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 weekly or daily schedule. Standard methods such as the Bayesian Logistic Regression Model 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. To avoid such ad-hoc approaches, 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 compartment which admits a delay between the PK and the actual effect, the occurrence of a DLT. The effect compartment measure is used as exposure measure and set directly proportional to the instantaneous hazard of the time-to-first DLT event process. The model is 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 performance in terms of investigated measures across a range of dose-toxicity profiles including single and varying dosing regimens. The proposed model is motivated and illustrated by a real-life example. The software to implement the proposed model (R and Stan code) is publicly available.

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

1 Introduction

Phase I dose-escalation trials constitute the first step in investigating the safety of potentially promising drugs in humans.1 In oncology, such trials traditionally focused on identifying the maximum tolerated dose (MTD) and/or the recommended phase II dose through a series of dose escalation steps. The almost exclusive focus on safety in oncology is driven by the fact that cytotoxic drugs are generally most effective at the MTD. While safety is central to all drug therapy, its role in dose selection for other mechanisms of action is more nuanced.

Dose-escalation trials in oncology traditionally enroll small cohorts of patients who are treated in cycles. Typically, the estimation of the MTD is based on the toxicity data of the first cycle data only. The observed toxicities are classified into dose-limiting toxicities (DLT) and non-DLTs. Each time a cohort finishes its first cycle at a given dose intensity, the available data is assessed to decide how the trial proceeds. A commonly accepted target for the MTD is to allow for a DLT probability of 33% per cycle of treatment.2 To facilitate effective and safe learning in the dose escalation trials, adaptive model based approaches such as the Continual Reassessment Method (CRM)3 or the Bayesian Logistic Regression Model (BLRM)4,2 are commonly used. Both of these methods predict the toxicity profile for all doses planned in a given trial, which includes a prediction for already tested and yet untested dose-levels. These model based assessments are used to guide the dose-escalation trial in order to warrant the
safety of patients by avoiding unacceptable high risks for DLTs. The BLRM is a two parameter version of the CRM which avails of the so-called Escalation-With-Overdose-Control (EWOC) principle; i.e. requires that for a given dose the probability for a DLT must not exceed the maximal admissible DLT probability by a fixed uncertainty margin. The BLRM has been shown to have good performance in extensive simulation studies, and has been used for many phase I trials including drug combination trials (see e.g.). Furthermore, historical data can be incorporated via meta-analytic predictive (MAP) prior to improve predictive performance.

A key limitation of the BLRM is that it cannot naturally take into account differing dosing regimens (different dosing amounts and frequencies) which are more commonly used in oncology, for example starting with a weekly dosing regimen and then changing to a daily dosing regimen. Changes in regimens mean that scaling by dose alone is no longer necessarily a valid assumption because for a given dose level very different responses may be observed depending on the frequency of administration. A trivial analogy is that it matters if we drink 3 units of alcohol in 1 hour or over 3 hours. Often, ad hoc approaches such as dose re-scaling are used in an attempt to account for the regimen effect. Such ad hoc approaches are always context specific approximation, meaning multiple models are necessary for multiple regimens and in addition data from different regimens must be discounted due to the often simplistic non-model based bridging of the available data. This means, the underlying dosing regimen-DLT relationship needs to be learned repeatedly from a discounted base data set, which increases the required sample sizes and strongly limits the use of existing data to predict the dose-toxicity relationship of untested regimens.

A more rational approach to account for dosing regimen is to draw on the theory and practice underlying pharmacokinetic-pharmacodynamic (PK/PD) models. In particular, we are suggesting to use PK principles to model the relationship between time-to-first DLTs and the planned dosing regimen in a model-based approach following the spirit of Cox et al. The key point here is to account for the overall kinetic properties implied by drug input rate of a regimen, drug elimination from the body of the patient and delays between drug exposure and actual drug effect. Our novel model, a time-to-event pharmacokinetic model henceforth referred as TITE-PK, requires data on the exact dosing schedule and adverse event history. TITE-PK includes a latent pseudo-PK based on the preplanned dosing regimen and is therefore considered like a (time-varying) baseline covariate. Formally, the latent pseudo-PK process is used to define a time-varying exposure metric, which we use to construct a time-varying Poisson process describing the DLT event process. TITE-PK assumes that a given dose input over time, produces a proportional signal that drives the probability of observing a response subsequent to dosing. This signal decays exponentially similar to drug concentration in a one compartment model. Similar to PK/PD models, the signals associated with repeated dosing are superimposed in a manner that accounts for the loss of signal since administration of the previous dose(s). Systematic delays between the signal and the observed responses are accounted for by a further exponential function akin to a so-called effect compartment that can be used to account for delays in the distribution of drug from plasma to the effect site. The instantaneous hazard of the time-to-first DLT is directly proportional to the pseudo PK signal. Analogous to the monotonicity assumption in the BLRM, the proportionality constant which drives the Poisson process is constrained to be strictly positive. Two parameters are required to account for the decay and the delay. Prior information on all parameters may be included by adopting a Bayesian framework.

The proposed approach builds on the positive experience with the BLRM, but has the added benefit of allowing changes in dose and dosing regimens to be taken into account in a systematic manner that draws on the significant positive experience from PK/PD analyses. Note that in the proposed model, PK analysis and safety analysis are not combined as is done for example by Ursino et al. This simplification is made to ensure the operational applicability of our approach in a realistic
clinical trial setting. In clinical trials it is often not feasible to obtain reliable PK data in time for dose-escalation decision meetings. Instead, the model is conditioned on known PK parameters from previous analyses following the work of Cox et al.\textsuperscript{10}

The main contribution of this paper is to introduce a novel approach, TITE-PK, for analysing and guiding phase I dose-escalation trials with different dosing regimens. Our approach builds on experience with the BLRM which has demonstrated the value of the EWOC principle implemented within a Bayesian framework. The \texttt{R} and \texttt{Stan} code for the implementation of the TITE-PK are available from Github (https://github.com/gunhanb/TITEPK_code). In Section 2, we describe a motivating phase I trial example from oncology which investigated daily and weekly dosing regimens. In Section 3, we review the BLRM and its ad-hoc extensions for combining regimens, and introduce the proposed TITE-PK model. In Section 4, the BLRM and TITE-PK are applied to the motivating example. Finally, the performance of both approaches are compared in a simulation study in Section 5. Scenarios involving simple and complex dosing regimens are considered. We close with discussion and conclusions.

2 Motivating example: Everolimus trial

Everolimus (RAD001) is an oral inhibitor of mammalian target of rapamycin, that is being developed as an antitumor agent.\textsuperscript{12} Everolimus is approved by the US FDA to treat various conditions including certain types of pancreatic cancer and gastrointestinal cancer,\textsuperscript{14} and certain type of tuberous sclerosis.\textsuperscript{13} Everolimus is also approved to treat transplant rejection.\textsuperscript{12} Everolimus was included in a phase Ib trial in combination with standard of care (etoposide and cisplatin chemotherapy) to identify a feasible dosing regimen in the treatment of small cell lung cancer (ClinicalTrials.gov identifier: NCT00466466).\textsuperscript{14} The trial was open-label and multi-centered. Patients were assigned alternately to either weekly or daily regimens of everolimus in treatment cycles of 21 days. The final data can be obtained from the supplementary material of Besse et al.\textsuperscript{14} All DLTs were reported at day 15. The elimination half-life and the absorption rate of everolimus for cancer patients are reported as 30 (hours) and 2.5 (1/hours), respectively.\textsuperscript{15} A Bayesian time-to-event model was used to inform the dose-escalation decisions.\textsuperscript{16} A dosing regimen of 2.5 mg/day everolimus was identified as the MTD.

Table 1: Data of the Everolimus trial. The dosing regimens that are used, the doses that are administered in mg., number of patients, and number of DLTs are given.

| Regimen | Dose (mg) | Number of patients | Number of DLTs |
|---------|----------|--------------------|----------------|
| Weekly  | 20.0     | 5                  | 0              |
| Weekly  | 30.0     | 13                 | 4              |
| Daily   | 2.5      | 4                  | 2              |
| Daily   | 5.0      | 6                  | 3              |

We used this trial to compare the performance of the TITE-PK and BLRM methods because: (1) the trial evaluated two different regimens (weekly and daily dosing), and (2) the large number of DLTs allow a good assessment on the relative performance of the respective methods.
3 Methods

In this section, we briefly review the BLRM and an extension of the BLRM which is necessary to account for the multiple regimens. Subsequently, we describe the proposed TITE-PK model, and its software implementation. Our primary focus is the application of these methods to phase I dose-escalation trials with more than one dosing regimen, although we also consider trials with only one dosing regimen. For simplicity, consider there are two dosing regimens, R1 and R2, and the aim is to determine the MTD characterized by the dosing amount and the dosing regimen.

3.1 The BLRM

The BLRM is a logistic regression model in the logarithm of a standardized dose. For dose $d$, the number of patients with a DLT ($r_d$) in a cohort of size $n_d$ are assumed to be binomially distributed

\[ r_d \sim \text{Bin}(\pi_d, n_d) \]  

with DLT probabilities ($\pi_d$) and two parameters ($\alpha_1$ and $\alpha_2$)

\[ \text{logit}(\pi_d) = \log(\alpha_1) + \alpha_2 \log(d/d^*) \]  

where $d^*$ is the reference dose used for standardization of the dose. At the reference dose the odds of the DLT are $\alpha_1$. Thus, the reference dose is critical in choosing a prior for $\alpha_1$ and is usually defined such that the reference dose $d^*$ is set to the anticipated MTD at which an odds of $1/2$ is used as mean for the $\alpha_1$ prior.

In the absence of relevant historical data, Neuenschwander et al\(^2\) suggest the use of weakly informative priors (WIPs) for $\alpha_1$ and $\alpha_2$. Their suggested WIP is a bivariate normal distribution $(\log(\alpha_1), \log(\alpha_2)) \sim N(m, S)$ with means $(m_1 = \text{logit}(\pi_d^*), m_2 = 0)$, standard deviations $(s_1 = 2, s_2 = 1)$, and the correlation $\rho = 0$.

To inform the dose-escalation decisions, the posterior distribution of the DLT probability $\pi_d$ is used. The DLT probabilities are classified into three categories as follows

(i) $\pi_d < 0.16$ Underdosing (UD)
(ii) $0.16 \leq \pi_d < 0.33$ Targeted toxicity (TT)
(iii) $\pi_d \geq 0.33$ Overdosing (OD)

Escalation or de-escalation decisions are informed using the overdosing probability of dose $d$, $P(\pi_d \geq 0.33)$. The EWOC criteria is fulfilled, if $P(\pi_d \geq 0.33)$ is smaller than the pre-specified feasibility bound, $a$, which was recommended as $0.25$ by Babb et al\(^5\). In this paper, we use $a = 0.25$ throughout the manuscript, unless another value is stated explicitly.

The BLRM does not distinguish in which frequency doses are administered to the patients (for example weekly dosing frequency or daily dosing frequency), but only the dosing amounts. Hence, an extension of the BLRM is used to incorporate different dosing regimens in a phase I trial, which we describe now.

3.1.1 The BLRM MAP

The BLRM with a meta-analytic predictive (MAP) approach\(^14\) can be used for informing dose-escalation decisions in a phase I study with more than one dosing regimen. Hereafter we refer this method as the BLRM MAP. In the BLRM MAP approach, the doses from the first dosing regimen
(R1) are re-scaled so that two sets of doses from different regimens are comparable. For example, if R1 is weekly dosing and R2 is daily dosing, the doses from R1 are divided by 7. This ensures that the respective nominal dose in each regimen results in the same cumulative dose. Then, a meta-analytic-predictive (MAP) prior is derived using the data of the R1 assuming some between-regimen heterogeneity for the parameters. The idea is that the data coming from R1 is treated as current data (co-data). The degree of heterogeneity depends on the switch between R1 and R2. For instance, one may assume less heterogeneity for the switch between “twice in a day” to daily compared to a switch between weekly to daily regimen. Furthermore, it may be desirable to make the MAP prior more robust for possible unwarranted use of data from R1. To achieve this, the robust MAP prior (BVNRMAP) can be obtained by mixing the MAP prior (BVNMAP) with the WIP (BVNWIP) as follows:

\[
BVNRMAP = w \times BVNMAP + (1 - w) \times BVNWIP, 
\]

where \(w\) is the weight which can be chosen, for example, from the range of 0.5 and 0.9. Neuenschwander et al. suggested the use of 0.8, and in this paper we follow their suggestion. After the robust MAP prior is derived, the BLRM is used to inform dose-escalation decisions. Note, that the BLRM MAP approach leads to distinct dose-DLT models for each regimen and is difficult to conduct in case data is generated concurrently for R1 and R2 at the same time.

3.2 The proposed method: TITE-PK

The basic concept in this method is inspired by Cox et al. Instead of modelling the number of DLTs as in the BLRM, the time-to-first DLTs are modeled using a time-varying (non-homogeneous) Poisson process. A time-varying Poisson process can be defined using the instantaneous hazard function \(h(t)\) for a DLT occurring at time \(t\) as

\[
h(t) = \lim_{\delta t \to 0^+} \frac{P(t \leq T < t + \delta t | T \geq t)}{\delta t}. 
\]

The hazard function corresponds to the probability that a patient experiences a DLT in the time interval \((t, t + \delta t]\) given that they did not experience a DLT until time \(t\). The hazard is modeled as a time-dependent function which is directly proportional to an exposure measure of the drug \(E(t)\) as

\[
h(t) = \beta E(t), 
\]

where \(\beta\) is the proportionality parameter to estimate. Note that, here, the exposure measure refers to the drug concentration as in a exposure-response model, and the calculation of \(E(t)\) will be explained in Section 3.2.1. Furthermore, if we integrate both sides of Equation (5), we obtain

\[
H(t) = \beta \text{AUC}_E(t), 
\]

where AUC\(_E(t)\) is the area under the curve of the exposure measure over time and \(H(t)\) is the cumulative hazard function, respectively.

From the event history analysis, we know that the probability density for an event to occur at time-point \(t\) is

\[
f(t) = h(t) \exp(-H(t)) 
\]
and the survivor function for the event to occur past some time-point \( t \) is given by

\[
S(t) = P(T > t) = \exp(-H(t)).
\]  

(8)

In the following we use \( C_j \) to denote the censoring time of patient \( j \). By convention we restrict the follow-up period for all patients to cycle 1 only. Thus, all patients without a DLT up to the end of cycle 1 will be censored at the end of cycle 1, \( C_j = t^* \). Long-term DLTs will thus not be considered, which will be discussed later. Furthermore, we denote with \( \delta_j \) an event indicator which is set to 0 for censored events and 1 for DLT events. The overall likelihood can be written as

\[
L(T, C|\beta) = \prod_{j=1}^{J} f(T_j|\beta)^{\delta_j} S(C_j|\beta)^{(1-\delta_j)},
\]  

(9)

where \( J \) is the total number of the patients. Now, we discuss the exposure measure of the drug.

### 3.2.1 Pseudo-PK model

The proposed exposure model in the TITE-PK model does not rely on measured drug concentration data, as this data is not routinely available in a form that it may be used directly in the model to support escalation decisions in a timely manner. For this reason, PK is considered as latent variable which we refer to as pseudo-PK. The pseudo-PK is used to account for the dosing history and the expected accumulation in exposure over time that ultimately drive pharmacological responses, including safety. The main purpose of the pseudo-PK model is to account for the natural “waxing and waning” of exposure observed after dosing of drug. This pseudo-PK model has a “central” compartment into which the drug is administered which accounts for drug elimination as a linear first order process; i.e. the elimination rate is proportional to the amount of drug in the compartment.\(^{23}\)

\[
\frac{dC(t)}{dt} = -\frac{\log(2)}{T_e} C(t),
\]  

(10)

where \( C(t) \) is the concentration of drug in the central compartment and \( T_e \) is the elimination half-life. As the volume of the central compartment cannot be identified for a latent pseudo-PK, we set it by convention to unity. The elimination half-life \( T_e \) is assumed to be known from previous analyses and we will evaluate the sensitivity of the approach to misspecification of the elimination half-life.

To account for delays between the instantaneous drug concentration in the central compartment, we use a so-called effect compartment.\(^{23}\)

\[
\frac{dC_{eff}(t)}{dt} = k_{eff} (C(t) - C_{eff}(t)),
\]  

(11)

where \( C_{eff}(t) \) is the drug concentration in the effect compartment, and \( k_{eff} \) is the PK parameter which governs the delay between the concentration in the central compartment \( (C(t)) \) and the concentration in the effect compartment \( (C_{eff}(t)) \).

The ordinary differential equations (ODEs) \(^{(10)}\) and \(^{(11)}\) account dosing over time through administration into the central compartment. The analytical solution to the ODE system for multiple doses is obtained through the use of the superposition principle which holds for linear ODE systems (see e.g.\(^{23}\)). This model can account for the natural history of any number of dosing regimens over time. In order to simplify the notation, we restrict ourselves here to regular dosing regimens which have a dosing frequency \( f \) (in units of \( 1/h \)), start at time \( t = 0h \) and use the same dose amount \( d \) for all dosing events. With these simplifications (in notation) the solution to the above ODE system is

\[
C_{eff}(t|d, f) = d \sum_{i=0}^{\infty} \Theta(t - \frac{i}{f}) \frac{k_{eff}}{k_{eff} - \frac{\log(2)}{T_e}} (e^{-\frac{\log(2)}{T_e} (t-\frac{i}{f})} - e^{-k_{eff}(t-\frac{i}{f})}),
\]  

(12)
where Θ denotes the Heaviside step function (or unit step function).

To facilitate meaningful interpretation of the parameter β, and hence to help prior specification, the exposure measure E(t) is obtained by scaling C_{eff}(t) using a reference regimen including a reference dose \( d^* \) and a reference dosing frequency \( f^* \) at the end of cycle 1 \( t^* \) such that

\[
E(t|d, f) = \frac{C_{eff}(t|d, f)}{\int_0^{t^*} C_{eff}(t|d^*, f^*) \, dt},
\]

\[
AUC_E(t^*|d^*, f^*) = \int_0^{t^*} E(t|d^*, f^*) \, dt = 1.
\]

Note that this is analogous to the usage of a reference dose in the BLRM as discussed in Section 3.1. For illustrative purposes, the calculated C(t), E(t), and AUC_E(t) of the Everolimus trial for 20 mg/weekly and 5 mg/daily dosing using different k_{eff} values are displayed in Figure 1. Notice that AUC_E(t) of 5 mg/daily at week 3 is 1, since 5 mg/daily is taken as the reference regimen and the length of cycle 1 is 3 weeks.

### 3.2.2 Informing dose-escalation decisions

To inform escalation decisions during the phase I trial, TITE-PK uses an adapted EWOC criteria analogous to the BLRM metric. Hence, the probability that a patient experiences at least one DLT \( P(T ≤ t^*|d, f) \) is our measure of interest. By using the relationship between \( P(T ≤ t^*|d, f) = 1 - P(T > t^*|d, f) \) and combining Equation (8) with (6) it follows that

\[
P(T > t^*|d, f) = \exp(-H(t^*|d, f)) = 1 - P(T ≤ t^*|d, f)
\]

\[
⇒ \log(H(t^*|d, f)) = \log(- \log(1 - P(T ≤ t^*|d, f))) = \text{cloglog}(P(T ≤ t^*|d, f)). \tag{13}
\]

Since the cumulative hazard \( H(t|d, f) \) is set proportional, see Equation (6), to the area under curve of the exposure metric \( AUC_E(t|d, f) \) this leads to

\[
\text{cloglog}(P(T ≤ t^*|d, f)) = \log(\beta) + \log(AUC_E(t^*|d, f)). \tag{14}
\]

For the reference regimen with dose \( d^* \) and dosing frequency \( f^* \) the AUC of the exposure measure up to the reference time-point is unity, \( AUC_E(t^*|d^*, f^*) = 1 \), such that \( \text{cloglog}(P(T ≤ t^*|d^*, f^*)) = \log(\beta) \) holds which highlights the importance of the reference regimen to specify the prior for the parameter \( \beta \).

We consider two models, a one-parameter TITE-PK model and a two-parameter TITE-PK model. In the one-parameter model, the only parameter to estimate is the regression coefficient \( \beta \), and the PK parameter \( k_{eff} \) is assumed to be known. In the two-parameter model, \( k_{eff} \) is considered unknown. The elimination half-life \( T_e \) is assumed to be known for both models.

### 3.3 Software implementation

The BLRM and the BLRM MAP can be implemented using Markov chain Monte Carlo (MCMC), for example, via BUGS-variant programs such as WinBUGS or JAGS. Code for the BLRM and the Robust MAP are included in the Appendix of Neuenschwander et al. and the supplementary material to the paper by Schmidli et al. respectively. For our implementations, we use JAGS via the R2jags R package to generate four parallel chains of 100,000 MCMC samples after a 10,000 iteration warm-up. To check MCMC convergence, we used the Gelman-Rubin statistics, trace plots and lag 1 sample autocorrelations.
Figure 1: Illustration of concentration in the central compartment ($C(t)$), the exposure measure of the drug ($E(t)$), and the AUC over exposure measure ($\text{AUC}_E(t)$) for 20 mg/weekly and 5 mg/daily regimens of the Everolimus trial, respectively. Reference regimen is 5 mg/daily, and the length of cycle 1 is 3 weeks. Different $k_{\text{eff}}$ values, a high value of $k_{\text{eff}}$ ($k_{\text{eff}} = 2$) and a low value of $k_{\text{eff}}$ ($k_{\text{eff}} = 0.05$), are used to show the influence on the $E(t)$. 
The proposed model TITE-PK is implemented in Stan via rstan R package. The corresponding code for the implementation of the TITE-PK method is available from Github (https://github.com/gunhanb/TITEPK_code). Four parallel chains of 1,000 MCMC iterations after warm-up of 1,000 iterations are generated. Convergence diagnostics are checked using the Gelman-Rubin statistics and traceplots. There were no divergences reported for the implementation of the application.

4 Revisiting the Everolimus trial

Returning to the data set described in Section 2, consider the Everolimus trial shown in Table 1. Firstly, we analyse the data only from the daily regimen using the BLRM, the one-parameter TITE-PK, and the two-parameter TITE-PK. Secondly, we analyse the data considering both weekly and daily regimen using the BLRM MAP, one-parameter TITE-PK, and the two-parameter TITE-PK. Note that although the cohorts of weekly and daily regimen are administered simultaneously in the Everolimus trial, we analyse the dataset as if the trial is conducted sequentially, specifically daily regimen after weekly regimen. This is because, we want to compare the proposed method with the BLRM MAP, which is only applicable for phase I trials involving different regimens conducted sequentially. The proposed method TITE-PK can be used for phase I trials in which data is generated concurrently for different regimen at the same time, but we come to this point at the discussion. The reference regimen is determined using dosing amount of 5 mg ($d^* = 5$ mg) and dosing frequency of 24 hours ($f^* = 1/24$ 1/h). For TITE-PK both models, the elimination half-life is taken as $T_e = 30$ (hours).

To compare the BLRM and TITE-PK models, priors are constructed so that a priori DLT probabilities from BLRM and end-of-cycle 1 DLT probabilities from TITE-PK models are similar. To define a WIP for BLRM, we choose a bivariate normal prior with following parameters ($m_1 = \text{logit}(\pi_{d^*} = 0.175), m_2 = 0, s_1 = 1.25, s_2 = 1, \rho = 0$). For TITE-PK models, a normal WIP is chosen such that $\log(\beta) \sim N(c\text{loglog}(P(T \leq t^*|d^*, f^*) = 0.175), 1.25^2)$. For two-parameter TITE-PK, a WIP for the parameter $k_{eff}$ is derived using the cycle length and the absorption rate. Specifically, a log-normal distribution is setup by matching the inverse of cycle length, $1/504$ (1/h), and the absorption rate, 2.5 (1/h) as the 0.025 and 0.975 quantiles, respectively. This gives a log-normal distribution with mean parameter 0.41 and the standard deviation parameter 0.27. For the one-parameter TITE-PK model, $k_{eff}$ is taken as the mean of the derived WIP for $k_{eff}$. The summaries of a priori DLT probabilities of the BLRM, the one-parameter TITE-PK, and the two-parameter TITE-PK models are shown in Figure 2A. Points, thick lines and thin lines correspond to median estimates, the 50% and the 95% equitailed credible intervals, respectively. Vertical dashed lines (0.16-0.33) are the boundaries of the targeted toxicity interval. If the upper bound of 50% credible interval of a dose is higher than the 0.33 value, then the overdosing probability of the corresponding dose exceeds the pre-specified feasibility bound 0.25. Therefore, the corresponding dose is an overdose based on the EWOC criteria. From Figure 2A, we can see that for all three models, a priori, doses of 7.5 mg and 10 mg are overdoses, while doses of 2.5 mg and 5 mg are not.

Figure 2B displays the posterior estimates of DLT probabilities, when we only consider daily regimen data. Results obtained by one parameter TITE-PK and two parameter TITE-PK models are very similar. To compare those two models, we also calculate approximate leave-one-out cross validation (LOO) values using the loo R package. LOO values of one parameter TITE-PK and two parameter TITE-PK models are 81.1 (standard error 27.6) and 81.5 (standard error 27.7), respectively. The difference of the expected log pointwise predictive density of LOO values between one parameter TITE-PK and two parameter TITE-PK is -0.2 (standard error 0.1). If we compare BLRM and TITE-PK models, all three methods suggest that all doses are overdoses, meaning that the trial should be
stopped without any dose declared as the MTD. This seems reasonable, since 2 DLTs observed from 4 patients in 2.5 mg, and 3 DLTs from 6 patients in 5 mg dose.

![Figure 2: Everolimus trial: Prior (A), posterior medians daily (B), and weekly + daily (C), 50% equitailed credible intervals (thick lines), and 95% equitailed credible intervals (thin lines) of daily doses for DLT probabilities obtained by BLRM (BLRM MAP for weekly + daily) and for end-of-cycle 1 DLT probabilities obtained by one parameter TITE-PK and two parameter TITE-PK models. “Weekly + Daily” refers that data from both weekly and daily dosing regimens are included in the analysis, whereas “Daily” means data only from daily dosing regimen is considered. Vertical dashed lines (0.16-0.33) are the boundaries of the targeted toxicity interval.]

We continue by combining weekly and daily regimen data. We estimate the DLT probabilities of daily doses but also taking into consideration the data coming from the weekly data. As explained in Section 3.1.1 to implement BLRM MAP, the doses of weekly regimen, namely 20 mg and 30 mg, are re-scaled dividing them by 7. The Robust MAP prior is constructed by mixing the MAP prior and the WIP using the weight of 0.8 ($w = 0.8$). Finally, the BLRM is fitted and posterior estimates of DLT probabilities are obtained. On the other hand, our method TITE-PK, naturally, combines information from different regimens without requiring any ad-hoc method. Figure 2C displays the estimated posterior summaries of DLT probabilities of daily doses obtained by one parameter and two parameter TITE-PK and BLRM MAP approaches. As in Figure 2B, two parameter TITE-PK model did not show any improvement compared to one parameter TITE-PK model in terms of the LOO estimate. Hence, hereafter we only consider one parameter TITE-PK model, and use TITE-PK to refer one parameter TITE-PK model.

For both TITE-PK and BLRM MAP, the overdosing probability of dose 2.5 mg/daily is decreased substantially, namely from 0.49 to 0.27 for BLRM MAP, and from 0.28 to 0.01 for TITE-PK. The reduction of the overdosing probabilities of 2.5 mg/daily seems reasonable, since in the weekly regimen data, 0 DLTs occurred from 5 patients in 20 mg/weekly and 4 DLTs occurred from 13 patients in 30 mg/weekly. However, the interval estimates obtained by TITE-PK are shorter, hence more precise estimates compared to BLRM MAP. Unlike BLRM MAP, TITE-PK suggests that 2.5 mg/daily is not an overdose, hence it can be declared as the MTD which was the conclusion of the original phase I trial. Also it must be noted that results of BLRM MAP depends on the choice of the weights which are used for the construction of the Robust MAP prior. For instance, if we choose the weight of 1.0 for BVN_MAP instead of 0.8, then the overdosing probability of 2.5 mg/daily reduces to 0.20 which is not an overdose based on the EWOC criteria. It is also worthwhile to point out that conceptually BLRM
MAP is different in comparison to TITE-PK. The BLRM MAP approach for different regimens is a two-step approach which establishes two distinct models; one per dosing regimen. The TITE-PK model instead combines in a model based approach all available information.

As pointed out in Section 3.2.1 by construction of TITE-PK, the elimination half-life $T_e$ is treated as known. To investigate the influence of misspecification of the $T_e$ parameter, we fit TITE-PK using $T_e$ ranging from 5 to 50 hours. The timing of all DLTs (in total 9 DLTs) were reported at day 15. To examine what would be the influence of the timing of DLTs, we also fit TITE-PK to two hypothetical datasets. Early DLTs dataset and late DLTs dataset are created by changing timing of DLTs from day 15 to day 1.5 and to day 20.5, respectively. Posterior estimates of DLT probabilities for different $T_e$ values and for different timing of DLTs are shown in Figure 3. The middle plot corresponds to the original Everolimus trial data. Firstly, the posterior medians and credible intervals obtained by different $T_e$ values look very similar. Note that it is highly probable to not to have a precise estimate of elimination half-life during a phase I trial, hence these results are reassuring for the practicality of TITE-PK. Secondly, timing of DLTs have a crucial affect on the posterior estimates, and hence the overdosing probabilities. Having the same number of DLTs, the earlier the DLT happened, the higher the overdosing probability of the corresponding dose estimated. This makes sense, since one would expect the drug is more toxic if DLTs happened earlier than later.

![Figure 3: Misspecification of elimination half-life $T_e$ and different timing of DLTs. Using different values of $T_e$, posterior median, 50% and 95% equitailed credible intervals for end-of-cycle 1 DLT probabilities obtained by TITE-PK for two hypothetical datasets (early DLTs and late DLTs) and the original Everolimus trial dataset are shown. Early DLTs dataset and late DLTs dataset are created by changing timing of DLTs from day 15 to day 1.5 and to day 20.5, respectively. Data from both weekly and daily dosing regimens are included in the analysis.](image)

5 Simulation study

In order to assess the performance of the TITE-PK and to compare with the BLRM under different true dose-DLT profiles and different regimens, various scenarios are investigated in a simulation study.

5.1 Simulation settings

Simulation study follows the clinical scenario evaluation framework introduced by Benda et al. In all scenarios, by mimicking the Everolimus trial, PK parameters are chosen such that $T_e = 30$
(hours) and log(k_{eff}) = 0.41. Weekly doses of 8, 16, 32, 64, 115, 230 (mg/weekly) and daily doses of 1, 2, 4, 8, 15, 30 (mg/daily) and are considered. Reference dose and reference dosing frequency are determined using 8 mg (d^* = 8 mg) and 24 hours (f^* = 1/24 1/h). Cycle length is taken as 28 days instead of 21 day as in Everolimus trial, since the former is more common. As in the Everolimus application, WIPs are constructed so that a priori DLT probabilities of BLRM and TITE-PK are similar. For BLRM, we choose a BVN prior with following parameters: (m_1 = \logit(\pi_d^* = 0.175), m_2 = 0, s_1 = 2, s_2 = 1, \rho = 0). For TITE-PK model, a normal WIP is chosen such that log(\beta) \sim N(cloglog(P(T \leq t^*|d^*, f^*) = 0.175), 1.75^2). Although the choice of prior can have an influence on posterior estimates for a Bayesian phase I design, we did not consider to vary the priors. This is because our aim is to compare the BLRM and TITE-PK given that they have a priori similar DLT probabilities for all doses. However, we recommend varying priors as part of sensitivity analyses when TITE-PK is used for an application as is the case with other Bayesian phase I models.

For the first setting of scenarios, six different dose-DLT profiles with only daily dosing are considered as shown in Figure 4B. Scenario 3 is the basis and equals to the mean of a priori medians of the TITE-PK and BLRM. DLT probabilities of Scenario 1 and 2 are 0.25 and 0.75 of the DLT probabilities of Scenario 3, respectively. Thus Scenario 1 and 2 have lower toxicity compared to the basis (Scenario 3). Similarly, Scenario 4 and 5 are 1.25 and 1.75 of Scenario 5, respectively, hence more toxic scenarios. Finally, Scenario 6 is an extreme scenario that is highly inconsistent with the prior, and it is taken from Babb et al.\(^5\) In the second and third set of scenarios, we consider switching regimen scenarios. We assumed that after the MTD declaration of the weekly dosing, daily dosing is administered to the patients and then MTD is declared for the daily dosing. For the daily dosing, the scenarios illustrated in Figure 4B are used. Figure 4A displays the true dose-DLT profiles used in the weekly dosing scenarios and they are calculated using same procedure with daily dosing scenarios. In the second simulation set of scenarios, we consider the same true dose-DLT profiles between different regimens. For example, a trial is started with weekly dosing of Scenario 3, after MTD declaration, it is switched to the daily dosing of Scenario 3. In third set of scenarios, we consider the situations when there is conflict of true dose-DLT profiles between weekly and daily regimens. For instance, in the weekly regimen, Scenario 2 is used, and then switched to the daily dosing of Scenario 3.

The data generation processes for BLRM and TITE-PK are different, since the former uses a binomial distribution whereas the latter uses a time-varying Poisson process. Hence, we run the simulations separately for two methods. For BLRM, specification of the true dose-DLT profiles are enough to simulate data. But for TITE-PK, we also need to specify the cycle length as well as the PK parameters T_e and k_{eff}. For both TITE-PK and BLRM, data for 1,000 trials were generated. The following criteria for the simulations are taken from Neuenschwander et al.\(^2\) Sample sizes were randomly chosen cohorts of size 3-6. The maximum number of patients per trial was set to 60. The trial was stopped when one of the following criteria were met:

(i) At least six patients have been treated at the recommended MTD.

(ii) The MTD dose satisfies one of the following conditions:

- The probability of targeted toxicity at recommended MTD dose exceeds 50%.
- A minimum of 21 patients have already been treated in the trial.

5.2 Results

To assess the performance of the BLRM and TITE-PK in the simulations, we used six measures which are demonstrated in Table 2. Performance measures obtained by TITE-PK and BLRM for the first set of scenarios (only daily dosing) are shown in Figure 5. For all six scenarios, the percentage of
trials with MTD identified in targeted toxicity (TT) region (correctly identifying MTD) are higher in TITE-PK compared to the BLRM. On the other hand, for scenarios 2, 4, and 5, the percentage of trials with an overdose identified MTD is higher in TITE-PK compared to BLRM, although only scenario 4 can be seen as problematic (14.3% in TITE-PK vs 7.1% in BLRM). However, the percentage of patients receiving an overdose is not extremely higher in TITE-PK in comparison to BLRM (10% in TITE-PK vs 8.3% in BLRM). Furthermore, to improve these results, we consider TITE-PK using a modified EWOC, namely using pre-specified feasibility bound $a = 0.20$ instead of $a = 0.25$. Note that reducing the feasibility bound results the conservative dose-escalation decisions, that is reducing the percentage of trials with an overdose identified MTD but also reducing the percentage of trials with correctly identified MTD. The percentage of trials with correctly identified MTD obtained by TITE-PK using $a = 0.20$ is decreased to 11.1%, while in all scenarios, TITE-PK outperforms BLRM in terms of this metric. Scenario 6 needs special consideration. For this very toxic scenario, while the measure for correctly identifying MTD are higher in both TITE-PK methods in comparison to the BLRM, the percentage of patients treated at overdoses is also considerably lower compared to BLRM.
(26.6% in TITE-PK using $a = 0.20$ vs 35.8% in BLRM). What is more, the percentage of patients receiving an overdose obtained by BLRM is higher compared to both TITE-PK using $a = 0.25$ and TITE-PK using $a = 0.20$. In terms of average number of DLTs and average number of sample sizes, BLRM and TITE-PK methods give similar results, although latter is slightly higher.

Figure 5: Performance measures for the first set of scenarios (only daily dosing regimens). Three methods are considered: BLRM, TITE-PK, and TITE-PK using a decreased pre-specified feasibility bound ($a = 0.20$). Description of scenarios are given in the main text.

Now, we consider the second set of the scenarios, switching regimen scenarios with no conflict of true dose-DLT profiles of weekly and daily regimens. Performance measures of TITE-PK and BLRM MAP are shown in Figure 6. Firstly, we can compare both methods to their performances for the first set of scenarios as shown in Figure 5. It can be clearly seen that for all measures, TITE-PK is improved. For example, the percentage of trials with an overdose identified MTD of Scenario 4 now reduces to 12.1% from 14.1%. And the percentage of trials with correctly identified MTD of Scenario 4 increases to 71.3% from 55%. Although in many measures BLRM is also improved, there are some measures in which its performance are getting worse, for example the percentage of trials with correctly identified MTD of Scenario 5 reduces from 29.5% to 21.4%. Most importantly, if we compare BLRM MAP and TITE-PK, it can be easily seen that TITE-PK outperforms BLRM MAP.
in many measures especially for correctly identifying MTDs.

Figure 6: Performance measures for the second set of scenarios, switching regimen scenarios with no conflict of true dose-DLT profiles of weekly and daily regimens. Two methods are considered: TITE-PK and BLRM MAP. X axis values, for example Sc. 1 and Sc. 1, refers to starting with weekly regimen of Scenario 1, then continue with daily regimen of Scenario 1. Description of scenarios are given in the main text.

Lastly, we consider the third set of the scenarios, switching regimen scenarios with conflict of true dose-DLT profiles of weekly and daily regimens. Performance measures of TITE-PK and BLRM MAP are shown in Figure 7. Firstly, we can notice that TITE-PK outperforms BLRM MAP in all considered scenarios in terms of the percentage of trials with correctly identified MTD. For the fifth scenario (starting with weekly regimen of Scenario 4, then continue with daily regimen of Scenario 1: Sc. 4 and Sc. 1), the difference is 40%, for example. For the percentage of trials with an overdose identified MTD, we see that TITE-PK has lower or equal value compared to BLRM MAP except the third scenario (Sc. 3 and Sc. 4). Note that here we consider the measures of daily regimen of Scenario 4, hence we can compare these results to Scenario 4 of the first set of scenarios to see the influence of the inclusion of the weekly regimen of Scenario 3. In the first set of the scenarios, the percentage of trials with an overdose identified MTD of TITE-PK for Scenario 4 was 14.1%, and
now it increases to 21.5%. On the other hand, the percentage of trials with an overdose identified MTD of BLRM MAP is only slightly increased when we compare the first set and third set of scenarios for Scenario 4, from 7.1% to 8.5%. However, the percentage of patients receiving an overdose obtained by TITE-PK is not unacceptably high in compared to the BLRM (11.2% in TITE-PK vs 6.7% in BLRM). Note that the difference of these scenarios compared to previous ones is that the assumption that the end-of-cycle 1 DLT probability is increasing with higher AUC of the exposure of the drug is violated. This is analogous to the monotonicity assumption of the BLRM. For example, in the third scenario (starting with with weekly regimen of Scenario 3, then continue with daily regimen of Scenario 5: Sc. 3 and Sc. 5), true DLT probability of dose 32 mg/weekly (0.10) is smaller than true DLT probability of dose 4 mg/daily (0.15), while AUC(t*) of dose 32 mg/weekly is bigger than AUC(t*) of dose 4 mg/daily. This assumption is more relevant for TITE-PK than BLRM-MAP, since in the latter, data from the weekly regimen is used to construct the prior, but not used as data.

6 Discussion and Conclusion

We propose a Bayesian adaptive model, TITE-PK, to support design, analysis and guidance of phase I dose-escalation trials, where the drug is administered by different dosing regimens and dosing decisions are determined by dose limiting toxicities. TITE-PK preserves the advantages of the BLRM including interpretable parameters, and being able to use the EWOC criteria. It uses PK principles to combine different dosing regimens in a model-based approach. A real application involving weekly and daily dosing is used to show the usage of TITE-PK. Moreover, we have demonstrated by means of simulations that TITE-PK shows better performance in terms of the investigated measures compared to BLRM for single regimen scenarios and compared to BLRM MAP for combining different regimens in realistic scenarios.

We considered two models, one parameter TITE-PK model and two parameter TITE-PK model. The second model has the extra parameter of $k_{\text{eff}}$ which governs a possible delay between the putative concentration in the central compartment and manifestation of effect. Note, in this case it also accounts for the delay between the administration and the manifestation of the putative concentration. In the Everolimus trial, posterior estimates were not changed when we used the two parameter TITE-PK model, also the estimated leave-one-out cross validation values were not improved. Hence, we suggest the usage of one parameter TITE-PK model which is computationally less expensive. An advantage of using time-to-first DLTs as in TITE-PK instead of only numbers of DLTs as in BLRM is that censored patients can also be included in the analysis. There are some suggested time to event models for phase I trials, for example TITE-CRM which, additionally, models long term DLTs not only DLTs occurring in the first cycle as in TITE-PK. TITE-PK can be extended to also incorporate long term DLTs which requires the modelling of the recurrent DLTs, and two parameter TITE-PK model could be more useful for such long-term safety analysis.

In the simulation study, we only considered the scenarios when different regimens are administered to the cohort of patients sequentially. That is, the MTD is estimated for the first regimen (R1), then the second regimen (R2) is administered to the patients, finally the MTD for the second regimen is estimated. As an alternative design, the data can be generated concurrently for R1 and R2 at the same time. TITE-PK can be used to inform dose-escalation decisions for both designs. However, we did not investigate the latter design scenarios, since we want to compare the TITE-PK with the BLRM MAP, which is only applicable for the former design.

We have used a linear PK model for the pseudo-PK to calculate the exposure measure of the drug. This implies that the constructed exposure metric is proportional to the administered dose which extends to the key metric of the model, the end-of-cycle 1 DLT probability. When there is
Figure 7: Performance measures for the third set of scenarios, switching regimen scenarios with conflict of true dose-DLT profiles of weekly and daily regimens. Two methods are considered: TITE-PK and BLRM MAP. X axis values, for example Sc. 2 and Sc. 3, refers to starting with weekly regimen of Scenario 2, then continue with daily regimen of Scenario 3. Description of scenarios are given in the main text.
a clear conflict in dose-DLT profiles between different regimens, this assumption can be seen as a
limitation of TITE-PK. To relax this assumption, one can consider more complicated PK models
including a non-linear PK model which may not have an analytical solution. Such extensions may be
implemented in Stan which has a built-in differential equation solver. However, more complicated
modelling approaches always need to be calibrated well given the sparseness of the phase I dose-
escalation data sets. Alternatively, one can consider an ad-hoc extension of one parameter TITE-PK
model. For instance, similar to the idea of power model, a pseudodose such as \((\frac{d}{d^*})^\gamma\) can be used
instead of dose \(d\) in the model which may be helpful to relax the linear PK assumption.

When relevant historical information or data from a different study population exists, it is desirable
to include such information in the analysis of the phase I trial, for example using a MAP prior. Since
TITE-PK is parametrized by mimicking the interpretable parameters of the BLRM, it can be also
extended to use a MAP approach like the BLRM. A key strength of the TITE-PK approach is it’s
ability to integrate the data from different dosing regimens in a model based approach. This makes
ad-hoc approaches used for the BLRM obsolete which reduces the need for strong discounting of
historical data from different regimens. However, discounting may still be needed to account for other
sources of heterogeneity in the data under consideration.

Another crucial aspect of the methods for phase I trials is the ability to analyse the combination
of drugs. Although, we only consider the single agent case here, it is possible to extend TITE-PK
to analyse drug combinations which is complicated by the need to model possible drug interactions.
Moreover, we only considered the fixed feasibility bound to use EWOC, that is a dose is considered an
overdose if the overdosing probability of a dose exceeds a fixed bound. However, one can also consider
varying feasibility bounds as suggested by Wheeler et al.

In summary, we expect that with TITE-PK the available historical data can be used more efficiently
and that phase I trials can more flexibly explore dosing regimens in dose-escalation trials. This is
achieved through the use of pharmacokinetic principles in the TITE-PK model.

Acknowledgement

We thank Heinz Schmidli who contributed valuable comments and pointed us to several important
references, and Michael Looby for carefully proofreading this, and recommending several changes that
lead to an improved presentation of this paper.

Conflict of interest

S.W. and A.S. are employees of Novartis, and T.F. is a consultant to Novartis and has served on data
monitoring committees for Novartis. Novartis is the manufacturer of everolimus, an everolimus trial
was used to motivate and illustrate the investigations presented here (see Section 2 and Section 4).
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