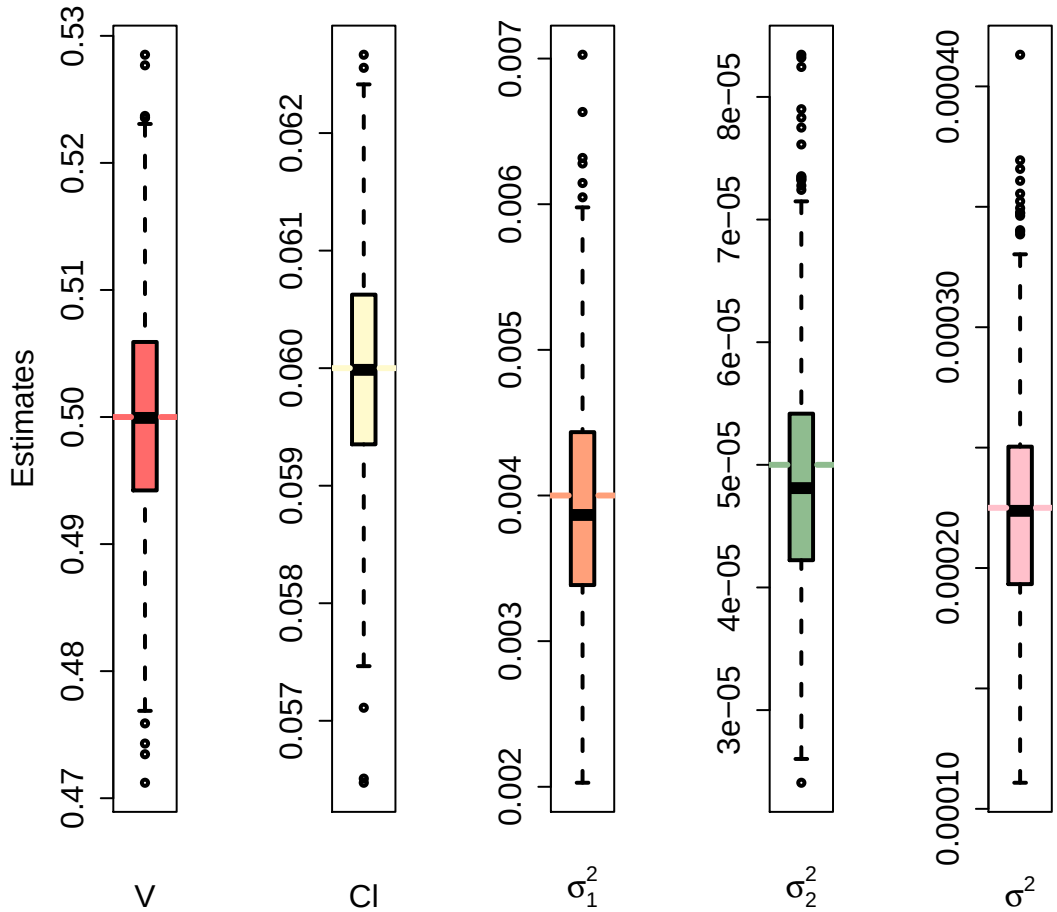

Figure 8: Box plots of the PK parameter estimates for scenario 3 obtained from simulations. The dotted horizontal lines indicate the respective true parameter values used in the simulations.

Average Cohorts Used

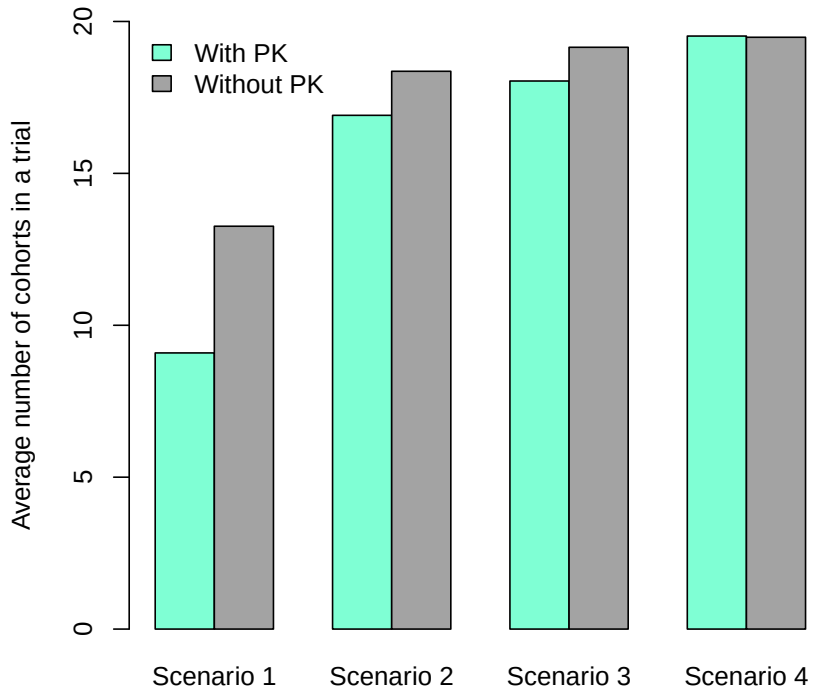

Figure 9: Average number of cohorts used in different scenarios by two different dose allocation scheme.

Discussion

- The presented design is conceptually similar to that of Zhang et al. (2006), but their design does not incorporate PK responses.
- The new design has been found to limit overdosing by a considerable amount depending on the location of the OD in the scenario.
- The OD has also been identified more accurately.
- The design also assigns most of the 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 most of the dose-response parameter estimates from the PK guided approach are slightly smaller than that of the other approach.
- The design is efficient and ethical.

References

Bazzoli, C., T. T. Nguyen, A. Dubois, E. Retout, S. Comets, and F. Mentré (2010). *PFIM 3.2 User Guide*. Université Paris Diderot and INSERM.

Fan, S. K. and K. Chaloner (2004). Optimal designs and limiting optimal designs for a trinomial response. *Journal of Statistical Planning and Inference 126*(1), 347–360.

Zhang, W., D. J. Sargent, and S. Mandrekar (2006). An adaptive dose-finding design incorporating both toxicity and efficacy. *Statistics in Medicine 25*(14), 2365–2383.

Thank you