PoD-TPI: Probability-of-Decision Toxicity Probability Interval Design to Accelerate Phase I Trials

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Abstract

Cohort-based enrollment can slow down dose-finding trials since the outcomes of the previous cohort must be fully evaluated before the next cohort can be enrolled. This results in frequent suspension of patient enrollment. The issue is exacerbated in recent immune oncology trials where toxicity outcomes can take a long time to observe. We propose a novel phase I design, the probability-of-decision toxicity probability interval (PoD-TPI) design, to accelerate phase I trials. PoD-TPI enables dose assignment in real time in the presence of pending toxicity outcomes. With uncertain outcomes, the dose assignment decisions are treated as a random variable, and we calculate the posterior distribution of the decisions. The posterior distribution reflects the variability in the pending outcomes and allows a direct and intuitive evaluation of the confidence of all possible decisions. Optimal decisions are calculated based on 0-1 loss, and extra safety rules are constructed to enforce sufficient protection from exposing patients to risky doses. A new and useful feature of PoD-TPI is that it allows investigators and regulators to balance the trade-off between enrollment speed and making risky decisions by tuning a pair of intuitive design parameters. Through numerical studies, we evaluate the operating characteristics of PoD-TPI and demonstrate that PoD-TPI shortens trial duration and maintains trial safety and efficiency compared to existing time-to-event designs.

Keywords: Clinical trial design; Decision theory; Dose finding; Late-onset toxicity; Maximum tolerated dose

1 Introduction

Phase I clinical trials in oncology aim to find the maximum tolerated dose (MTD) of a new drug. The MTD is defined as the highest dose with a dose limiting toxicity (DLT) probability close to or

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lower than a pre-specified target level \( p_T \). Many phase I dose-finding designs like the 3+3 design \cite{Storer1989} and the continual reassessment method (CRM, \cite{O'Quigley1990}) have been proposed for this purpose, along with the goal of maximizing the chance of treating patients at safe and efficacious doses. In practice, usually a set of candidate dose levels (from low to high) \( \{1, \ldots, D\} \) is pre-specified, and both the toxicity and the efficacy of the drug are assumed to monotonically increase with dose level. Let \( p_d \) denote the true and unknown DLT probability of dose \( d \), \( p_1 \leq \cdots \leq p_D \). The value of \( p_d \) is estimated according to the DLT outcomes of the treated patients, and the selection of the MTD is based on the estimate of \( p_d \).

In practical trials, due to limited sample size, the DLT probability \( p_d \) is estimated with uncertainty. To account for the uncertainty, a class of interval-based dose-finding designs has been proposed. \cite{Cheung2002} introduced the idea of indifference interval, where any dose with \( p_d \in [p_T - \epsilon, p_T + \epsilon] \) can be treated as an estimated MTD for a small value \( \epsilon \). Later, \cite{Ji2007} proposed a phase I design that solely depends on properties of toxicity probability intervals (TPI), known as the TPI design. The TPI design was further extended and polished by \cite{Ji2010, Ji2013, Guo2017}, leading to the modified TPI (mTPI) and mTPI-2 designs. Simpler model-assisted designs like the cumulative cohort design (CCD, \cite{Ivanova2007}) and the Bayesian optimal interval design (BOIN, \cite{Liu2015}) also uses intervals as the basis for decision making. The latest i3+3 design \cite{Liu2019} is again based on interval rules, but without a model.

The last decade has seen a growth of the use of immunotherapies for treating cancer. The toxicities of immunotherapies can be late-onset \cite{Kanjanapan2019}, meaning it can take longer time to observe than traditional cytotoxic cancer therapies. This presents some challenges to traditional phase I designs like the mTPI-2, as these designs can only make dose decisions when all the previous DLT outcomes are ascertained. In other words, if some patients are still being followed within their assessment windows, patient accrual has to be suspended while waiting for the previous outcomes, resulting in waste of precious patient resources and prolonged trial duration. As a result, there is a need of novel designs that can shorten the duration of phase I trials. Several phase I designs have been proposed to allow dose decisions in the presence of incomplete DLT outcomes. These include the time-to-event continual reassessment method (TITE-CRM, \cite{Cheung2000}), rolling six design \cite{Skolnik2008}, time-to-event Bayesian optimal
interval design (TITE-BOIN, [Yuan et al., 2018]), time-to-event keyboard design (TITE-keyboard, [Lin and Yuan, 2018]) and rolling TPI design (R-TPI, [Guo et al., 2019]). Safety of these designs have not been fully explored and is often a concern in practice. For example, what is the risk of making a wrong escalation decision when not all the toxicity outcomes have been observed from existing patients in the trial? Questions like this need to be carefully addressed to help investigators and regulators understand the impact of reduction in trial duration.

In this paper, we propose the probability-of-decision toxicity probability interval (PoD-TPI) design to accelerate phase I trials. We calculate the posterior distribution of the number of DLTs among the pending outcomes, with which we then infer the posterior probability of possible dose-finding decisions. Importantly, the posterior distribution of decisions enables a direct and intuitive evaluation of the confidence of the possible decisions, which can be used to assess the risk of any decision rules based on the posterior distribution. The decision with the highest PoD is the optimal decision to make. When the PoD of the optimal decision is high enough, or the optimal decision is not risky (e.g., de-escalation), the decision may be executed without waiting for the pending outcomes. On the other hand, if the PoD of the optimal decision is not high enough, and the optimal decision is risky (e.g., escalation), the sensible decision is to suspend the enrollment and wait for some more outcomes to be observed before making a decision. Through these reasoning, the proposed PoD-TPI design quantifies the risk of making aggressive decisions and present them via simulation studies. Adopting to an optimal and conservative decision framework and balancing the need to shorten trial duration and protect patient safety, the PoD-TPI design might be a new and useful method for practical trials.

The idea of PoD-TPI is different from existing TITE designs. In TITE-CRM, TITE-BOIN and TITE-keyboard, the follow-up times of the pending patients are incorporated in the likelihood of the DLT probabilities. Interest lies in the estimation of \( p_d \), and the dose decision is deterministic based on \( p_d \). In contrast, in PoD-TPI, the follow-up times are used to estimate the probability of a pending patient experiencing DLT in the future. Interest now lies in the posterior distribution of the random number of DLTs if all patients were fully followed, and the dose decision is treated as a random variable. The idea of PoD-TPI is also different from the R-TPI design. The R-TPI consists of fixed decision rules that accommodate pending outcomes. To ensure safety, dose escalation is only allowed when the mTPI-2 decision is still escalation even if all pending outcomes are DLTs.
However, R-TPI does not make use of the follow-up times thus is less efficient. In addition to
the modeling and application of PoDs, PoD-TPI has two other unique features: (1) the use of
probability cutoffs to calibrate the risks to patients, and (2) the proposed risk as a metric for
assessing the operating characteristics of designs that do not use complete data. These features
will be more clear in the following discussion.

The rest of the paper is organized as follows. In Section 2, we review the mTPI-2 design, upon
which the PoD-TPI design is built. In Section 3, we propose the PoD-TPI design based on a
probability model for the time to DLT, which is developed in Section 4. In Section 5, we illustrate
the PoD-TPI design through two hypothetical trial examples. In Section 6, we conduct extensive
simulation studies to evaluate the operating characteristics of the PoD-TPI design. In Section 7,
we conclude with a discussion.

2 Review of mTPI-2

We first give a brief review of the mTPI-2 design (Guo et al., 2017), upon which the PoD-TPI
design is anchored. Under the mTPI-2 design, patients are usually enrolled in cohorts, and the first
cohort is treated at the lowest dose. At a certain moment in the trial, suppose dose $d$ is currently
used to treat patients, and denote by $p_d \in [0, 1]$ its true (and unknown) DLT probability. After the
toxicity outcomes of the previous cohort are observed, physicians need to make a decision $A$ for
the treatment of the next cohort. Here $A \in \{-1, 0, 1\}$, corresponding to a decision of de-escalation
($-1$) to the next lower dose, stay (0) at the current dose, or escalation (1) to the next higher dose,
respectively. Accordingly, the dose $(d + A)$ will be used to treat the next cohort, subject to some
additional safety rules. In the case that $d$ is the lowest dose and $A = -1$, or $d$ is the highest dose
and $A = 1$, the dose $d$ will be kept for the next cohort, i.e., $A = 0$.

In mTPI-2, the dose decision $A$ is based on posterior inference of $p_d$. Suppose a total of $N$
patients have been treated. We use $Y_i$ and $Z_i$ to denote the DLT outcome and dose assignment
of patient $i$, where $Y_i = 1$ (or 0) indicates a DLT (or non-DLT) outcome, and $Z_i \in \{1, \ldots, D\}$,
$i = 1, \ldots, N$. Here, a DLT outcome means the patient experiences DLT within some assessment
window. If the patient does not experience DLT during the time window, we declare that the
patient has no DLT. The DLT outcome is modeled by a Bernoulli distribution,

\[ Y_i \mid Z_i = d \sim \text{Bernoulli}(p_d). \]

Let \( n_d \) represent the number of patients who have experienced DLT at dose \( d \), and let \( m_d \) denote those who have not. That is, \( n_d = \sum_{i=1}^{N} 1(Y_i = 1, Z_i = d) \) and \( m_d = \sum_{i=1}^{N} 1(Y_i = 0, Z_i = d) \). The likelihood of \( p_d \) is

\[ L(p_d \mid n_d, m_d) = p_d^{n_d}(1 - p_d)^{m_d}. \tag{1} \]

Suppose the \((N + 1)\)-th patient is just enrolled and the DLT outcomes for the previous patients are fully observed. To make a proper dose assignment for the new patient, mTPI-2 considers a partition of the parameter space of \( p_d \), the \([0, 1]\) interval, into the following three intervals,

\[ I_E = [p_T - \epsilon_1, p_T + \epsilon_2] \quad \text{(equivalence interval)}, \]
\[ I_U = [0, p_T - \epsilon_1) \quad \text{(underdosing interval)}, \]
\[ I_O = (p_T + \epsilon_2, 1] \quad \text{(overdosing interval)}. \]

The values \( \epsilon_1 \) and \( \epsilon_2 \) are elicited by physicians, such that the doses within \( I_E \) are considered so close to the MTD that the physicians would agree to select them as the estimated MTD. The lengths of the three intervals \( I_E, I_U \) and \( I_O \) are different. To avoid undesirable decisions due to the effect of Ockham’s razor [Jefferys and Berger 1992], the intervals \( I_U \) and \( I_O \) are further divided into subintervals \( \{I_{U1}, \ldots, I_{U K_1}\} \) and \( \{I_{O1}, \ldots, I_{O K_2}\} \). The subintervals have an equal length of \( (\epsilon_1 + \epsilon_2) \), except those reaching the boundary of \([0, 1]\). For example, when \( p_T = 0.3 \) and \( \epsilon_1 = \epsilon_2 = 0.05 \), the equivalence interval is \( I_E = [0.25, 0.35] \). The underdosing interval is divided into \( K_1 = 3 \) subintervals, \( I_{U1} = [0.15, 0.25], \ I_{U2} = [0.05, 0.15] \) and \( I_{U3} = [0, 0.05] \), and the overdosing interval is divided into \( K_2 = 7 \) subintervals, \( I_{O1} = (0.35, 0.45], \ I_{O2} = (0.45, 0.55], \ I_{O3} = (0.55, 0.65], \ I_{O4} = (0.65, 0.75], \ I_{O5} = (0.75, 0.85], \ I_{O6} = (0.85, 0.95] \) and \( I_{O7} = (0.95, 1] \).

Finally, mTPI-2 casts the dose-finding decision as a model selection problem under a decision theoretic framework. Let model \( \mathcal{M}_d = j \in \{U_1, \ldots, U_{K_1}, E, O_1, \ldots, O_{K_2}\} \) be an indicator of \( p_d \in I_j \). Each candidate model is assigned a prior probability, and a prior distribution is constructed for \( p_d \) given \( \mathcal{M}_d \) being the true model. Specifically,

\[ \Pr(\mathcal{M}_d = j) = 1/(K_1 + K_2 + 1), \text{ for } j = U_1, \ldots, U_{K_1}, E, O_1, \ldots, O_{K_2}; \]
\[ p_d \mid \mathcal{M}_d \sim \text{TBeta}(1, 1; I_{\mathcal{M}_d}), \]
where TBeta(·, ·; I) represents a truncated beta distribution restricted to interval I. Let $\mathcal{M}^* = \arg\max_j \Pr(\mathcal{M}_d = j \mid n_d, m_d)$. The decision rule of mTPI-2 is given by

$$
\mathcal{A} = \begin{cases} 
0, & \text{if } \mathcal{M}^* = E; \\
1, & \text{if } \mathcal{M}^* \in \{U_1, \ldots, U_{K_1}\}; \\
-1, & \text{if } \mathcal{M}^* \in \{O_1, \ldots, O_{K_2}\}; 
\end{cases}
$$

It is shown in Guo et al. (2017) that the decision rule is optimal in the sense that it minimizes the posterior expected loss under a 0-1 loss.

Suppose $p_T, \epsilon_1$ and $\epsilon_2$ are given and fixed. The decision $\mathcal{A}$ only depends on the values of $n_d$ and $m_d$. As a result, we can write $\mathcal{A} = \mathcal{A}(n_d, m_d) : \mathbb{N} \times \mathbb{N} \to \{-1, 0, 1\}$ as a deterministic function of $n_d$ and $m_d$. For example, with $p_T = 0.30$ and $\epsilon_1 = \epsilon_2 = 0.05$, we have $\mathcal{A}(0, 3) = 1, \mathcal{A}(1, 2) = 0, \mathcal{A}(2, 1) = -1$ and $\mathcal{A}(3, 0) = -1$. The notation of $\mathcal{A}(n_d, m_d)$ will be used in the PoD-TPI design next.

3 The PoD-TPI Design

As noted in Section 1, a potential limitation of the mTPI-2 design (and many other cohort-based phase I designs) is that the toxicity outcomes for the previous cohorts must be fully observed before a dose decision can be made for the next cohort. While waiting for the DLT assessment of the previous patients, patient accrual needs to be suspended and eligible patients have to be turned away. Such trial suspension is undesirable in practice. The PoD-TPI design is motivated by the need to reduce the frequency of enrollment suspension but at the same time maintain safety.

Under the PoD-TPI design, patients are enrolled in cohorts, say, of size 3. The first cohort of patients is treated at the starting dose level, denoted by $d_0$. In most cases, $d_0$ is chosen as the lowest dose level, $d_0 = 1$.

At a given moment of the trial, suppose a total of $N$ patients have been treated, the current dose is $d$, and the $(N + 1)$-th patient is available for enrollment. Recall that $Y_i$ and $Z_i$ denote the DLT outcome and dose assignment of patient $i$, respectively, $i = 1, \ldots, N$. In particular, $Y_i = 1$ (or 0) represents that patient $i$ experiences (or does not experience) DLT within the assessment window. Since patients enter clinical trials at random time, it is often the case that when the $(N + 1)$-th patient is eligible for enrollment, some previously enrolled patients are still
being followed without definitive DLT outcomes, thus their DLT outcomes $Y_i$’s are unknown. Let $B_i$ be the indicator for an unknown DLT outcome, where $B_i = 1$ (or 0) denotes that the DLT outcome of patient $i$ is unknown (or observed). We write $n_d = \sum_{i=1}^{N} \mathbb{1}(Y_i = 1, Z_i = d, B_i = 0)$ and $m_d = \sum_{i=1}^{N} \mathbb{1}(Y_i = 0, Z_i = d, B_i = 0)$ the numbers of patients with observed DLTs and non-DLTs, respectively. In addition, we use $r_d = \sum_{i=1}^{N} \mathbb{1}(Z_i = d, B_i = 1)$ to denote the number of patients with pending outcomes and write $I_d = \{i : Z_i = d, B_i = 1\}$ the index set of these patients. Lastly, we denote $S_d = \sum_{i=1}^{N} \mathbb{1}(Y_i = 1, Z_i = d, B_i = 1)$ the number of DLTs among the $r_d$ pending patients that would have been seen had these patients finished their DLT assessment. Since these patients are still being followed, $\{Y_i : i \in I_d\}$ are not observed and are random variables, and so as $S_d$. We have $S_d \in \{0, 1, \ldots, r_d\}$. The following figure summarizes the patient statistics at dose $d$.

If $S_d$ is known, then the dose-finding decision is given by $A_d = A(n_d + S_d, m_d + r_d - S_d)$, where $A$ is the decision function of mTPI-2 (Section 2). However, since $S_d$ is not observed and random, the decision $A_d$ becomes a random variable too. Suppose through statistical inference one could calculate the posterior probability $\Pr(S_d = s \mid \text{data})$, then we define

$$\Pr(A_d = a \mid \text{data}) = \sum_{s : A(n_d + s, m_d + r_d - s) = a} \Pr(S_d = s \mid \text{data}),$$

which gives the PoD for each decision $a \in \{-1, 0, 1\}$ based on mTPI-2. Details about the probability model and statistical inference are described in the next section. If $d$ is the lowest dose, de-escalation is not possible. Similarly, if $d$ is the highest dose, escalation is not possible. To ensure that the PoD is well defined, in Supplementary Section S1 we show that $\Pr(A_d = a \mid \text{data})$ sums up to 1 over the space of $a$. If there is no pending patient at the current dose ($r_d = 0$), we have $S_d \equiv 0$, and $A_d \equiv A(n_d, m_d)$, i.e., the mTPI-2 decision.

Next, define $\ell(A_d = a, A_d^{\text{true}} = b)$ the loss of making dose decision $a$ if $b$ is the true dose decision that should have been made. We consider the 0-1 loss,

$$\ell(a, b) = \begin{cases} 1, & \text{if } a \neq b; \\ 0, & \text{if } a = b, \end{cases} \quad \text{for } a, b \in \{-1, 0, 1\}.$$
Let $A_d^* = \min\{\arg\max_a \Pr(A_d = a \mid \text{data})\}$ denote the most conservative decision within the set of decisions that have the highest PoD. In other words, if $\arg\max_a \Pr(A_d = a \mid \text{data})$ returns a single decision among $\{-1, 0, 1\}$, then $A_d^*$ equals that decision. Otherwise, if multiple decisions tie for the highest PoD, we choose the more conservative one using the “min” function. It is easy to see that the dose decision $A_d^*$ minimizes the posterior expected loss under the loss function (3), thus is the optimal decision to make, i.e., Bayes’ rule.

Denote by $\gamma_{d,a} = \Pr(A_d = a \mid \text{data})$ for $a \in \{-1, 0, 1\}$. To ensure the safety of the design, we introduce two essential suspension rules.

| If $A_d^* = 1$, i.e. escalation: | We suspend the trial if (i) $\gamma_{d,1} < \pi_E$ for some threshold $\pi_E \in [0.33, 1]$ or (ii) $m_d = 0$. Condition (i) reflects that escalation is not allowed if the confidence of escalation is less than $\pi_E$. A larger $\pi_E$ represents more conservative dose escalations. Condition (ii) means escalation is not allowed until at least one patient at the current dose has finished the DLT assessment and does not experience DLT, similar to the rule in [Normolle and Lawrence (2006)](normolle2006). |
| If $A_d^* = 0$, i.e. stay: | We suspend the trial if $\gamma_{d,-1} > \pi_D$ for some threshold $\pi_D \in [0, 0.5]$. This means stay is not allowed if there is a relatively high chance of de-escalation. A smaller $\pi_D$ represents more conservative stays. |

If none of the suspension rule is triggered, the optimal decision $A_d^*$ is made. In real applications, the values $\pi_E$ and $\pi_D$ should be chosen according to the desired extent of safety. To ensure safety, we recommend choosing $\pi_E \geq 0.8$ and setting $\pi_D \leq 0.25$. For example, in the simulation studies (Section 6), we use $\pi_E = 1$ and $\pi_D = 0.15$, which eliminate the chance of risky escalations. We will discuss more about the important role of $\pi_E$ and $\pi_D$ in Section 6. The dose assignment rules of PoD-TPI is summarized in Algorithm 1.

For practical concerns, similar to existing designs (for example, [Ji et al., 2010](ji2010) and [Yuan et al., 2018](yuan2018)), we include the following two safety rules in PoD-TPI throughout the trial.

**Safety rule 1 (early termination):** At any moment in the trial, if $n_1 + m_1 \geq 3$ and $\Pr(p_1 > p_T \mid n_1, m_1) > 0.95$, terminate the trial due to excessive toxicity;

**Safety rule 2 (dose exclusion):** At any moment in the trial, if $n_d + m_d \geq 3$ and $\Pr(p_d > p_T \mid n_d, m_d) > 0.95$, suspend dose $d$ and higher doses from the trial.
Algorithm 1 Dose assignment rule of PoD-TPI. Current dose level is $d$.

1: if $r_d = 0$ then
2: Assign the patient to dose $d + \mathcal{A}(n_d, m_d)$
3: else if $r_d > 0$ then
4: Calculate $\gamma_{d,a} = \Pr(A_d = a \mid \text{data})$ and $A_d^* = \min\{\arg\max_a \Pr(A_d = a \mid \text{data})\}$
5: if $A_d^* = 1$ then
6: if $\gamma_{d,1} < \pi_E$ or $m_d = 0$ then
7: Suspend accrual
8: else
9: Assign the patient to $(d + 1)$
10: end if
11: else if $A_d^* = 0$ then
12: if $\gamma_{d,-1} > \pi_D$ then
13: Suspend accrual
14: else
15: Assign the patient to $d$
16: end if
17: else if $A_d^* = -1$ then
18: Assign the patient to $(d - 1)$
19: end if
20: end if

In other words, if a sufficient number ($\geq 3$) of patients has been treated at dose $d$ with observed outcomes, and these outcomes suggest $d$ is deemed higher than the MTD, then this dose and higher doses are excluded from the trial. The posterior probability $\Pr(p_d > p_T \mid n_d, m_d)$ is calculated using the observed data at dose $d$ with a prior distribution $p_d \sim \text{Beta}(1, 1)$. It is possible that a dose $d$ and higher doses are excluded when some outcomes at $d$ are pending. In this case, we allow these doses to be re-included if the pending outcomes are observed later and the safety rule is no longer violated. If safety rule 1 is triggered while some outcomes at the lowest dose are pending, we suspend the trial. The trial is resumed if the pending outcomes are observed later and the safety rule is no longer violated, and the trial is permanently terminated otherwise.
The trial is completed if the number of enrolled patients reaches the pre-specified maximum allowable sample size $N^*$ or safety rule 1 is triggered. The last step is to recommend an MTD based on the DLT outcomes. If the trial is terminated due to safety rule 1, no MTD is selected. Otherwise, after DLT assessment for all patients is finished, we use the same procedure as in Ji et al. (2007) to report an MTD. See Supplementary Section S2 for details.

4 Probability Model

4.1 Likelihood Construction

We construct the likelihood function for the observed data, with which we make inference about the distribution of the time to DLT and calculate the posterior distribution of $S_d$ and $A_d$ (Equation 2).

We first introduce some additional notation. Let $\tau$ denote the length of the DLT assessment window. In oncology, $\tau$ is usually 21 or 28 days, corresponding to a cycle of treatment. Denote by $T_i$ the time to DLT for patient $i$, $i = 1, \ldots, N$; recall that we assume $N$ patients have been treated. By definition, $Y_i = 1(T_i \leq \tau)$, because $Y_i$ represents whether patient $i$ experiences DLT within the assessment window. Conditional on the dose assignments ($Z_i$’s), the $T_i$’s are assumed to be independent and identically distributed with probability density function $f_{T|Z}$ and survival function $S_{T|Z}$.

Next, the following notations are defined with respect to the time when the $(N+1)$-th patient is available for enrollment. To simplify notation, we do not explicitly write out the dependency on time. Let $U_i = \min\{\tau, e_{N+1} - e_i\}$ denote the potential censoring time for patient $i$, where $e_i$ is the enrollment time for patient $i$, and $(e_{N+1} - e_i)$ is the time between the enrollment time of patient $i$ and the time when the new patient $(N+1)$ becomes available. Let $V_i = \min\{T_i, U_i\}$ denote the follow-up time, and let $\delta_i = 1(T_i \leq U_i)$ indicate whether the DLT is observed ($\delta_i = 1$) or censored ($\delta_i = 0$). We note that the case $\{\delta_i = 1\}$ corresponds to $\{Y_i = 1, B_i = 0\}$, and $\{\delta_i = 0\}$ includes $\{Y_i = 0, B_i = 0\}$ and $\{B_i = 1\}$.

Based on survival modeling (see, e.g., Klein and Moeschberger 2006), patients with observed DLTs ($\delta_i = 1$) contribute $f_{T|Z}$ to the likelihood, and patients with censored observations ($\delta_i = 0$)
contribute $S_{T|Z}$ to the likelihood. Therefore, the likelihood function is

$$L = \prod_{i=1}^{N} \left[ f_{T|Z}(v_i \mid z_i)^{1(\delta_i=1)} S_{T|Z}(v_i \mid z_i)^{1(\delta_i=0)} \right]. \quad (4)$$

We define a model for $f_{T|Z}(v_i \mid z_i)$ next.

### 4.2 Sampling Model for Time to Toxicity

We assume a parametric distribution for $T_i$ as follows. First, as in the mTPI-2 design, we assume

$$\Pr(T_i \leq \tau \mid Z_i = d, p_d) = \Pr(Y_i = 1 \mid Z_i = d, p_d) = p_d. \quad (5)$$

That is, with probability $p_d$, the DLT for a patient treated by dose $d$ occurs within $(0, \tau]$.

Conditional on $[T_i \leq \tau]$ (i.e., $[Y_i = 1]$), we assume a piecewise uniform distribution for $[T_i \mid Y_i = 1, Z_i = d]$ on the interval $(0, \tau]$. That is, we partition $(0, \tau]$ into $K$ sub-intervals $\{(h_{k-1}, h_k), k = 1, \ldots, K\}$, where $0 = h_0 < h_1 < \cdots < h_K = \tau$. For simplicity, we consider $K = 3$ sub-intervals with equal length, $h_k = k\tau/K$ for $k = 0, 1, 2, 3$. The $k$-th sub-interval is assigned a weight $w_k$, and $\sum_{k=1}^{K} w_k = 1$. Conditional on $[Y_i = 1, Z_i = d]$, $T_i$ falls into $(h_{k-1}, h_k]$ with probability $w_k$ and follows a uniform distribution within this interval. The conditional probability density function of $[T_i \mid Y_i = 1, Z_i = d]$ is thus

$$f_{T|Y,Z}(t \mid Y_i = 1, Z_i = d, w) = w_k \cdot \frac{1}{h_k - h_{k-1}}, \quad \text{for } h_{k-1} < t \leq h_k. \quad (6)$$

Implicitly in (6), $T_i$ and $Z_i$ are conditionally independent given $[T_i \leq \tau]$, meaning the conditional distribution of the time to DLT is the same across doses. In other words, the parameter $w$ is shared across doses. As toxicity data are typically sparse in phase I trials, the conditional independence assumption allows borrow of information across doses and helps the estimation of $w$.

Next, according to the law of total probability,

$$f_{T|Z}(t \mid Z_i = d, p_d, w) = \sum_{y \in \{0,1\}} f_{T|Y,Z}(t \mid Y_i = y, Z_i = d, w) \Pr(Y_i = y \mid Z_i = d, p_d)$$

$$= p_d \cdot w_k \cdot \frac{1}{h_k - h_{k-1}}, \quad \text{for } h_{k-1} < t \leq h_k.$$
Here, \( f_{T \mid Y,Z}(t \mid Y_i = 0, Z_i = d, w) = 0 \) for \( t \leq \tau \), since \( \{Y_i = 0\} \) indicates \( \{T_i > \tau\} \). The survival function of \( T_i \) is

\[
S_{T \mid Z}(t \mid Z_i = d, p_d, w) = 1 - \int_0^t f_{T \mid Z}(v \mid Z_i = d, p_d, w) \, dv 
= 1 - p_d \sum_{k=1}^K w_k \beta(t, k), \quad \text{for } t \leq \tau,
\]

where

\[
\beta(t, k) = \begin{cases} 
1, & \text{if } v > h_k; \\
\frac{t-h_{k-1}}{h_k-h_{k-1}}, & \text{if } v \in (h_{k-1}, h_k], k = 1, \ldots, K; \\
0, & \text{otherwise}.
\end{cases}
\]

Finally, writing out the parametric forms of \( f_{T \mid Z} \) and \( S_{T \mid Z} \) in Equation (4), we obtain the likelihood of \( p \) and \( w \),

\[
L \triangleq L(p, w \mid \text{data}) \propto \prod_{k=1}^K w_k^{n_k} \prod_{d=1}^D \left\{ p_d^{n_d} (1 - p_d)^{m_d} \prod_{i \in \mathcal{I}_d} \left[ 1 - p_d \sum_{k=1}^K w_k \beta(v_i, k) \right] \right\}. \tag{7}
\]

Here, \( n_k = \sum_{i : y_i = 1} 1(h_{k-1} < v_i \leq h_k) \) is the number of patients (across all doses) who have experienced DLT in the time interval \( (h_{k-1}, h_k] \). The pending patients’ follow-up times are included in the likelihood via \( \beta(v_i, k) \). If the DLT outcomes are fully observed, i.e., \( \mathcal{I}_d = \emptyset \), the likelihood of \( p_d \) reduces to the Bernoulli likelihood.

### 4.3 Prior and Posterior

We complete the probability model with prior models for the parameters \( p = (p_1, \ldots, p_D) \) and \( w = (w_1, \ldots, w_K) \). We assume

\[
p_d \sim \text{Beta}(\theta_{d1}, \theta_{d2}), \quad \text{and } w \sim \text{Dir}(\eta_1, \ldots, \eta_K). \tag{8}
\]

Here, \( \theta_{d1} \) and \( \theta_{d2} \) can be chosen based on prior guess of the DLT probability of each dose, and \((\eta_1, \ldots, \eta_K)\) can be chosen based on prior knowledge of the time to DLT falling into each sub-interval. If such information is not available, we recommend simply setting \( \theta_{d1} = \theta_{d2} = 1 \) and \( \eta_1 = \cdots = \eta_K = 1 \).
Posterior of $A_d$. With the likelihood (7) and the prior model (8), we can conduct posterior inference on $p$ and $w$. Specifically,

$$
\pi(p, w \mid \text{data}) \propto \prod_{d=1}^{D} \pi_0(p_d) \times \pi_0(w) \times L(p, w \mid \text{data}),
$$

where $\pi_0(p_d)$ and $\pi_0(w)$ are the prior models as in (8). Markov chain Monte Carlo simulation is used to draw samples from the posterior distribution $\pi(p, w \mid \text{data})$.

Based on the sampling models (5) and (6), we can calculate the probability that a patient experiences DLT within the assessment window given the patient has been followed for $v_i < \tau$, i.e., the conditional probability of $\{Y_i = 1\}$ for $i \in I_d$. Recall that $I_d$ contains the indices of the pending patients. For a patient $i \in I_d$, we have

$$
q_i(v_i, d, p_d, w) \triangleq \Pr(Y_i = 1 \mid T_i > v_i, Z_i = d, p_d, w)
= \frac{\Pr(T_i > v_i \mid Y_i = 1, Z_i = d, w) \Pr(Y_i = 1 \mid Z_i = d, p_d)}{\sum_{y=0}^{K} \Pr(T_i > v_i \mid Y_i = y, Z_i = d, w) \Pr(Y_i = y \mid Z_i = d, p_d)}
= \frac{1 - \sum_{k=1}^{K} w_k \beta(v_i, k) p_d}{1 - \sum_{k=1}^{K} w_k \beta(v_i, k) p_d + (1 - p_d)}, \quad (v_i < \tau).
$$

Recall that $S_d$ is the number of patients that will experience DLTs among the pending patients at dose $d$. Therefore, mathematically $S_d = \sum_{i \in I_d} Y_i$. By definition, given the observed data (including the pending patients’ follow-up times), $[S_d \mid p_d, w, \text{data}]$ follows a Poisson binomial distribution,

$$
S_d \mid p_d, w, \text{data} \sim \text{Poisson-binomial}(q_i, i \in I_d).
$$

Here, the Poisson binomial distribution is the distribution of the sum of independent Bernoulli random variables that not necessarily have the same success probabilities. See, for example, Chen and Liu (1997) for an introduction. Furthermore, we have

$$
\Pr(S_d = s \mid \text{data}) = \int_w \int_{p_d} \Pr(S_d = s \mid p_d, w, \text{data}) \pi(p_d, w \mid \text{data}) dp_d dw.
$$

This integral can be approximated using posterior samples of $p_d$ and $w$. Finally, we can calculate $\Pr(A_d = a \mid \text{data})$ according to Equation (2).
5 Hypothetical Trial Examples

We illustrate the PoD-TPI design through two hypothetical trials in Figure 1. Suppose the target DLT probability is $p_T = 0.3$, and the DLT assessment window is $\tau = 28$ days. We use $\epsilon_1 = \epsilon_2 = 0.05$ as the bounds of the equivalence interval. In addition, we set the thresholds $\pi_E = 1$ and $\pi_D = 0.15$ for trial suspension, and let $\theta_{d1} = \theta_{d2} = 1$ and $\eta_1 = \cdots = \eta_K = 1$. In the first trial, by the time the new patient 7 arrives on day 63, 6 patients have been treated at dose $d$, among whom patients 1, 2, 3 and 4 have observed outcomes with two DLTs and two non-DLTs ($n_d = 2$ and $m_d = 2$). The times to DLTs for patients 3 and 4 are $t_3 = 9$ days and $t_4 = 26$ days, respectively. Patients 5 and 6 are still pending ($r_d = 2$) with follow-up times $v_5 = 15$ days and $v_6 = 8$ days. Assume $d$ is neither the lowest dose nor the highest dose, thus both de-escalation and escalation are possible. Via the probability model introduced in Sections 3 and 4, using the observed DLT data on patients 1–4 and time-to-event data on patients 5 and 6, PoD-TPI estimates $Pr(S_d = 2 \mid \text{data}) = 0.12$, $Pr(S_d = 1 \mid \text{data}) = 0.46$ and $Pr(S_d = 0 \mid \text{data}) = 0.42$ and calculates the PoDs $Pr(A_d = a \mid \text{data})$, as seen in Figure 1. De-escalation ($A_d = -1$) has the highest PoD, and PoD-TPI recommends de-escalating the dose for patient 7 although two patients are still pending. In this way, PoD-TPI saves time and avoids trial suspension compared to mTPI-2. In the second trial, the only difference is that patient 4 does not have a DLT ($n_d = 1$ and $m_d = 3$). In this case, $Pr(S_d = 2 \mid \text{data}) = 0.03$, $Pr(S_d = 1 \mid \text{data}) = 0.30$ and $Pr(S_d = 0 \mid \text{data}) = 0.67$. Escalation has the highest PoD, which is 0.67. However, the PoD of escalation does not reach the safety threshold $\pi_E$, meaning there is a chance (0.33) that escalation is not preferred. In practice, overly aggressive escalations can cause tremendous risk to patients, thus we use a conservative threshold $\pi_E = 1$ to prevent risky escalations even though the PoD for escalation is 0.67, the largest. Enrollment is suspended, and patient 7 is turned away. Later, a new patient (still labeled as the 7th patient in the trial) arrives on day 77, and by this time it turns out that patients 5 and 6 had DLTs. Therefore, the dose is de-escalated for patient 7. In this way, PoD-TPI avoids the risky escalation and maintains the safety of the trial.

Differences with other TITE designs. The two trial examples highlight the key feature of PoD-TPI: the use of posterior distribution of decisions. In the other TITE designs, such as TITE-CRM, TITE-BOIN and TITE-keyboard, the pending outcomes and the follow-up times are
Figure 1: Two hypothetical dose-finding trials using the PoD-TPI design. In both trials, by the time patient 7 arrives, patients 1, 2, 3 and 4 have observed outcomes, and patients 5 and 6 are still being followed without definitive outcomes. In trial 1, based on the posterior probabilities of decisions, patient 7 is assigned to the next lower dose. In trial 2, due to safety concerns, the trial is suspended, and patient 7 is turned away. After the pending outcomes are observed, the next patient is assigned to the next lower dose.

incorporated into the survival likelihood \( \text{[7]} \) to help estimate \( p_d \). Dose decision is then based on inference about \( p_d \), instead of the PoDs of the decisions. For example, TITE-CRM is an extension of the CRM [O’Quigley et al., 1990] and models \( p_d \) using a parametric curve, \( p_d = \phi(d, \alpha) \). Here \( \alpha \) is the parameter that defines the dose-toxicity curve, e.g., a regression parameter in a power curve.
as $p_d = p_0^{\exp(\alpha)}$, where $p_0$'s are pre-specified. Then, a weighted likelihood for $\alpha$ is constructed through survival modeling,

$$L(\alpha \mid \text{data}) = \prod_{i=1}^{N}[\rho_i\phi(z_i, \alpha)]^{1(\delta_i=1)}[1 - \rho_i\phi(z_i, \alpha)]^{1(\delta_i=0)}.$$ 

The value $\rho_i$ is the weight of patient $i$, $\rho_i = 1$ if the patient has observed outcome, and $\rho_i = \rho(v_i) \in [0, 1]$ otherwise. By default, $\rho(v_i) = v_i/\tau$. TITE-BOIN is an extension of the BOIN design (Liu and Yuan, 2015), which estimates $p_d$ by

$$\hat{p}_d \propto \frac{n_d + \frac{n_d + 0.5p}{m_d + 1 - 0.5p}}{n_d + m_d + r_d} \left[r_d - \sum_{i \in I_d}(v_i/\tau)\right].$$

TITE-keyboard is an extension of the keyboard design (Yan et al., 2017), which estimates $p_d$ through the likelihood,

$$L(p_d \mid \text{data}) = p_d^{n_d}(1 - p_d)^{m_d} \prod_{i \in I_d}(1 - \rho_ip_d).$$

Again, $\rho_i$ is the weight of patient $i$. In either cases, one can conduct inference on $p_d$ and make a dose decision based on the same rules in CRM, BOIN or keyboard. In contrast, PoD-TPI takes a different approach by making inference on decisions. The advantage of PoD-TPI over existing TITE designs is that PoD-TPI formally takes into account the variability of the pending outcomes and uses probability cutoffs to control the chance of risky decisions. Consider the second trial example in Figure 1. When patient 7 arrives on day 63, using the TITE-CRM, TITE-BOIN or TITE-keyboard designs, based on the estimate of $p_d$, patient 7 will be treated by the next higher dose ($d + 1$). However, as the outcomes of patients 5 and 6 turn out to be DLTs later, the escalation decision puts patient 7 in an overly toxic dose. Such decisions are of major concern to safety committees as they tend to expose patients to unnecessary risks. Some designs take additional steps to suspend enrollment to enhance safety. For example, TITE-BOIN has a suspension rule when more than 50% of the outcomes at the current dose are pending, and TITE-keyboard has a suspension rule when fewer than two patients at the current dose level have been completely followed. Nevertheless, as in this example, such suspension rules cannot fully account for the variability of the pending outcomes and the risks of different decisions and would still allow the risky escalation.
6 Numerical Studies

We conduct extensive computer simulations to assess the operating characteristics of the proposed PoD-TPI design. The implementation of PoD-TPI requires the specification of a few parameters, $\pi_E$, $\pi_D$, $(\theta_{d1}, \theta_{d2})$ and $(\eta_1, \ldots, \eta_K)$, in the suspension rule and prior model. We use $\pi_E = 1$, $\pi_D = 0.15$, $\theta_{d1} = \theta_{d2} = 1$ and $\eta_1 = \cdots = \eta_K = 1$. Note that $\pi_E = 1$ means that escalation must have PoD equal to 1 to be selected as the dose decision when there are pending patients.

We consider the 60 dose-toxicity scenarios reported in Guo et al. (2019), which cover different target DLT probabilities $p_T \in \{0.10, 0.17, 0.30\}$, numbers of doses $D \in \{3, 4, 5, 6\}$ and dose-toxicity curves. See Supplementary Table S1. To obtain the mTPI-2 decision rule $A$, it is necessary to define the equivalence interval. We use $\epsilon_1 = \epsilon_2 = 0.03$ when $p_T = 0.10$, and $\epsilon_1 = \epsilon_2 = 0.05$ when $p_T = 0.17$ or 0.30. As in typical phase I oncology trials, we set the length of the DLT assessment period at $\tau = 28$ days. For a scenario with a total of $D$ doses, we use a maximum sample size of $6D$ patients. We generate the arrival time between two consecutive patients from an exponential distribution with rate $\delta$ per day, meaning the average inter-arrival time is $1/\delta$ days. The time to DLT for a patient treated by dose $d$ is generated from a Weibull distribution with shape $\zeta_d$ and scale $\lambda_d$,

$$(T_i \mid Z_i = d) \sim \text{Weibull}(\zeta_d, \lambda_d),$$

such that $\Pr(T_i \leq \tau \mid Z_i = d) = p_d$. To uniquely identify $\zeta_d$ and $\lambda_d$, we impose another constraint, $\Pr(T_i \leq (1 - \gamma)\tau \mid Z_i = d) = (1 - \alpha)p_d$ for some $0 < \gamma < 1$ and $0 < \alpha < 1$, which means if a DLT occurs within the assessment window, with probability $\alpha$ it occurs within the last fraction of $\gamma$. This leads to

$$\zeta_d = \log \left[ \frac{\log(1 - p_d)}{\log(1 - p_d + \alpha p_d)} \right] / \log \left( \frac{1}{1 - \gamma} \right), \quad \lambda_d = \frac{\tau}{[-\log(1 - p_d)]^{1/\zeta_d}}.$$ 

For each dose-toxicity scenario, we consider the following four settings that cover different accrual rates and DLT time profiles.

**Setting 1:** inter-arrival time is 10 days, and 50% of DLTs occur in the second half of the assessment window, meaning $\delta = 0.1$, $\alpha = 0.5$ and $\gamma = 0.5$;

**Setting 2:** inter-arrival time is 5 days, and 50% of DLTs occur in the second half of the assessment window, meaning $\delta = 0.2$, $\alpha = 0.5$ and $\gamma = 0.5$;
**Setting 3:** inter-arrival time is 10 days, and 80% of DLTs occur in the last quarter of the assessment window, meaning $\delta = 0.1$, $\alpha = 0.8$ and $\gamma = 0.25$.

**Setting 4:** inter-arrival time is 5 days, and 80% of DLTs occur in the last quarter of the assessment window, meaning $\delta = 0.1$, $\alpha = 0.8$ and $\gamma = 0.25$.

We do not directly consider a setting with a different length of assessment window, as it is equivalent to varying the accrual rate after rescaling the time. Finally, for each scenario and accrual rate and DLT time setting, we simulate 1,000 trials using PoD-TPI as the design.

The performance of the PoD-TPI design is first evaluated based on its reliability and safety. Specifically, the reliability can be measured by the percentage of trials that the MTD is correctly selected (PCS), and the safety can be measured by the average percentages of patients that are correctly allocated to the MTD (percentage of correct allocation, PCA) and are allocated to doses higher than the MTD (percentage of overdosing allocation, POA). Furthermore, we calculate the percentage of trials concluding a dose above the true MTD (percentage of overdosing selection, POS) and the average percentage of toxicity outcomes (POT). The average trial duration is also reported.

In addition to the metrics mentioned above, as noted in Section 5, a major concern for designs allowing patient enrollment with pending DLT information is the possibility of making an inconsistent decision, which is another important aspect of reliability and safety. Here, an inconsistent decision refers to a decision that is different from what would be made if complete outcomes were observed. There are six types of inconsistent decisions: (1) should de-escalate but stayed (DS), (2) should de-escalate but escalated (DE), (3) should stay but escalated (SE), (4) should stay but de-escalated (SD), (5) should escalate but de-escalated (ED), and (6) should escalate but stayed (ES). DE and SE are the most risky decisions, as they can expose patients to overly toxic doses. DS is also risky for the same reason. SD, ED and ES are conservative decisions, which can allocate too many patients to sub-therapeutic doses but are less severe than the overly aggressive decisions.

The performance of PoD-TPI is benchmarked against mTPI-2, which can be seen as a performance upper bound. In addition, we implement R-TPI, TITE-CRM and TITE-BOIN for comparison. Specifically, for TITE-CRM, we use the empiric model, $p_d = \phi(d, \alpha) = P_{\text{bd}}^{\text{exp}(\alpha)}$. The skeleton $p_{\text{bd}}$’s are chosen based on [Lee and Cheung (2009)] using an initial MTD guess of $\lceil D/2 \rceil$; the prior for $\alpha$ is $N(0, 1.34^2)$. The mTPI-2 can only make dose assignments with complete DLT
outcomes, thus we suspend accrual after treating each cohort of patients until all DLT outcomes are fully observed. By default, for R-TPI, the trial is suspended if more than 3 patients at the current dose are still being followed without outcomes. For TITE-CRM, available patients are always enrolled without suspension. For TITE-BOIN, the trial is suspended if more than half of the outcomes at the current dose are pending. The same safety rules (Section 3) are applied to all designs. Also, dose escalation is prohibited until at least one patient at the current dose has finished DLT assessment without experiencing toxicity \cite{normolle2006}. 

The simulation results are summarized in Tables 1 and 2 which show averages over the 60 dose-toxicity scenarios. The scenario-specific operating characteristics are reported in Supplementary Figures S1 and S2. The PCS, PCA, POA, POS and POT of PoD-TPI, reported in Table 1, are comparable to those of mTPI-2. On average, the trial duration is shortened by 70 days using PoD-TPI compared to mTPI-2. On the other hand, R-TPI, TITE-CRM and TITE-BOIN also yield performances generally comparable to those of mTPI-2. We note that the duration of the trial solely depends on the suspension rules, i.e. how many times an available patient is turned away. As a result, TITE-CRM achieves the optimal trial speed as it does not have a suspension rule. However, the reliability of TITE-CRM is decreased when accrual is fast (Settings 2 and 4).

The frequencies of inconsistent decisions are reported in Table 2, where the dose assignment decisions of the TITE designs are compared with the decisions that would be made by mTPI-2 if complete outcomes were observed. An alternative way of defining inconsistent decisions is to compare each TITE decision with its complete data counterpart, e.g., comparing TITE-CRM with CRM and comparing TITE-BOIN with BOIN. The frequencies of inconsistent decisions defined in this way is reported in Supplementary Table S2, which is similar to those reported in Table 2. As discussed in Section 5, the chance of making inconsistent decisions is a major concern for drug companies and regulatory agencies. It is impossible to eliminate inconsistent decisions in the presence of pending outcomes, but the chance of making such decisions can be controlled by suspension rules. We report a few summaries of Table 2.

1. By applying confidence thresholds to decisions, PoD-TPI has the smallest frequencies of risky inconsistent decisions (DS, DE and SE) among all designs.
2. In particular, PoD-TPI never makes risky escalations (DE and SE).
3. Notably, on average, the frequency of overly conservative inconsistent decisions made by PoD-
Table 1: Performance of PoD-TPI compared with mTPI-2, R-TPI, TITE-CRM and TITE-BOIN. Values shown are averages over simulated trials and the 60 dose-toxicity scenarios. The unit of PCS, PCA, POA, POS and POT is %, and the unit of duration (Dur) is day.

| Method     | PCS  | PCA  | POA  | POS  | POT  | Dur |
|------------|------|------|------|------|------|-----|
| Setting 1  |      |      |      |      |      |     |
| mTPI-2     | 52.3 | 38.2 | 24.9 | 17.5 | 16.3 | 458 |
| R-TPI      | 51.0 | 38.9 | 22.8 | 15.6 | 15.7 | 400 |
| TITE-CRM   | 51.2 | 38.4 | 24.3 | 28.1 | 16.3 | 280 |
| TITE-BOIN  | 51.7 | 37.3 | 25.2 | 24.8 | 16.3 | 336 |
| PoD-TPI    | 52.2 | 38.2 | 24.0 | 17.4 | 16.1 | 389 |
| Setting 2  |      |      |      |      |      |     |
| mTPI-2     | 52.5 | 38.0 | 25.8 | 17.9 | 16.4 | 339 |
| R-TPI      | 51.4 | 38.4 | 22.9 | 15.8 | 15.8 | 300 |
| TITE-CRM   | 48.6 | 34.9 | 18.2 | 29.7 | 14.4 | 155 |
| TITE-BOIN  | 51.4 | 37.1 | 24.6 | 23.8 | 16.1 | 227 |
| PoD-TPI    | 51.5 | 37.6 | 23.2 | 17.2 | 15.8 | 265 |
| Setting 3  |      |      |      |      |      |     |
| mTPI-2     | 53.1 | 38.3 | 25.3 | 17.5 | 16.3 | 469 |
| R-TPI      | 52.0 | 38.8 | 24.6 | 16.6 | 16.3 | 413 |
| TITE-CRM   | 52.4 | 37.6 | 27.0 | 27.3 | 17.0 | 282 |
| TITE-BOIN  | 52.0 | 37.0 | 27.4 | 26.2 | 17.0 | 343 |
| PoD-TPI    | 52.3 | 37.9 | 24.4 | 17.8 | 16.2 | 402 |
| Setting 4  |      |      |      |      |      |     |
| mTPI-2     | 52.7 | 38.1 | 25.9 | 17.5 | 16.5 | 351 |
| R-TPI      | 51.8 | 38.1 | 24.5 | 17.2 | 16.2 | 315 |
| TITE-CRM   | 49.6 | 34.0 | 22.7 | 29.6 | 15.5 | 156 |
| TITE-BOIN  | 52.1 | 36.7 | 27.5 | 26.1 | 16.9 | 234 |
| PoD-TPI    | 51.5 | 37.6 | 24.0 | 17.5 | 16.1 | 279 |

TPI is also the smallest among all designs.

We note that the inconsistent decisions do not necessarily affect the metrics like PCS, PCA,
POA, POS and POT, since the selection of MTD is always based on complete data. Also, the
inconsistent decisions can be either too aggressive or too conservative thus cancel out in the
calculation of PCA and POA. Instead, the inconsistent decisions are more about patients and
their risks of being exposed to toxic doses. If a dose escalation decision has large uncertainty, it is
unethical to expose future patients to higher doses, and the safety review boards should express
concerns regarding such decision. From this point of view, PoD-TPI is more favorable compared
to the other TITE designs.

**Sensitivity analysis.** An attractive feature of PoD-TPI is the flexibility in calibrating the values
of $\pi_E$ and $\pi_D$ to achieve the desired trade-off between speed and safety. The threshold $\pi_E$ controls
the rates of DE and SE decisions, and $\pi_D$ controls the rate of SD decisions. They both affect the
speed of the trial through suspension rules.

We conduct additional simulations to demonstrate the performance of PoD-TPI with five
combinations of $\pi_E$ and $\pi_D$. The results are summarized in Table 3. By setting $\pi_E = 1$ and
$\pi_D = 0$, we achieve the safest version of PoD-TPI, which never makes any inconsistent and risky
decision (DS, DE and SE) and has the highest PCA and the lowest POA. As a trade-off, the trial
duration of the safest version is longer than that of the default version by 20 days. On the other
hand, by setting $\pi_E = 0.8$ and $\pi_D = 0.25$, we obtain the fastest version of PoD-TPI, the speed of
which is comparable to TITE-BOIN. The trial duration of the fastest version is shorter than that
of the default version by 50 days. As a trade-off, the safety profile of the fastest version is worse
than the other versions.

**Benchmark against rolling six.** The rolling six (R6) design (Skolnik et al., 2008) is a widely
used phase I design that allows for continual accrual of up to six patients onto a dose level. So far,
it has 139 citations (according to Google Scholar) and was used in many real-world trials (e.g.,
Mossé et al., 2013 and von Stackelberg et al., 2016). R6 consists of a set of algorithmic decision
rules that determine the dose-finding decisions and MTD selection. The rules are transparent and
are interpretable to clinicians.

We conduct additional simulations to benchmark the performance of PoD-TPI against R6.
The aim is to show that PoD-TPI has a lower risk than R6, thereby further establish the potential
utility of the PoD-TPI design in practice. For a fair comparison, we consider the 20 dose-toxicity
Table 2: Frequencies of inconsistent decisions compared to the decisions that would be made by mTPI-2 if complete outcomes were observed. Values are shown in $1/10^3$. The decisions in square brackets are inconsistent and risky.

| Method     | [DS] | [DE] | [SE] | SD  | ED  | ES  | Sum  |
|------------|------|------|------|-----|-----|-----|------|
|            |      |      |      |     |     |     |      |
| Setting 1  |      |      |      |     |     |     |      |
| R-TPI      | 30.7 | 0.0  | 0.0  | 0.0 | 0.0 | 93.7| 124.4|
| TITE-CRM   | 99.3 | 4.1  | 14.6 | 4.8 | 1.5 | 108.1| 232.4|
| TITE-BOIN  | 10.9 | 5.8  | 30.4 | 46.6| 0.2 | 20.4 | 114.3|
| PoD-TPI    | **6.1** | 0.0  | 0.0  | 25.0| 1.0 | **7.9** | **40.0** |
| Setting 2  |      |      |      |     |     |     |      |
| R-TPI      | 40.3 | 0.0  | 0.0  | 0.0 | 0.0 | 84.3| 124.6|
| TITE-CRM   | 66.2 | 3.8  | 14.7 | 2.7 | 1.0 | 69.8| 158.2|
| TITE-BOIN  | 15.3 | 6.7  | 26.8 | 51.5| 0.6 | 33.7| 134.6|
| PoD-TPI    | **7.8** | 0.0  | 0.0  | 43.9| 0.3 | **20.9** | **72.9** |
| Setting 3  |      |      |      |     |     |     |      |
| R-TPI      | 49.3 | 0.0  | 0.0  | 0.0 | 0.0 | 94.4| 143.7|
| TITE-CRM   | 103.6| 7.8  | 18.3 | 6.1 | 2.9 | 92.6| 231.3|
| TITE-BOIN  | 22.9 | 11.3 | 40.0 | 39.8| 0.1 | 17.5| 131.6|
| PoD-TPI    | **11.7** | 0.0  | 0.0  | 23.1| 1.1 | **9.8** | **45.7** |
| Setting 4  |      |      |      |     |     |     |      |
| R-TPI      | 57.5 | 0.0  | 0.0  | 0.0 | 0.0 | 89.9| 147.4|
| TITE-CRM   | 53.3 | 7.2  | 19.8 | 3.1 | 1.7 | 50.9| 136.0|
| TITE-BOIN  | 31.1 | 12.1 | 37.8 | 41.4| 0.4 | 28.1| 150.9|
| PoD-TPI    | **16.7** | 0.0  | 0.0  | 35.9| 0.4 | **23.6** | **76.6** |

scenarios with a target DLT probability of $p_T = 0.17$ and calibrate the maximum sample size of PoD-TPI to match the average sample size of R6. Specifically, for each scenario, we first simulate 1,000 trials using R6 as the design. Next, we calculate the average sample size for R6 across the simulated trials. Finally, we round up the average sample size for R6 and use it as the maximum sample size for PoD-TPI. The average sample size of R6 across the 20 scenarios is around 19
Table 3: Performance of PoD-TPI with different choices of $\pi_E$ and $\pi_D$. Values shown are averages over simulated trials and the 60 dose-toxicity scenarios. The unit of PCS, PCA and POA is %, the unit of inconsistent decisions (DS, DE, SE, SD, ED, ES) is $1/10^3$, and the unit of duration (Dur) is day. The decisions in square brackets are inconsistent and risky.

| $\pi_E$ | $\pi_D$ | PCS  | PCA  | POA  | Dur  | [DS] | [DE] | [SE] | SD  | ED  | ES  |
|---------|---------|------|------|------|------|------|------|------|-----|-----|-----|
|         |         | 52.3 | 38.2 | 24.9 | 458  | 0.0  | 0.0  | 0.0  | 25.0 | 1.0 | 7.9 |
| (mTPI-2)| 1 0.15  | 52.2 | 38.2 | 24.0 | 389  | 6.1  | 0.0  | 0.0  | 24.9 | 1.1 | 7.3 |
|         | 1 0     | 51.8 | 38.2 | 23.8 | 410  | 0.0  | 0.0  | 0.0  | 24.9 | 1.1 | 7.3 |
|         | 0.9 0.25| 51.9 | 38.0 | 24.5 | 352  | 11.5 | 1.5  | 5.0  | 25.5 | 1.2 | 11.5|
|         | 0.9 0.15| 52.0 | 37.9 | 24.5 | 359  | 6.1  | 1.5  | 5.1  | 25.5 | 1.0 | 7.9 |
|         | 0.8 0.25| 52.2 | 37.9 | 25.2 | 336  | 11.8 | 1.0  | 4.8  | 25.7 | 1.2 | 11.1|
|         |         | 52.5 | 38.0 | 25.8 | 339  | 0.0  | 0.0  | 0.0  | 24.9 | 1.1 | 7.3 |
|         | 1 0.15  | 51.5 | 37.6 | 23.2 | 265  | 7.8  | 0.0  | 0.0  | 43.9 | 0.3 | 20.9|
|         | 1 0     | 51.5 | 37.7 | 22.9 | 285  | 0.0  | 0.0  | 0.0  | 43.0 | 0.3 | 19.4|
|         | 0.9 0.25| 51.4 | 37.3 | 23.9 | 231  | 13.6 | 1.9  | 6.6  | 44.4 | 1.5 | 28.5|
|         | 0.9 0.15| 51.7 | 37.5 | 24.0 | 237  | 7.8  | 1.9  | 6.7  | 45.1 | 1.1 | 20.0|
|         | 0.8 0.25| 51.2 | 36.9 | 24.5 | 221  | 13.7 | 4.2  | 13.0 | 44.6 | 1.6 | 27.7|
|         |         | 53.1 | 38.3 | 25.3 | 469  | 0.0  | 0.0  | 0.0  | 22.8 | 1.1 | 8.9 |
|         | 1 0.15  | 52.3 | 37.9 | 24.4 | 402  | 11.7 | 0.0  | 0.0  | 23.1 | 1.1 | 9.8 |
|         | 1 0     | 52.2 | 38.1 | 24.0 | 422  | 0.0  | 0.0  | 0.0  | 22.8 | 1.1 | 8.9 |
|         | 0.9 0.25| 52.5 | 37.5 | 26.0 | 367  | 21.8 | 4.4  | 10.7 | 23.3 | 1.3 | 14.3|
|         | 0.9 0.15| 52.4 | 37.7 | 25.8 | 374  | 12.6 | 4.5  | 10.9 | 23.9 | 1.1 | 9.2 |
|         | 0.8 0.25| 52.3 | 37.4 | 27.5 | 350  | 22.6 | 9.8  | 21.3 | 24.2 | 1.2 | 13.1|
|         |         | 52.7 | 38.1 | 25.9 | 351  | 0.0  | 0.0  | 0.0  | 23.1 | 1.1 | 9.8 |
|         | 1 0.15  | 51.7 | 37.6 | 23.9 | 279  | 16.9 | 0.0  | 0.0  | 36.3 | 0.4 | 23.9|
|         | 1 0     | 51.5 | 37.7 | 23.2 | 299  | 0.0  | 0.0  | 0.0  | 36.0 | 0.3 | 21.7|
|         | 0.9 0.25| 52.1 | 36.9 | 25.9 | 246  | 28.9 | 6.1  | 14.5 | 37.0 | 1.3 | 31.1|
|         | 0.9 0.15| 52.0 | 37.2 | 26.0 | 253  | 18.1 | 6.1  | 15.3 | 38.0 | 0.7 | 21.7|
|         | 0.8 0.25| 52.1 | 36.5 | 27.6 | 236  | 29.7 | 11.7 | 25.9 | 38.0 | 1.4 | 29.1|

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patients.

The simulation results of R6 and PoD-TPI are summarized in Tables 4 and 5. The trial speed of R6 is faster than that of PoD-TPI. However, the reliability and safety of PoD-TPI are uniformly better than R6. In practice, usually safety is the most important criterion, thus PoD-TPI is more favorable compared to R6.

Table 4: Performance of PoD-TPI compared with rolling six (R6). Values shown are averages over simulated trials and the 60 dose-toxicity scenarios. The unit of PCS, PCA, POA, POS and POT is %, and the unit of duration (Dur) is day.

| Method | PCS | PCA | POA | POS | POT | Dur |
|--------|-----|-----|-----|-----|-----|-----|
| Setting 1 |     |     |     |     |     |     |
| R6     | 48.4| 34.2| 24.9| 27.7| 17.5| 245 |
| PoD-TPI| 50.5| 37.6| 19.4| 14.8| 13.5| 299 |
| Setting 2 |     |     |     |     |     |     |
| R6     | 48.7| 34.0| 25.4| 27.6| 17.3| 175 |
| PoD-TPI| 49.0| 36.9| 19.6| 15.7| 13.4| 217 |
| Setting 3 |     |     |     |     |     |     |
| R6     | 48.4| 34.1| 25.4| 27.6| 17.4| 251 |
| PoD-TPI| 49.8| 37.2| 19.7| 16.2| 13.4| 311 |
| Setting 4 |     |     |     |     |     |     |
| R6     | 48.3| 33.7| 25.7| 27.5| 17.3| 177 |
| PoD-TPI| 49.6| 36.9| 19.8| 15.4| 13.4| 225 |

7 Discussion

We have proposed the PoD-TPI design to accelerate phase I trials. We have developed a statistical methodology to calculate the posterior distribution of a dose assignment decision in the presence of pending toxicity outcomes. The posterior distribution directly reflects the confidence of all possible decisions, and the optimal decision is computed under a decision-theoretic framework. Intuitive suspension rules are added based on the risk of the optimal decision, minimizing the
Table 5: Frequencies of inconsistent decisions compared to the decisions that would be made by mTPI-2 if complete outcomes were observed. Values are shown in $1/10^3$. The decisions in square brackets are inconsistent and risky.

| Method   | [DS] | [DE] | [SE] | SD  | ED  | ES | Sum   |
|----------|------|------|------|-----|-----|----|-------|
| Setting 1 |      |      |      |     |     |    |       |
| R6       | 118.1| 0.0  | 43.0 | 0.0 | 0.0 | 3.5| 183.7 |
| PoD-TPI  | 4.5  | 0.0  | 0.0  | 17.8| 1.6 | 3.5| 27.4  |
| Setting 2 |      |      |      |     |     |    |       |
| R6       | 77.9 | 0.0  | 43.7 | 0.0 | 0.0 | 5.1| 51.1  |
| PoD-TPI  | 6.7  | 0.0  | 0.0  | 37.9| 0.5 | 10.7| 55.8  |
| Setting 3 |      |      |      |     |     |    |       |
| R6       | 95.4 | 0.0  | 42.3 | 0.0 | 0.0 | 4.0| 180.9 |
| PoD-TPI  | 9.6  | 0.0  | 0.0  | 22.8| 1.8 | 3.9| 38.1  |
| Setting 4 |      |      |      |     |     |    |       |
| R6       | 32.5 | 0.0  | 43.0 | 0.0 | 0.0 | 5.0| 50.4  |
| POD-TPI  | 14.4 | 0.0  | 0.0  | 43.2| 0.5 | 13.2| 71.3  |

chance of making inconsistent decisions. Specifically, the probability threshold for suspension can be flexibly adjusted to balance between speed and safety.

The PoD-TPI design is built upon the mTPI-2 design. Nevertheless, the proposed strategy can be applied to other model-free or model-assisted designs such as 3+3 (Storer 1989), BOIN (Liu and Yuan 2015), keyboard (Yan et al. 2017) or i3+3 (Liu et al. 2019). It suffices to change the deterministic decision function $A$ according to the specific design.

The PoD-TPI design has an early stopping rule when the lowest dose is too toxic. If desired, another early stopping rule can be added when the MTD has been identified with high confidence. For example, when $\Pr(p_d \in I_E \mid \text{data}) > 0.95$ for some dose level $d$.

In PoD-TPI, the likelihood of the unknown parameters $p$ and $w$ is constructed based on survival modeling (Equation 7), which implicitly assumes that all of the study subjects will eventually experience the event of interest (DLT) if they are followed long enough. Such assumption may not
be valid for immunotherapies, because they may not induce DLT events at all in some patients. In such cases, we can use a cure rate model \cite{Boag1949}, assuming with non-zero probability that patients may never experience DLT. Little would change in the overall setup; see Supplementary Section S4 for a discussion.

Finally, in practice, it is desirable to tabulate the dose decision rules of the design before the trial begins, so that the rules are transparent and can be examined by clinicians. We note that this is generally not possible for model-based or model-assisted time-to-event designs without some approximation (see, e.g., \cite{Yuan2018} and \cite{Lin2018}). A future direction is to explore what approximation is needed for PoD-TPI so that its decision rules can be pre-tabulated.

References

Boag, J. W. (1949). Maximum likelihood estimates of the proportion of patients cured by cancer therapy. *Journal of the Royal Statistical Society: Series B (Methodological)*, 11(1):15–53.

Chen, S. X. and Liu, J. S. (1997). Statistical applications of the Poisson-binomial and conditional Bernoulli distributions. *Statistica Sinica*, 7(4):875–892.

Cheung, Y. K. and Chappell, R. (2000). Sequential designs for phase I clinical trials with late-onset toxicities. *Biometrics*, 56(4):1177–1182.

Cheung, Y. K. and Chappell, R. (2002). A simple technique to evaluate model sensitivity in the continual reassessment method. *Biometrics*, 58(3):671–674.

Guo, W., Ji, Y., and Li, D. (2019). R-TPI: Rolling toxicity probability interval design to shorten the duration and maintain safety of phase I trials. *Journal of Biopharmaceutical Statistics*. In press.

Guo, W., Wang, S.-J., Yang, S., Lynn, H., and Ji, Y. (2017). A Bayesian interval dose-finding design addressing Ockham’s razor: mTPI-2. *Contemporary Clinical Trials*, 58:23–33.

Ivanova, A., Flournoy, N., and Chung, Y. (2007). Cumulative cohort design for dose-finding. *Journal of Statistical Planning and Inference*, 137(7):2316–2327.
Jefferys, W. H. and Berger, J. O. (1992). Ockham’s razor and Bayesian analysis. *American Scientist*, 80(1):64–72.

Ji, Y., Li, Y., and Nebiyou Bekele, B. (2007). Dose-finding in phase I clinical trials based on toxicity probability intervals. *Clinical Trials*, 4(3):235–244.

Ji, Y., Liu, P., Li, Y., and Nebiyou Bekele, B. (2010). A modified toxicity probability interval method for dose-finding trials. *Clinical Trials*, 7(6):653–663.

Ji, Y. and Wang, S.-J. (2013). Modified toxicity probability interval design: A safer and more reliable method than the 3+3 design for practical phase I trials. *Journal of Clinical Oncology*, 31(14):1785–1791.

Kanjanapan, Y., Day, D., Butler, M., Wang, L., Joshua, A., Hogg, D., Leighl, N., Razak, A. A., Hansen, A., Boujos, S., Chappell, M., Chow, K., Sherwin, B., Stayner, L.-A., Soultani, L., Zambrana, A., Siu, L., Bedard, P., and Spreafico, A. (2019). Delayed immune-related adverse events in assessment for dose-limiting toxicity in early phase immunotherapy trials. *European Journal of Cancer*, 107:1–7.

Klein, J. P. and Moeschberger, M. L. (2006). *Survival Analysis: Techniques for Censored and Truncated Data*. Springer Science & Business Media.

Lee, S. M. and Cheung, Y. K. (2009). Model calibration in the continual reassessment method. *Clinical Trials*, 6(3):227–238.

Lin, R. and Yuan, Y. (2018). Time-to-event model-assisted designs to accelerate phase I clinical trials. *arXiv preprint arXiv:1807.08393*.

Liu, M., Wang, S.-J., and Ji, Y. (2019). The i3+3 design for phase I clinical trials. *arXiv preprint arXiv:1901.01303*.

Liu, S. and Yuan, Y. (2015). Bayesian optimal interval designs for phase I clinical trials. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, 64(3):507–523.

Mossé, Y. P., Lim, M. S., Voss, S. D., Wilner, K., Ruffner, K., Laliberte, J., Rolland, D., Balis, F. M., Maris, J. M., Weigel, B. J., Ingle, A. M., Ahern, C., Adamson, P. C., and Blaney, S. M.
(2013). Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: A children’s oncology group phase 1 consortium study. *The Lancet Oncology*, 14(6):472–480.

Normolle, D. and Lawrence, T. (2006). Designing dose-escalation trials with late-onset toxicities using the time-to-event continual reassessment method. *Journal of Clinical Oncology*, 24(27):4426–4433.

O’Quigley, J., Pepe, M., and Fisher, L. (1990). Continual reassessment method: A practical design for phase I clinical trials in cancer. *Biometrics*, 46(1):33–48.

Skolnik, J. M., Barrett, J. S., Jayaraman, B., Patel, D., and Adamson, P. C. (2008). Shortening the timeline of pediatric phase I trials: The rolling six design. *Journal of Clinical Oncology*, 26(2):190–195.

Storer, B. E. (1989). Design and analysis of phase I clinical trials. *Biometrics*, 45(3):925–937.

von Stackelberg, A., Locatelli, F., Zugmaier, G., Handgretinger, R., Trippett, T. M., Rizzari, C., Bader, P., O’Brien, M. M., Breton, B., Bhojwani, D., Schlegel, P. G., Borkhardt, A., Rheingold, S. R., Cooper, T. M., Zwaan, C. M., Barnette, P., Messina, C., Michel, G., DuBois, S. G., Hu, K., Zhu, M., Whitlock, J. A., and Gore, L. (2016). Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *Journal of Clinical Oncology*, 34(36):4381–4389.

Yan, F., Mandrekar, S. J., and Yuan, Y. (2017). Keyboard: A novel Bayesian toxicity probability interval design for phase I clinical trials. *Clinical Cancer Research*, 23(15):3994–4003.

Yuan, Y., Lin, R., Li, D., Nie, L., and Warren, K. E. (2018). Time-to-event Bayesian optimal interval design to accelerate phase I trials. *Clinical Cancer Research*. Article No. 0246.
Supplementary Materials

S1 Probability of Decisions

We show that the PoD
\[
\Pr(A_d = a \mid \text{data}) = \sum_{s \in A(n_d + s, m_d + r_d - s) = a} \Pr(S_d = s \mid \text{data})
\]
sums up to 1 over the space of \( a \in \{-1, 0, 1\} \). Note that for any \( s \in \{0, 1, \ldots, r_d\} \), \( A(n_d + s, m_d + r_d - s) \in \{-1, 0, 1\} \). On the other hand, the support of \( S_d \) is \( \{0, 1, \ldots, r_d\} \). Therefore,
\[
\Pr(A_d \in \{-1, 0, 1\} \mid \text{data}) = \sum_{s \in \{0,1,\ldots,r_d\}} \Pr(S_d = s \mid \text{data}) = 1.
\]

S2 Selection of the MTD

The trial is completed if the number of enrolled patients reaches the pre-specified maximum allowable sample size \( N^* \) or safety rule 1 is triggered. The last step is to recommend an MTD based on the DLT outcomes. If the trial is terminated due to safety rule 1, no MTD is selected. Otherwise, after DLT assessment for all patients is finished, we use the same procedure as in Ji et al. (2007) to report an MTD. The isotonically transformed posterior means are used as estimates of \( p_d \)'s subject to the order constraint \( p_1 \leq \cdots \leq p_D \). In particular, we first calculate posterior means and variances of the DLT probabilities, \( \{\tilde{p}_1, \ldots, \tilde{p}_D\} \) and \( \{\nu_1, \ldots, \nu_D\} \). Then, we solve the optimization problem, minimizing
\[
\sum_{d=1}^{D}(\hat{p}_d - \tilde{p}_d)^2/\nu_d \text{ subject to } \hat{p}_j \geq \hat{p}_i \text{ for } j > i.
\]
Such optimization can be done using the pooled adjacent violators algorithm, and \( \{\hat{p}_1, \ldots, \hat{p}_D\} \) are estimated DLT probabilities satisfying the order constraint. Let \( \mathcal{D} = \{d : \hat{p}_d \in I_E\} \) and \( \mathcal{D}_- = \{d : \hat{p}_d \in I_U\} \). The procedure of selecting the MTD is summarized in Algorithm 2. We note that the recommended dose for the last patient needs not be the selected MTD.
Algorithm 2 MTD selection rule. Here $|\mathcal{D}|$ is the cardinality of set $\mathcal{D}$.

1: if $|\mathcal{D}| = 0$ then
2:  
3:  if $|\mathcal{D}_-| \geq 1$ then
4:  
5:  Select the highest dose in $\mathcal{D}_-$ as the MTD
6:  else
7:  No MTD is selected
8: end if
9: else if $|\mathcal{D}| = 1$ then
10:  Select the dose in $\mathcal{D}$ as the MTD
11: else if $|\mathcal{D}| > 1$ then
12:  Let $\mathcal{D}_0 = \arg \min_{d \in \mathcal{D}} |\hat{p}_d - p_T|$
13:  if $|\mathcal{D}_0| = 1$ then
14:  
15:  Select the dose in $\mathcal{D}_0$ as the MTD
16:  else if $|\mathcal{D}_0| > 1$ then
17:  
18:  Let $\mathcal{D}_{0-} = \{d : \hat{p}_d \in \mathcal{D}_0, \hat{p}_d \in [p_T - \epsilon_1, p_T]\}$
19:  if $|\mathcal{D}_{0-}| \geq 1$ then
20:  
21:  Select the highest dose in $\mathcal{D}_{0-}$ as the MTD
22:  else
23:  
24:  Select the lowest dose in $\mathcal{D}_0$ as the MTD
25: end if
26: end if
27: end if
S3 Simulation Details

We provide supplementary tables and figures that are referenced in the manuscript. Table S1 summarizes the 60 dose-toxicity scenarios used in the simulation studies. Tables S2 and S3 report the frequencies of inconsistent decisions by comparing the decisions made by R-TPI, TITE-CRM, TITE-BOIN and PoD-TPI with their complete data counterparts. Figures S1 and S2 show the scenario-specific operating characteristics.

Table S1: 60 dose-toxicity scenarios with different target DLT probabilities $p_T \in \{0.10, 0.17, 0.30\}$, numbers of doses $D \in \{3, 4, 5, 6\}$ and true DLT probabilities $\{p_1, \ldots, p_D\}$.

| Scn. | $p_T$ | $D$ | $p_1$ | $p_2$ | $p_3$ | $p_4$ | $p_5$ | $p_6$ |
|------|-------|-----|-------|-------|-------|-------|-------|-------|
| 1    | 0.10  | 3   | 0.05  | 0.10  | 0.15  |       |       |       |
| 2    | 0.10  | 3   | 0.03  | 0.06  | 0.28  |       |       |       |
| 3    | 0.10  | 3   | 0.06  | 0.20  | 0.30  |       |       |       |
| 4    | 0.10  | 3   | 0.10  | 0.20  | 0.30  |       |       |       |
| 5    | 0.10  | 3   | 0.21  | 0.32  | 0.43  |       |       |       |
| 6    | 0.10  | 4   | 0.05  | 0.10  | 0.15  | 0.20  |       |       |
| 7    | 0.10  | 4   | 0.03  | 0.06  | 0.10  | 0.15  |       |       |
| 8    | 0.10  | 4   | 0.02  | 0.04  | 0.06  | 0.28  |       |       |
| 9    | 0.10  | 4   | 0.05  | 0.10  | 0.20  | 0.30  |       |       |
| 10   | 0.10  | 4   | 0.05  | 0.20  | 0.35  | 0.50  |       |       |
| 11   | 0.10  | 5   | 0.05  | 0.10  | 0.15  | 0.20  | 0.25  |       |
| 12   | 0.10  | 5   | 0.02  | 0.04  | 0.08  | 0.10  | 0.16  |       |
| 13   | 0.10  | 5   | 0.02  | 0.04  | 0.06  | 0.08  | 0.28  |       |
| 14   | 0.10  | 5   | 0.03  | 0.07  | 0.12  | 0.15  | 0.25  |       |
| 15   | 0.10  | 5   | 0.06  | 0.19  | 0.32  | 0.45  | 0.58  |       |
| 16   | 0.10  | 6   | 0.05  | 0.10  | 0.15  | 0.20  | 0.25  | 0.30  |
| 17   | 0.10  | 6   | 0.02  | 0.05  | 0.08  | 0.12  | 0.16  | 0.20  |
| 18   | 0.10  | 6   | 0.02  | 0.04  | 0.06  | 0.08  | 0.10  | 0.28  |
| 19   | 0.10  | 6   | 0.11  | 0.15  | 0.21  | 0.25  | 0.30  | 0.35  |
| 20   | 0.10  | 6   | 0.06  | 0.17  | 0.28  | 0.39  | 0.50  | 0.61  |
Table S1: (continued)

| Scn. | $p_T$ | $D$ | $p_1$ | $p_2$ | $p_3$ | $p_4$ | $p_5$ | $p_6$ |
|------|------|-----|-------|-------|-------|-------|-------|-------|
| 21   | 0.17 | 3   | 0.08  | 0.17  | 0.25  |       |       |       |
| 22   | 0.17 | 3   | 0.06  | 0.12  | 0.34  |       |       |       |
| 23   | 0.17 | 3   | 0.10  | 0.26  | 0.35  |       |       |       |
| 24   | 0.17 | 3   | 0.04  | 0.08  | 0.12  |       |       |       |
| 25   | 0.17 | 3   | 0.27  | 0.37  | 0.47  |       |       |       |
| 26   | 0.17 | 4   | 0.08  | 0.17  | 0.25  | 0.33  |       |       |
| 27   | 0.17 | 4   | 0.06  | 0.12  | 0.17  | 0.23  |       |       |
| 28   | 0.17 | 4   | 0.04  | 0.08  | 0.12  | 0.34  |       |       |
| 29   | 0.17 | 4   | 0.03  | 0.06  | 0.09  | 0.12  |       |       |
| 30   | 0.17 | 4   | 0.12  | 0.26  | 0.40  | 0.54  |       |       |
| 31   | 0.17 | 5   | 0.08  | 0.17  | 0.25  | 0.33  | 0.41  |       |
| 32   | 0.17 | 5   | 0.04  | 0.08  | 0.12  | 0.17  | 0.25  |       |
| 33   | 0.17 | 5   | 0.03  | 0.06  | 0.09  | 0.12  | 0.34  |       |
| 34   | 0.17 | 5   | 0.03  | 0.06  | 0.09  | 0.12  | 0.15  |       |
| 35   | 0.17 | 5   | 0.13  | 0.25  | 0.37  | 0.49  | 0.61  |       |
| 36   | 0.17 | 6   | 0.08  | 0.17  | 0.25  | 0.33  | 0.41  | 0.49  |
| 37   | 0.17 | 6   | 0.03  | 0.10  | 0.15  | 0.20  | 0.25  | 0.30  |
| 38   | 0.17 | 6   | 0.03  | 0.06  | 0.09  | 0.12  | 0.15  | 0.34  |
| 39   | 0.17 | 6   | 0.04  | 0.08  | 0.10  | 0.12  | 0.14  | 0.16  |
| 40   | 0.17 | 6   | 0.14  | 0.24  | 0.34  | 0.44  | 0.54  | 0.64  |
| 41   | 0.30 | 3   | 0.15  | 0.30  | 0.45  |       |       |       |
| 42   | 0.30 | 3   | 0.10  | 0.20  | 0.44  |       |       |       |
| 43   | 0.30 | 3   | 0.18  | 0.38  | 0.46  |       |       |       |
| 44   | 0.30 | 3   | 0.08  | 0.16  | 0.24  |       |       |       |
| 45   | 0.30 | 3   | 0.39  | 0.48  | 0.57  |       |       |       |
| 46   | 0.30 | 4   | 0.15  | 0.30  | 0.45  | 0.60  |       |       |
| 47   | 0.30 | 4   | 0.10  | 0.20  | 0.30  | 0.40  |       |       |
| 48   | 0.30 | 4   | 0.08  | 0.16  | 0.24  | 0.44  |       |       |
Table S1: (continued)

| Scn. | $p_T$ | $D$ | $p_1$ | $p_2$ | $p_3$ | $p_4$ | $p_5$ | $p_6$ |
|------|------|-----|------|------|------|------|------|------|
| 49   | 0.30 | 4   | 0.06 | 0.12 | 0.18 | 0.24 |      |      |
| 50   | 0.30 | 4   | 0.26 | 0.38 | 0.50 | 0.62 |      |      |
| 51   | 0.30 | 5   | 0.15 | 0.30 | 0.45 | 0.60 | 0.75 |      |
| 52   | 0.30 | 5   | 0.08 | 0.16 | 0.24 | 0.30 | 0.38 |      |
| 53   | 0.30 | 5   | 0.06 | 0.12 | 0.18 | 0.24 | 0.44 |      |
| 54   | 0.30 | 5   | 0.05 | 0.10 | 0.15 | 0.20 | 0.25 |      |
| 55   | 0.30 | 5   | 0.27 | 0.37 | 0.47 | 0.57 | 0.67 |      |
| 56   | 0.30 | 6   | 0.14 | 0.30 | 0.44 | 0.58 | 0.72 | 0.86 |
| 57   | 0.30 | 6   | 0.06 | 0.12 | 0.18 | 0.24 | 0.30 | 0.36 |
| 58   | 0.30 | 6   | 0.05 | 0.10 | 0.15 | 0.20 | 0.25 | 0.44 |
| 59   | 0.30 | 6   | 0.04 | 0.08 | 0.12 | 0.16 | 0.20 | 0.24 |
| 60   | 0.30 | 6   | 0.27 | 0.36 | 0.45 | 0.54 | 0.63 | 0.72 |
Table S2: Frequencies of inconsistent decisions compared to the decisions that would be made by the corresponding complete data design. R-TPI is compared to mTPI-2, TITE-CRM is compared to CRM, TITE-BOIN is compared to BOIN, and PoD-TPI is compared to mTPI-2. Values are shown in $1/10^3$.

| Method   | DS  | DE  | SE  | SD  | ED  | ES  | Sum  |
|----------|-----|-----|-----|-----|-----|-----|------|
| R-TPI    | 30.7| 0.0 | 0.0 | 0.0 | 93.7| 124.4|
| TITE-CRM | 29.9| 1.1 | 5.5 | 0.0 | 53.6| 98.6 |
| TITE-BOIN| 11.0| 5.8 | 15.2| 0.2 | 31.8| 110.6|
| PoD-TPI  | 6.1 | 0.0 | 25.0| 1.0 | 7.9 | 40.0 |

| Method   | DS  | DE  | SE  | SD  | ED  | ES  | Sum  |
|----------|-----|-----|-----|-----|-----|-----|------|
| R-TPI    | 40.3| 0.0 | 0.0 | 0.0 | 84.3| 124.6|
| TITE-CRM | 20.8| 0.5 | 4.7 | 0.0 | 70.3| 106.7|
| TITE-BOIN| 15.3| 6.7 | 17.9| 0.7 | 50.4| 142.4|
| PoD-TPI  | 7.8 | 0.0 | 43.9| 0.3 | 20.9| 72.9 |

| Method   | DS  | DE  | SE  | SD  | ED  | ES  | Sum  |
|----------|-----|-----|-----|-----|-----|-----|------|
| R-TPI    | 49.3| 0.0 | 0.0 | 0.0 | 94.4| 143.7|
| TITE-CRM | 49.2| 2.8 | 15.5| 0.0 | 39.4| 111.0|
| TITE-BOIN| 22.9| 11.3| 25.9| 0.1 | 27.7| 127.7|
| PoD-TPI  | 11.7| 0.0 | 23.1| 1.1 | 9.8 | 45.7 |

| Method   | DS  | DE  | SE  | SD  | ED  | ES  | Sum  |
|----------|-----|-----|-----|-----|-----|-----|------|
| R-TPI    | 57.5| 0.0 | 0.0 | 0.0 | 89.9| 147.4|
| TITE-CRM | 30.6| 1.9 | 18.2| 0.0 | 37.2| 90.6 |
| TITE-BOIN| 31.2| 12.1| 28.9| 0.4 | 43.0| 157.0|
| PoD-TPI  | 16.7| 0.0 | 35.9| 0.4 | 23.6| 76.6 |
Table S3: Frequencies of inconsistent decisions compared to the decisions that would be made by the corresponding complete data design. R6 is compared to complete-data R6, and PoD-TPI is compared to mTPI-2. Values are shown in 1/10³.

| Method   | DS  | DE  | SE  | SD  | ED  | ES  | Sum   |
|----------|-----|-----|-----|-----|-----|-----|-------|
|          |     |     |     |     |     |     |  Setting 1 |
| R6       | 41.8| 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 146.1 | 187.9 |
| PoD-TPI  | 4.5 | 0.0 | 0.0 | 17.8| 1.6 | 3.5 | 27.4  |
|          |     |     |     |     |     |     |  Setting 2 |
| R6       | 43.8| 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 47.8  | 91.6  |
| PoD-TPI  | 6.7 | 0.0 | 0.0 | 37.9| 0.5 | 10.7| 55.8  |
|          |     |     |     |     |     |     |  Setting 3 |
| R6       | 48.1| 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 143.9 | 192.0 |
| PoD-TPI  | 9.6 | 0.0 | 0.0 | 22.8| 1.8 | 3.9 | 38.1  |
|          |     |     |     |     |     |     |  Setting 4 |
| R6       | 24.1| 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 47.0  | 71.1  |
| PoD-TPI  | 14.4| 0.0 | 0.0 | 43.2| 0.5 | 13.2| 71.3  |
Figure S1: Scenario-specific PCS, PCA and POA for mTPI-2, R-TPI, TITE-CRM, TITE-BOIN and PoD-TPI under Setting 1.
Figure S2: Scenario-specific frequencies of inconsistent and risky decisions for mTPI-2, R-TPI, TITE-CRM, TITE-BOIN and PoD-TPI under Setting 1.
S4 Cure Rate Model

To construct a cure rate model, we introduce an additional notation $G_i$, such that $G_i = 1$ (or 0) represents that patient $i$ experiences DLT eventually (or never experiences DLT during his/her lifetime). We model $G_i$ with a Bernoulli distribution, $G_i \mid Z_i = d \sim \text{Bernoulli}(\xi_d)$. It is easy to see that $\xi_d \geq p_d$, as $Y_i = 1$ always implies $G_i = 1$. We have $\Pr(Y_i = 1 \mid G_i = 1, Z_i = d) = p_d / \xi_d$.

Still, we assume a piecewise uniform distribution for $[T_i \mid Y_i = 1, G_i = 1, Z_i = d]$ on the interval $(0, \tau]$. The conditional density of $T_i$ is

$$f_{T \mid Y,G,Z}(t \mid Y_i = 1, G_i = 1, Z_i = d, w) = w_k \cdot \frac{1}{h_k - h_{k-1}}, \quad \text{for } h_{k-1} < t \leq h_k.$$ 

Next,

$$f_{T \mid Z}(t \mid Z_i = d, p_d, \xi_d, w) = \sum_{y \in \{0,1\}} \sum_{g \in \{0,1\}} \left[ f_{T \mid Y,G,Z}(t \mid Y_i = y, G_i = g, Z_i = d, w) \times \Pr(Y_i = y \mid G_i = g, Z_i = d, p_d, \xi_d) \Pr(G_i = g \mid Z_i = d, \xi_d) \right]$$

$$= w_k \cdot \frac{1}{h_k - h_{k-1}} \cdot \frac{p_d}{\xi_d} \cdot \xi_d + 0 + 0 = p_d \cdot w_k \cdot \frac{1}{h_k - h_{k-1}}, \quad \text{for } h_{k-1} < t \leq h_k,$$

and

$$S_{T \mid Z}(t \mid Z_i = d, p_d, \xi_d, w) = 1 - p_d \sum_{k=1}^{K} w_k \beta(t, k), \quad \text{for } t \leq \tau.$$ 

We can see the cure rate model does not change anything in the likelihood (7), i.e., $\xi_d$’s do not contribute to the likelihood. This is expected, as the data only provide information for $\xi_d$ up to $p_d$ ($\xi_d \geq p_d$). In other words, after patients have been followed for $\tau$, we do not care whether they experience DLT eventually. Nevertheless, the interpretations of $f_{T \mid Z}$ and $S_{T \mid Z}$ are slightly different, as we have $\int_0^t f_{T \mid Z}(v \mid Z_i = d, p_d, \xi_d, w) \, dv \leq \xi_d$ for any finite $t$. 

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