# Phase I dose-escalation trials with more than one dosing regimen

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Traditionally, phase I dose-escalation oncology trials are designed to find a dose at which an acceptable event rate of dose limiting toxicities (DLT) occur. However, nowadays the dosing regimen, which determines the timing of drug administration, is varied in addition to the drug amount itself; e.g. a daily or a weekly administration schedule. Standard methods like the Bayesian Logistic Regression Model[1] do not directly allow for more than one dosing regimen to be evaluated, and hence ad-hoc approaches like dose re-scaling are used to make dosing regimens comparable, which may result in strong discounting of the available information. To overcome this, we propose a new statistical model that uses pharmacokinetic (PK) principles to integrate varying dosing regimens. We propose to use a latent *pseudo-PK*, which uses the preplanned dosing regimen. We complement the *pseudo-PK* by an effect compartemet which admits a delay between the PK and the actual effect, the occurence of a DLT.[2] The effect compartement measure is used as exposure measure and set directly proportional to the instantaneous hazard of the time-to-first DLT event process.[3] The model formulated using interpretable parameters which facilitates the specification of priors. Moreover, we derive from the time-to-event model metrics which enable escalation with overdose control. In a Monte Carlo simulation study, the proposed model displayed desirable operating characteristics across a range of dose-toxicity profiles, especially with different dosing regimens. The proposed model is motivated and illustrated by a real-life example. The software to fit the proposed model is implemented in Stan.[4]

**Keywords**: Phase I dose-escalation trials, multiple dosing regimens, pharmacokinetic models, Stan

## References

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