Adaptive Dose Finding in Early Phase Clinical Trials Incorporating Pharmacokinetic Information

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

\[ y_{il} = f(\theta_i, t_{il}) + \epsilon_i = \frac{x}{V_i} \exp \left( -\frac{C_{li}}{V_i} t_{il} \right) + \epsilon_i, \]

where \( i = 1, \ldots, N \), \( l = 1, \ldots, n_i \), \( y_{il} \) is the concentration of a drug in the blood for the \( i \)th individual observed at time \( t_{il} \), \( x \) is the dose received and \( \theta_i = (V_i, C_{li})^T \) is the vector of parameters: volume of distribution and clearance.

- **Assumptions:**
  - \( \theta_i = \beta + b_i \), where \( \beta = (V, Cl)^T \) is the vector of mean population parameters and \( b_i = (b_{Vi}, b_{Cl_i})^T \) is the vector of random effects.
  - \( b_i \sim N_2(0, \Omega) \), where \( \Omega \) is a diagonal matrix with \( \sigma_1^2 \) and \( \sigma_2^2 \) on the diagonal.
  - \( \epsilon_i \sim N_{n_i}(0, \sigma^2 I) \).

- The vector of population parameters to be estimated is \( \Psi = (V, Cl, \sigma_1^2, \sigma_2^2, \sigma^2)^T \).
- The **Fisher information matrix** is derived to find the population \( D \)-optimal time points.
Dose-Response Model

- We consider a trinomial response $Y = (Y_0, Y_1, Y_2)^T$ 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 $\psi_0(x, \vartheta), \psi_1(x, \vartheta)$ and $\psi_2(x, \vartheta)$ so that $\psi_0(x, \vartheta) + \psi_1(x, \vartheta) + \psi_2(x, \vartheta) = 1$, where $\vartheta$ 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

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

and

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

where $\vartheta = (\vartheta_1, \vartheta_2, \vartheta_3, \vartheta_4)^T$ is the vector of parameters to be estimated.
Dose Selection Criteria

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

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

subject to the conditions that

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

and

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

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

<table>
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<th>$V$</th>
<th>$Cl$</th>
<th>$\sigma^2_1$</th>
<th>$\sigma^2_2$</th>
<th>$\sigma^2$</th>
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<td>0.5</td>
<td>0.06</td>
<td>0.004</td>
<td>0.00005</td>
<td>0.000225</td>
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</tbody>
</table>

- 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 $i$th 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 $\gamma = 0.20$.
- $AUC_{\text{target}}$ 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 $\vartheta$ 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.
Figure 3: Scenario 1 with the OD as 0.5.
Figure 4: Scenario 2 with the OD as 5.5.
OD and Dose Allocation

Figure 5: Scenario 3 with the OD as 6.5.
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.
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.
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


Thank you