A comparative analysis of Phase I dose-finding designs incorporating pharmacokinetics information

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Introduction

- "First-in-human" and Phase I studies aim at evaluating the safety of a candidate drug, along with pharmacokinetics (PK), and include a small sample of healthy volunteers or patients.
- Conventional randomized designs can be unethical with low sample size. Adaptive approaches using Bayesian designs, leveraging pre-existing data and/or expert opinion to make prior guesses, are often employed to assess the toxicity.
- In most Phase I and Phase I/II studies in patients, dose-finding and PK are still analyzed separately [1]. Various methods have been proposed in recent literature to integrate PK data in the toxicity estimation.

Objectives

- **Narrative review**: Explore how PK information is used in existing Bayesian prospective PK dose-finding designs.
- **Simulation study**: Assess the performance and robustness of these methods for accurate Maximum Tolerated Dose (MTD) identification and dose-toxicity curve.

PK dose-finding methods

We conducted a narrative review to identify existing Bayesian prospective PK dose-finding designs *(see Table).*

1. Preliminary review of well-known papers on dose-finding designs for early phase clinical trials.
2. Keyword searchs yielded more publications, totaling 84.
3. Filtering sequentially for eligibility based on abstract and full publication content resulted in 3 selected papers.

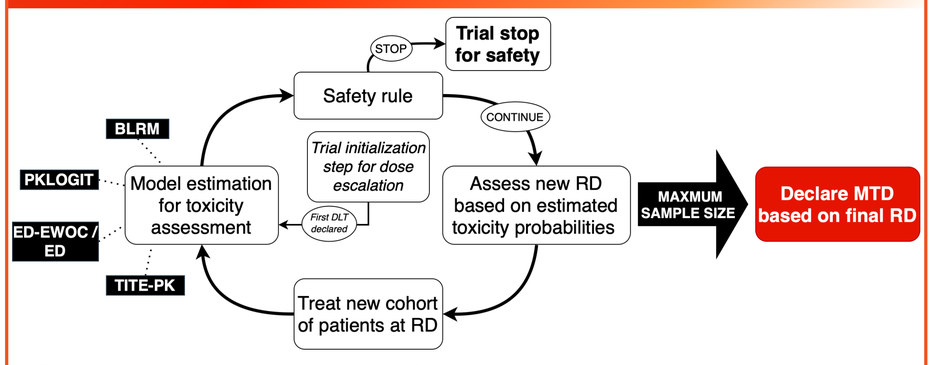
The Bayesian Logistic Regression Method (BLRM), which does not use PK data, was implemented as a benchmark.

Notations

- n the total number of patients in the trial ($i \in \{1, \dots, n\}$),
- p_T the probability of toxicity with $Y_i \sim \text{Bernoulli}(p_T)$,
- $\mathcal{D}$ the K-length set of doses with d_k the dose-level $k \in \{1, \dots, K\}$ and d^* the reference dose,
- d_i the dose received by the i-th patient,
- λ the target probability of toxicity,
- sampling times $\boldsymbol{t} = (t_1, \dots, t_j, \dots, t_J)$ with j ∈ $\{1, \dots, J\}$,
- $C_i(t_j)$ and c_{ij} respectively the actual and measured concentration of the drug in the i-th patient at time t_j,
- z_i the logarithm of the AUC of the i-th patient,
- and z^* the reference logarithm of the AUC based on d^*.

Name	Input data	Model
BLRM [2]	Toxicity Y_i Dose d_i	**Logistic regression** $\text{logit}(p_T(d_k, \boldsymbol{\beta})) = \log(\beta_1) + \beta_2(\log(d_k) - \log(d^*))$
PKLOGIT [3]	Toxicity Y_i Dose d_i *Trapezoidal rule:* Estimated z_i from c_{ij}	**Normal approximation of AUC** $z_i \mid \boldsymbol{\beta}, \nu \sim \mathcal{N}(\beta_0 + \beta_1 \log(d_i), \nu^2)$ **Logistic regression** $\text{logit}(p_T(z, \boldsymbol{\beta'})) = \beta_2 + \beta_3(z - z^*)$
ED-EWOC / ED [4]	Toxicity Y_i Dose d_i Measured concentrations c_{ij} Sampling times $\boldsymbol{t}$	**PopPK model** $C(t_j \mid d_i, \beta_{1i}) = c(d_i, t_j, \beta_{1i}) \times (1 + \epsilon_{ij})$, $\epsilon_{ij} \sim \mathcal{N}(0, \sigma_\epsilon^2)$ **Logistic regression** $\text{logit}(p_T(z_i \mid \beta_2, \beta_3)) = \beta_2 + \beta_3(z_i - z^*)$
Naive / Informed TITE-PK [5]	Toxicity Y_i Dose d_i Sampling times t_1 and t_J Time of administration t_0 Time of the DLT or censoring time	**K-PD: One-compartment model with IV** $\begin{cases} \frac{dC(t)}{dt} = -k_e C(t) \\ \frac{dC_{\text{eff}}(t)}{dt} = k_{\text{eff}}(C(t) - C_{\text{eff}}(t)) \end{cases}$ **Complementary log-log regression** $\text{cloglog}(P(T \le t^* \mid C_{\text{eff}}(t^* \mid d))) = \log(\beta) + \log(\text{AUC}_E(t^* \mid C_{\text{eff}}(t^* \mid d)))$

Simulation study: Trial procedure



Dose recommandation rule: After i patients have been included in the trial, the recommended dose (RD) $d_{(i+1)}$ for a hypothetical $(i+1)$-th patient is $d_{(i+1)} = \underset{k \in \mathcal{D}}{\text{argmin}} \left| \widehat{p(d_k)} - \lambda \right|$.

Safety rule: Based on a predefined safety probability threshold τ_{Safe}, the safety rule is expressed as $\mathbb{P}(p_T(d_1) > \lambda) < \tau_{\text{Safe}}$.

Simulation settings

All methods were evaluated for a Phase I dose-finding trial based on the PK model for the development of the TGF-β inhibitor LY2157299 [6], in a simulation study consisting of…

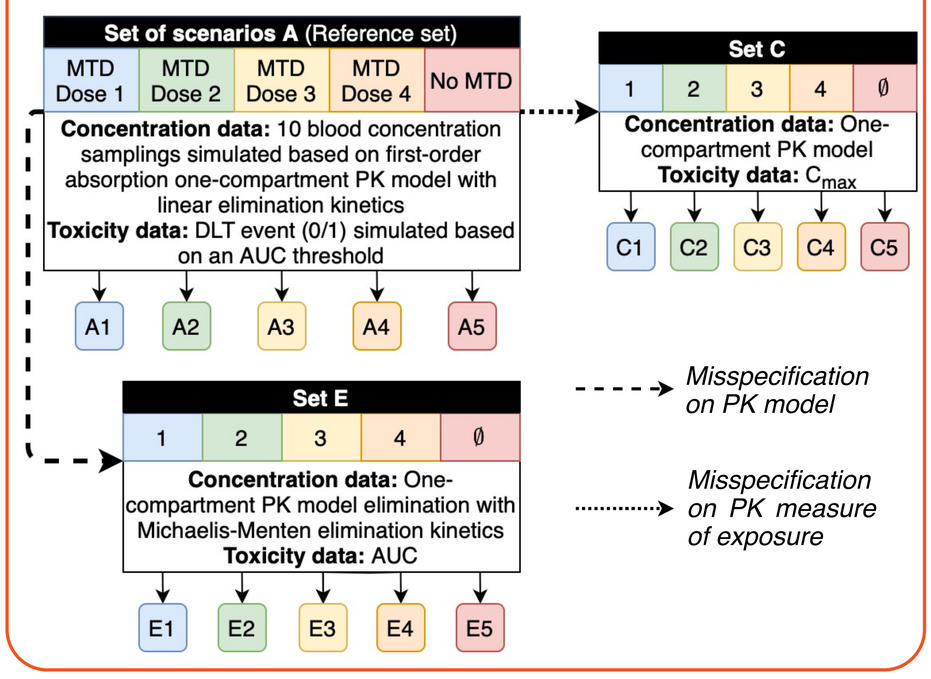
- 1000 clinical trials,
- 30 patients per trial,
- cohorts of size 2,
- 4 doses (30.6 mg, 50.69 mg, 93.69 mg, and 150.37 mg) with dose-level 3 as the reference,
- a targeted probability of toxicity $\lambda = 25\%$,
- and a threshold for the safety rule $\tau_{\text{Safe}} = 90\%$.

Scenarios

15 scenarios divided into 3 sets of scenarios (A, C, and E), each containing 5 scenarios to explore different settings:

- **Among each set**: Deviation on the position of the MTD
- **Across each set**: Misspecification of PK measures of exposure (AUC or C_{max}) and/or misspecification of PK model (e.g. number of compartiments).

For comparison purposes, the set of scenarios A is taken as the standard simulation framework.



Results

Dose-finding methods were compared using the probability of selecting the correct MTD based on its location from the simulation study. The estimated probabilities of toxicity were also evaluated for each method.

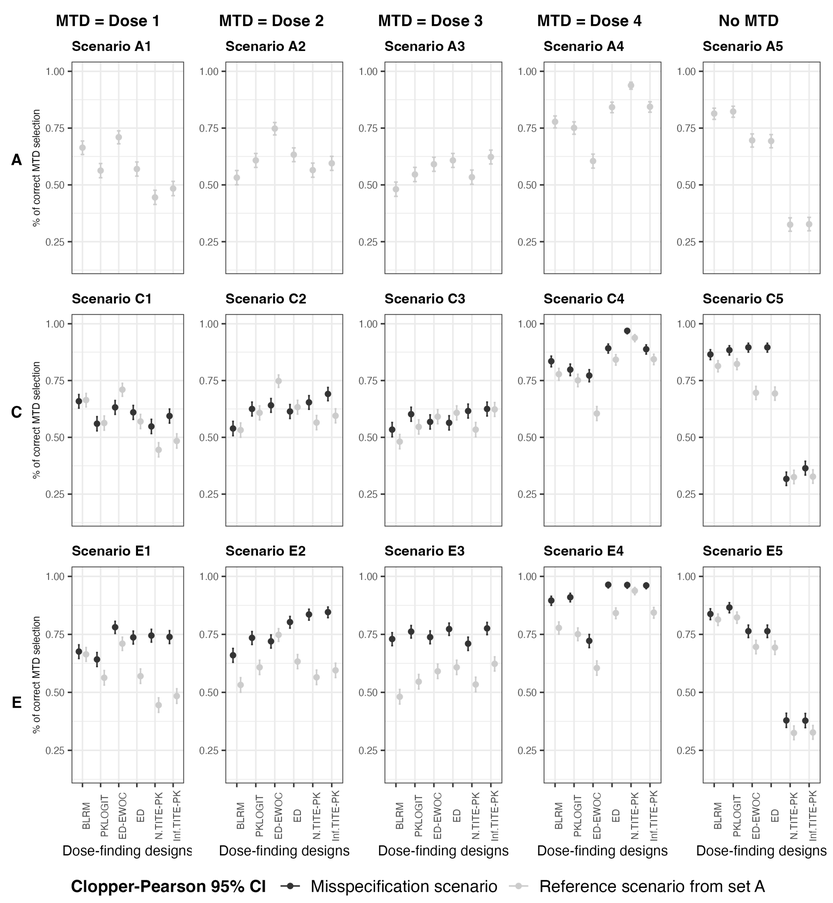
Comprehensive comparaison for the percentage (%) of accurate MTD selection.

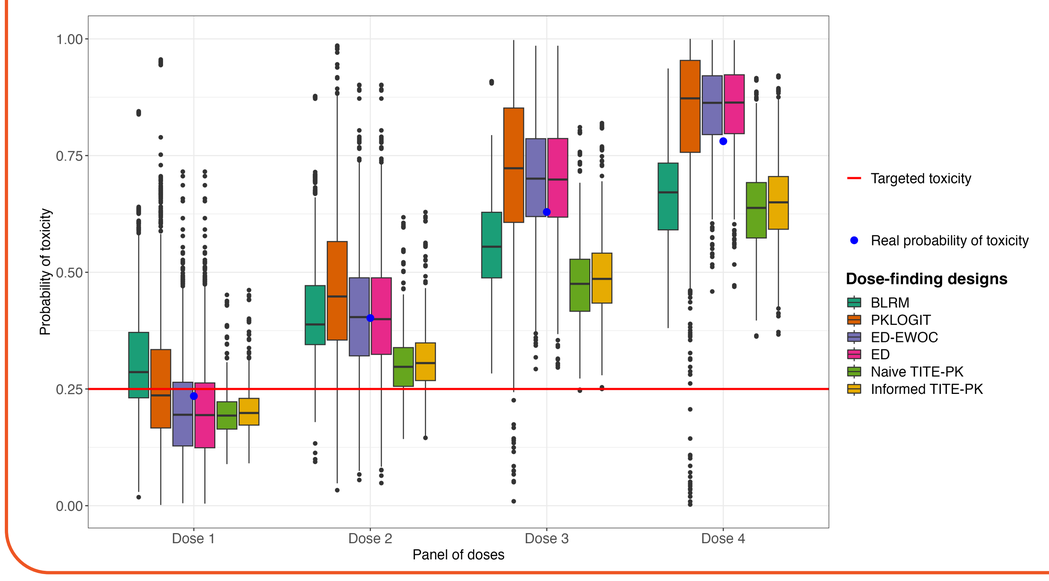
Set A

- PK dose-finding designs as accurate as BLRM on average with ED-EWOC leading in terms of correct MTD selection for scenario A1 and A2, except TITE-PK.
- Almost all PK methods performed better than BLRM in scenarios A3 and A4, with informed TITE-PK being on the top.
- PKLOGIT performed on average marginally worse than the most effective PK dose-finding methods in scenarios A1, A2, A3, and A4.
- ED-EWOC outperformed ED, showing effective overdose control for lower-dose MTD. However, in scenarios A3 and A4, the results were reversed.
- Naive and informed TITE-PK methods failed to stop early and overwhelmingly recommended dose-level 1 as the MTD for scenario A5 (64%).

- **Set C**: For scenarios C1, C2, C3 and C4, ED-EWOC and ED were respectively outperformed by informed and naive TITE-PK methods.

- **Set E:** Better performance in terms of correct MTD selection compared to set A.





Dose-toxicity curve

- BLRM completely failed to estimate the toxicity probabilities.
- Plausible estimates of the probabilities of toxicity obtained by PKLOGIT and ED(-EWOC), the latter being the best performer.
- Large variation in the estimate for PKLOGIT due to AUC modelling.
- TITE-PK fails to accurately estimate the probabilities of toxicity.

Figure: *Scenario A1 - Estimated probabilities of toxicity at all doses for all dose-finding methods where the MTD is on dose-level 1.*

Discussion & Conclusion

- PKLOGIT is the most straightforward approach for PK modelling and therefore underperforms slightly compared to other methods. ED-EWOC/ED shows high potential with the popPK approach, especially under misspecification, but is generally less accurate than TITE-PK for MTD selection. TITE-PK achieves consistent results, barring low-dose MTDs and misspecification scenarios.
- Model-based approaches incorporating PK information are likely to recommend, at least as much as the BLRM, accurate MTDs and achieve safer dose-escalation. Additionally, PK dose-finding methods can evaluate the full dose-toxicity curve and provide more or less plausible estimates of the probability of toxicity for each dose with a limited sample size.
- Combining popPK modeling and time-to-event approach for toxicity in Phase I dose-finding trial seems to offer promising perspective for future development of effective methods.

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