COMPARISON OF NOVEL PHASE I CLINICAL TRIAL DESIGNS BASED ON TOXICITY PROBABILITY INTERVALS

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ABSTRACT

Phase I clinical trial based on toxicity probability intervals is a new class of dose-finding designs characterized by integrating the concept of intervals, instead of point estimates, in detection of the maximum tolerated dose. The purpose of this article is to explore and compare the performance of three novel designs including the two-parameter logistic regression model with categorized posterior probability design (LRcat), the modified toxicity probability interval design (mTPI) and the Bayesian optimal interval design (BOIN). A thorough numeric study with eight potential scenarios was conducted to examine critical operating characteristics. Robustness of the novel designs to the change in the target interval width and mis-specified priors was investigated in a sensitivity analysis following the simulation study. In addition, we also retrospectively analyzed a recent cancer phase I clinical trial to explore the performance of these designs in real-world application

The results of our analysis showed that interval-based designs perform comparably to a traditional CRM design using posterior mean to define MTD in most scenarios. LRcat is more flexible than CRM and demonstrates robustness to the varying target toxicity interval. BOIN is safer than other designs and allocates less patients to overly-toxic levels. mTPI is more likely to allocate patients to suboptimal doses when the true MTD resides at the lowest/highest doses and performs poorly when the target interval is asymmetric.

PUBLIC HEALTH SIGNIFICANCE

Phase I cancer clinical trials are the indispensable step for the development of anticancer therapies. With the widespread application of phase I clinical trials, researchers and clinical investigators need up-to-date information about newly-developed phase I clinical trial methods. By providing the comparison result for a group of innovative phase I trial designs, our study facilitates choice of dose-finding method and leads to more efficient and ethical drug development to conquer cancer epidemic.

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1.0 INTRODUCTION

Phase I clinical trials serve as a vital part and generally the first-in-human studies in translating laboratory research into clinical practice. A phase I clinical trial in oncology aims to identify the maximum tolerated dose (MTD). For cytotoxic anticancer agents, the rationale of using MTD as the primary endpoint based on the assumption: the treatment efficacy increases monotonically with the probability of toxicity [1]. Therefore, by determining the MTD, oncological phase I clinical trials provide the most efficacious dose of a treatment with acceptable side effects. In 1997, the American Society of Clinical Oncology (ASCO) published a policy statement on the centrality of phase I clinical trials to the process of discovering anticancer agents and brought up the prosperity in the development and application of early-phase cancer trials [2].

Numerous dose-finding designs for phase I clinical trials have been invented over the past few decades. Most of these designs fall into one of the two major categories: algorithmic (rule-based) designs or model-based designs. Algorithmic designs are guided by predetermined rules and the dose limiting toxicity (DLT) information obtained from the last cohort of patients in the trial, whereas model-based designs use explicit parametric models and cumulative DLT information throughout the trial. Examples of algorithmic designs include: the traditional “3+3” design and its variations [3], the accelerated titration design proposed by Simon et al, Ivanova’s up-and-down design [4], among others. The most representative model-based designs include the continual reassessment method (CRM) [5] and its extensions, and the dose escalation with overdose control (EWOC) design [6].

Rule-based designs are well-recognized for their simplicity and transparency in application, but their slow convergence to the true MTD and lack of a prespecified target toxicity rate are indisputable drawbacks. On the other hand, model-based designs are praised for more rapid dose escalation and a complete use of cumulative trial information, but are frequently criticized for aggressiveness, ambiguous prior specifications and complex computations [7]. Confronted with the trade-offs between the two bodies of designs, researchers resort to seeking new designs that are more flexible, utilize more information, and yet do not compromise good operating characteristic and simplicity.

During the past decade, clinical researchers have witnessed the development of a new class of designs that utilize toxicity probability intervals, instead of a single point estimate, to determine the MTD. Ji et al. proposed a dose-finding method named toxicity posterior intervals (TPI) design. This design partitions beta posterior distributions for the toxicity probabilities of the current dose into three intervals. The toxicity intervals are labeled as high, acceptable, and low toxicity, each associated with the corresponding dose-assignment decision for future patients [9]. TPI design was further extended to a modified toxicity probability interval (mTPI) design, which depends the decision rules on maximizing unit probability mass (UPM) of the intervals [10]. Following in the footsteps of Ji and his colleagues, Yuan et al. proposed the Bayesian optimal interval (BOIN) in 2016. The design derives the boundaries of the target toxicity probability interval from a Bayesian decision making process rather than solely relying on a physician's judgement. Like the mTPI design, dose assignments in the BOIN design is determined by the location of the current toxicity rate with respect to the interval boundaries [11]. Meanwhile, Neuenschwander et al. introduced a design that is similar to TPI but inherits many features of a CRM procedure. The design, referred to as LRcat in the paper, adopts a two-parameter logistic model to obtain the posterior distribution

of toxicity probability. After each experiment, the posterior distributions are summarized for each dose by the probability of four categories: under-dosing, target, excessive toxicity, unacceptable toxicity. Then the next dose is recommended as the dose which has the maximum probability of target interval [11]. As is in the case with CRM design, LRcat design has a "jumping" nature in dose assignment. A variation of LRcat design (LRcat25) guides dose selection by maximizing the probability of target interval while controlling the risk of overdosing at 25%. Details about these innovative designs will be further discussed in Section 2.

Our study will focus on the newly-developed interval-based designs mentioned above. The primary objective of this article is to explore the operating characteristics of LRcat /LRcat25, mTPI and BOIN relative to the CRM in numerical study with various potential scenarios. We would like to see how robust are the three designs to a varying target interval width, and how sensitive is LRcat, comparing to CRM, to a mis-specified prior. In addition, we applied a post-hoc dose-escalation analysis using the real-life data from a recent cancer clinical trial to further investigate the application of these innovative designs. This study is innovative as no head-to-head comparison of these three designs, to our best knowledge, has been carried out ever before.

Starting in Section 2, we provide an overview of newly developed statistical designs for phase I cancer trial, LRcat, mTPI and BOIN. Section 3 presents the simulation study and the sensitivity analysis. In Section 4, a recent cancer phase I clinical trial will be reanalyzed via each of the novel designs. Finally, a discussion about practical implications of these designs will be given in Section 6.

2.0 PHASE I CLINICAL TRIAL DESIGNS BASED ON TOXICITY POSTERIOR INTERVALS

Researchers hold different opinions about optimalizing phase I clinical trial designs. Neuenswander suggested that plausible dose recommendations should use more informative posterior summaries and more flexible models [11]. He proposed the LRcat design, rendering it an extension of the CRM design to incorporate posterior intervals for the probabilities of DLT. However, from the perspective of application, designs that are easy to understand and implement for investigators are more favorable. This rationale leads to the development of mTPI and BOIN.

2.1 LR_{CAT} DESIGN

Suppose a trial has J doses and we aim at identifying the MTD from a set of doses $d_1 < d_2 < \cdots < d_J$. The probability of a DLT at dose d is denoted as $\pi_\theta(d)$ and is described by the logistic model:

$$\text{logit}[\pi_\theta(d_i;\ \alpha,\beta)] = \log\alpha + \beta \cdot \log(d_i/d^*) \qquad (1)$$

where $\alpha, \beta > 0$, and d^* is a reference dose allowing $\log(\alpha)$ to be the log-odds of toxicity when $d_i = d^*$. A bivariate normal prior for $(\log\alpha, \log\beta)$ is assumed:

$$\log(\boldsymbol{\theta}) = \begin{pmatrix}\log\alpha \\ \log\beta\end{pmatrix} \sim BVN\left(\begin{pmatrix}\mu_1 \\ \mu_2\end{pmatrix}, \boldsymbol{\Sigma}\right), \qquad \boldsymbol{\Sigma} = \begin{pmatrix}\sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2\end{pmatrix}$$

Neuenschwander postulated that placing a bivariate lognormal prior on the two parameters makes the model more flexible than a one-parameter power or logistic model commonly used in CRM design. An noninformative prior distribution for LRcat could be derived by matching quantiles with a minimally informative beta distribution as defined in [11]. Neuenschwander et al. also recommended the use of informative priors whenever is available.

The posterior distribution is then

$$f(\alpha, \beta | y_1, \dots, y_n) \propto f(\alpha, \beta) L(\alpha, \beta; y_1, \dots, y_n)$$

where $f(\alpha, \beta)$ is the joint prior distribution and $L(\alpha, \beta; y_1, \dots, y_n)$ is the likelihood function.

A Gibbs sampling procedure is then applied to elicit posterior samples of (α, β), and the posterior distribution of DLT at each dose level is obtained from the inversed model function (1)

$$\pi_\theta(d_i;\ \alpha, \beta) = \frac{\exp(\log\alpha + \beta \cdot \log(d/d^*))}{1 + \exp(\log\alpha + \beta \cdot \log(d/d^*))}$$

Next, the computed posterior distribution of $\pi_\theta(d_i)$ is partitioned by three cutpoints $(0.20, 0.35, 0.60)$ and is summarized into

Under-dosing	$P\{\pi_\theta(d) \in (0,\ 0.20]\}$
Targeted toxicity	$P\{\pi_\theta(d) \in (0.20,\ 0.35]\}$
Excessive toxicity	$P\{\pi_\theta(d) \in (0.35,\ 0.60]\}$
Unacceptable toxicity	$P\{\pi_\theta(d) \in (0.60,\ 1.00]\}$

These intervals are subject to change based on the specific setting of the study [12]. The dose recommended for the next cohort of patients is the dose that has a maximal posterior probability for the target interval. Figure 1 shows a flow chart illustrating the dose escalation scheme of LRcat design.

There are two variations of LRcat design. LRcat25 takes patient safety as the primary concern and enforces an overdose control on excessive and unacceptable toxicity intervals. The probability of the last two toxicity intervals are required to be less than 0.25.

$$\textit{select a dose level for each patient } s.t.$$
$$P\{\pi_\theta(d) \in (0.35,\ 0.60]\} + P\{\pi_\theta(d) \in (0.60,\ 1.00]\} < 0.25$$

This criteria is similar to the escalation with overdose control (EWOC) design introduced by Babb and his colleagues which restricts the predicted proportion of patients who receive an overdose to a feasibility bound [6].

Another variation adapts a fully Bayesian decision analytic approach using a formal loss function:

$$L(\theta, d) = \begin{cases} l_1 & if\ \pi_\theta(d) \in (0,\ 0.20] \\ l_2 & if\ \pi_\theta(d) \in (0.20,\ 0.35] \\ l_3 & if\ \pi_\theta(d) \in (0.35,\ 0.60] \\ l_4 & if\ \pi_\theta(d) \in (0.60,\ 1.00] \end{cases}$$

where l_k represents the distance of the corresponding interval from the true MTD. The optimal decision is the one that minimizes the corresponding Bayes risk: $Bayes\ risk = l_1 P\{\pi_\theta(d) \in (0,\ 0.20]\} + l_2 P\{\pi_\theta(d) \in (0.20,\ 0.35]\} + l_3 P\{\pi_\theta(d) \in (0.35,\ 0.60]\} + l_4 P\{\pi_\theta(d) \in (0.60,\ 1.00]\}$ [11]. The original LRcat design has an implicit 1-0-1-1 loss function. If a more conservative dose escalation design is sought, loss functions like 1-0-1-2 and 1-0-2-4 could lower the risk of selecting doses that are too toxic.

2.2 mTPI DESIGN

Let p_T denote the target toxicity probability and p_i the toxicity probability for dose $i = 1, \ldots, J$. An equivalence interval (EI), $[p_T - \epsilon_1, p_T + \epsilon_2]$, is defined. The width of EI depends on the phycisian's judgement. Any dose included in the EI is considered potential candidate for the true MTD. x_i, n_i represent number of patients treated and number of patients experiencing toxicity at dose i respectively. x's are assumed to follow a binomial distribution

$$f(x;\ n, p) = \binom{n}{x} p^x (1-p)^{n-x}$$

And the likelihood function is derived as

$$l(x_i|p_i) \propto \prod_{i=1}^{J} p_i^{x_i} (1-p_i)^{n_i - x_i}$$

A vague conjugate beta prior is assumed: $p_i \sim i.i.d. Beta(1,1)$. Followed from the Bayes theorem [9]

$$f(p_i|x_i) \propto f(p_i) l(x_i|p_i)$$
$$p_i|x_i \sim i.i.d. Beta(1+x_i, 1+n_i-x_i)$$

After obtaining the posterior distribution of p_i, the unit probability mass (UPM) is calculated for each of the three intervals partitioned by EI. UPM is defined as the probability of the interval divided by the length of the interval [10]. For example, Let $B(x; a, b)$ be the cumulative distribution function of the Beta distribution. The UPM of EI is

$$\frac{B(p_T + \epsilon_2, 1+x_i, 1+n_i-x_i) - B(p_T - \epsilon_1, 1+x_i, 1+n_i-x_i)}{\epsilon_1 + \epsilon_2}$$

One of the dose assignment decisions, escalation, stay at the same dose and de-escalation, is chosen depending on which of the three intervals, $(0, \mathrm{p}_T - \epsilon_1)$, $[p_T - \epsilon_1, p_T + \epsilon_2]$ and $(\mathrm{p}_\mathrm{T} + \epsilon_2, 1)$ has the largest UPM. This process repeats until a primary stopping rule (e.g. maximum sample size) is satisfied. At the end of the trial, we use a less informative beta prior, $Beta(0.005, 0.005)$, to obtain the posterior distribution. The isotonically transformed posterior mean for each dose level is calculated and the dose level with the smallest absolute difference between the posterior mean and the target toxicity is selected as the MTD [10].

There are two built-in safety rules for mTPI design. The first safety rule requires an early termination of the trial when the probability of dose 1 excessing the target toxicity is over 95%. The second one check the next dose in advance during dose escalation to prevent going to an overly

toxic dose [10]. Figure 1 provides a comparison of the dose-finding schemes for LRcat design and mTPI design.

2.3 BOIN DESIGN

Both LRcat and mTPI design assume that the interval boundaries of the posterior toxicity distribution are independent of dose level i and the number of patient treated at dose level i. Liu and her colleagues described a Bayesian framework to select interval boundaries based on the accumulated toxicity information throughout the trial [12]. Following the same notations from mTPI, $\hat{p}_i = x_i/n_i$ denotes the observed toxicity rate at dose level i. Three point hypothesis are formulated:

$$\begin{aligned} H_{0i}&: \ p_i = \phi \qquad \textit{The current dose is the MTD} \\ H_{1i}&: \ p_i = \phi_1 \qquad \textit{The current dose is subtherapeutic} \\ H_{2i}&: \ p_i = \phi_2 \qquad \textit{The current dose is too toxic} \end{aligned}$$

where p_i is the true toxicity probability of the current dose, ϕ is the target toxicity probability, ϕ_1, ϕ_2 are the toxicity probability of the highest sub-therapeutic and the lowest overly toxic dose respectively. The prior probability of each hypothesis being true is defined as $\pi_{ki} = \Pr(H_{ki}), k = 1,2,3$. The noninformative prior probability for the hypothesis is $\pi_{1i} = \pi_{2i} = \pi_{3i} = 1/3$. Let λ_{1i} and λ_{2i} respectively denote the dose escalation and de-escalation boundaries. The probability of making incorrect decision, denoted as $\alpha(\lambda_{1i}, \lambda_{2i})$, is computed based on the Bayes theorem:

$$\begin{aligned} \alpha(\lambda_{1i}, \lambda_{2i}) = Pr(H_{0i})\, Pr\{(\hat{p}_i \le \lambda_{1i}) \cup (\hat{p}_i \ge \lambda_{2i}) | H_{0i}\} \\ + Pr(H_{1i})\, Pr\{\hat{p}_i < \lambda_{2i} | H_{1i}\} + Pr(H_{2i})\, Pr\{\hat{p}_i > \lambda_{1i} | H_{0i}\} \end{aligned}$$

When $\pi_{1i} = \pi_{2i} = \pi_{3i}$, it can be shown that $\alpha(\lambda_{1i}, \lambda_{2i})$ is the likelihood-ratio hypothesis-testing boundaries

$$\lambda_{1i} = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} \quad , \quad \lambda_{2i} = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)}$$

Once the interval boundaries $\lambda_{1i}, \lambda_{2i}$ are decided, the next dose is selected based on the comparison of the current observed toxicity rate $\hat{p}_i$ with respect to the boundaries. If $\hat{p}_i \leq \lambda_{1i}$, we escalate to the next dose level; if $\hat{p}_i \geq \lambda_{2i}$, we de-escalate the dose; and if $\hat{p}_i \in (\lambda_{1i}, \lambda_{2i})$, we retain the current dose [13]. The dose assignment rule of the BOIN design is clearly an adaptation of a rule-based design. To eliminate an overly toxic dose for safety, BOIN design checks the toxicity rate of the lowest dose to see if it exceeds the target toxicity at 95%.

In the following analysis involving BOIN, we used $\phi_1 = 0.6\phi \; and \; \phi_2 = 1.4\phi$, which is recommended for general use by Liu et al. [13].

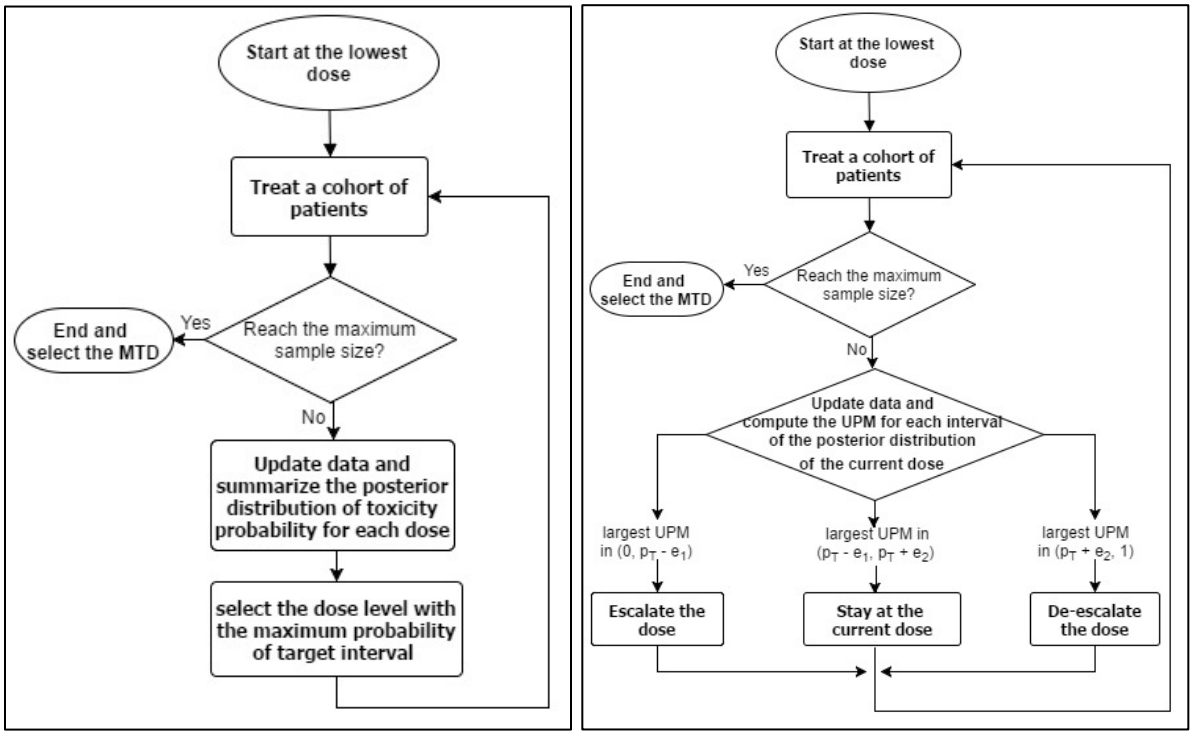


Figure 1. Comparison of dose assignment scheme for LRcat design (left) and mTPI design (right)

3.0 NUMERICAL STUDY

3.1 SIMULATION SETTING

We performed computer simulations on six phase I clinical designs: the traditional continual reassessment method with power model (CRM); a modified CRM constraining dose-skipping during escalation and only selecting doses with mean posterior probability of DLT lower than the target toxicity (mCRM) as the MTD; and the mTPI, BOIN and LRcat designs introduced in Section 2. In addition, we add the LRcat25 (LRcat with 25% overdose control) design as a variation of LRcat commensurable to mCRM. To obtain the operating characteristics of the six designs, 2000 trials for each scenario was simulated.

We considered a hypothetical phase I trial with seven dose levels (12.5, 25, 50, 100, 150, 200, 250) and a target toxicity rate of 30%. Assuming the desired dose is among these seven dose levels, eight scenarios were selected to represent a broad class of potential dose-toxicity relations (Figure 2). We specified the scenarios based on four parameters: the target toxicity and the corresponding dose; an unacceptable toxicity rate (0.90 for steep curves and 0.65 for flat curves) and the corresponding dose. Dose-toxicity curves generated from this method were slightly modified to obtain more distinctive characteristics. Scenarios 1 and 8 represent two boundary scenarios with MTD at dose level 1 and 7. When the true MTD is at dose levels 2, 4 and 6, we considered two plausible dose-toxicity curves: a steep one indicating there is an abrupt increase of toxicity rate just before the MTD, and a flat one indicating the toxicity rate increases steadily throughout the trial. The maximum sample size is 36. A similar simulation setting was used in Neuenswander's papar [11].

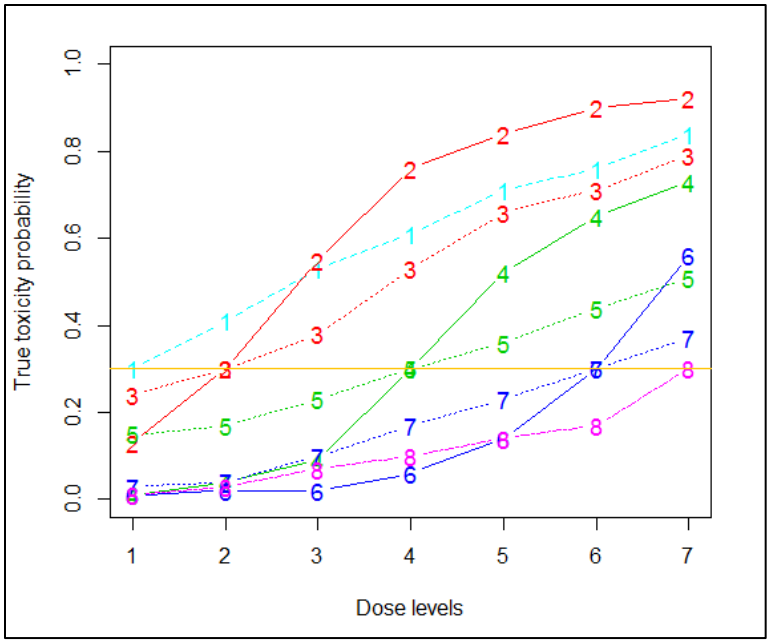


Figure 2. Dose-toxicity relationships of the eight simulation scenarios.
The horizontal line represents the target toxicity probability of 0.3.

Table 1. Scenarios for simulation study.

Dose	12.5	25	50	100	150	200	250
Scenario 1	**0.30**,	0.41,	0.53,	0.61,	0.71,	0.76,	0.84
Scenario 2	0.13,	**0.30**,	0.55,	0.76,	0.84,	0.90,	0.92
Scenario 3	0.24,	**0.30**,	0.38,	0.53,	0.66,	0.71,	0.79
Scenario 4	0.01,	0.04,	0.09,	**0.30**,	0.52,	0.65,	0.73
Scenario 5	0.15,	0.17,	0.23,	**0.30**,	0.36,	0.44,	0.51
Scenario 6	0.01,	0.02,	0.02,	0.06,	0.14,	**0.30**,	0.56
Scenario 7	0.03,	0.04,	0.10,	0.17,	0.23,	**0.30**,	0.37
Scenario 8	0.01,	0.03,	0.07,	0.10,	0.14,	0.17,	**0.30**

NOTE: The target dose is in boldface.

The CRM requires specification of a prior distribution and a set of initial guesses (skeleton) of the toxicity probabilities for the candidate doses to be used in the trial. For CRM and mCRM, the dose toxicity model is assumed to be empiric $\pi_\theta(d) = c_d^\theta$ with a vague prior distribution for $\log(\theta)$ specified as normal with $\mu = 0$ and $\sigma^2 = 1.34^2$ [5]. The skeleton c_d is calibrated using the algorithm elaborated in [14]. For the two-parameter logistic regression model in LRcat and LRcat25, we adapted the prior bivariate normal distributions for $\log(\alpha)$ and $\log(\beta)$ derived in Neuenschwander et al's paper from the quantile-based method [11]. To make the comparison

between CRM and LRcat more sensible, we used two pairs of matched priors as depicted in Table 2 and Figure 7. The first pair of priors (A) assumes the MTD at the highest dose level and prior (B) assumes the MTD at the second dose level. Prior (A) is used in the simulation study.

Table 2. Prior specification for CRM and LRcat

	CRM skeleton $(\boldsymbol{d_1}, \boldsymbol{d_2}, \ldots, \boldsymbol{d_7})$	**LRcat prior** BVN: $(\boldsymbol{\mu_1}, \boldsymbol{\mu_2}, \boldsymbol{\sigma_1}, \boldsymbol{\sigma_2}, \boldsymbol{\rho})$
A	(0.00, 0.00, 0.00, 0.01, 0.06, 0.16, 0.30)	(-0.847, 0.381, 2.015, 1.207, 0)
B	(0.16, 0.30, 0.45, 0.59, 0.71, 0.80, 0.86)	(2.27, 0.26, 1.98, 0.40, -0.16)

3.2 EVALUATION METRICS

A well-founded phase I trial design should lead to accurate estimation of the MTD while concentrating dose assignments at or closely below the MTD. It also should minimize dose assignments at suboptimal dose levels and associate greater penalty with overdosing compared to under-dosing [6]. In light of these criteria, we considered the following five metrics to measure the performance of the designs:

i. Distribution of the selection percentages of the MTD. Instead of using a single percentage of correct selection (PCS) on the true MTD dose level, we choose to exhibit the percentage of selecting the dose as the MTD for each dose levels. When PCS may give a similar conclusion about two designs, this metrics facilitates relative evaluation of suboptimal dose assignments.

ii. Distribution of number of patients treated on dose. This metrics presents the average number of patients treated at each dose across the simulated trials. The number treated at or above the true MTD will raise particular concerns.

iii. The risk of overdosing—the percentage of simulated trials in which more than 60% of patients are treated at doses above the MTD.

iv. The risk of under-dosing—the percentage of simulated trials in which more than 80% of patients are treated at doses below the MTD.

The above two risk measure provide more reliable information about the conservatism of the designs, comparing to the average number of patients treated at doses above MTD. The threshold for defining under-dosing is higher than that of the overdosing since under-dosing is of less concern in application [15].

v. The average proportion of toxicity. It is computed by $\frac{\text{average number of toxicity in trial}}{\text{average number of patients in trial}}$.

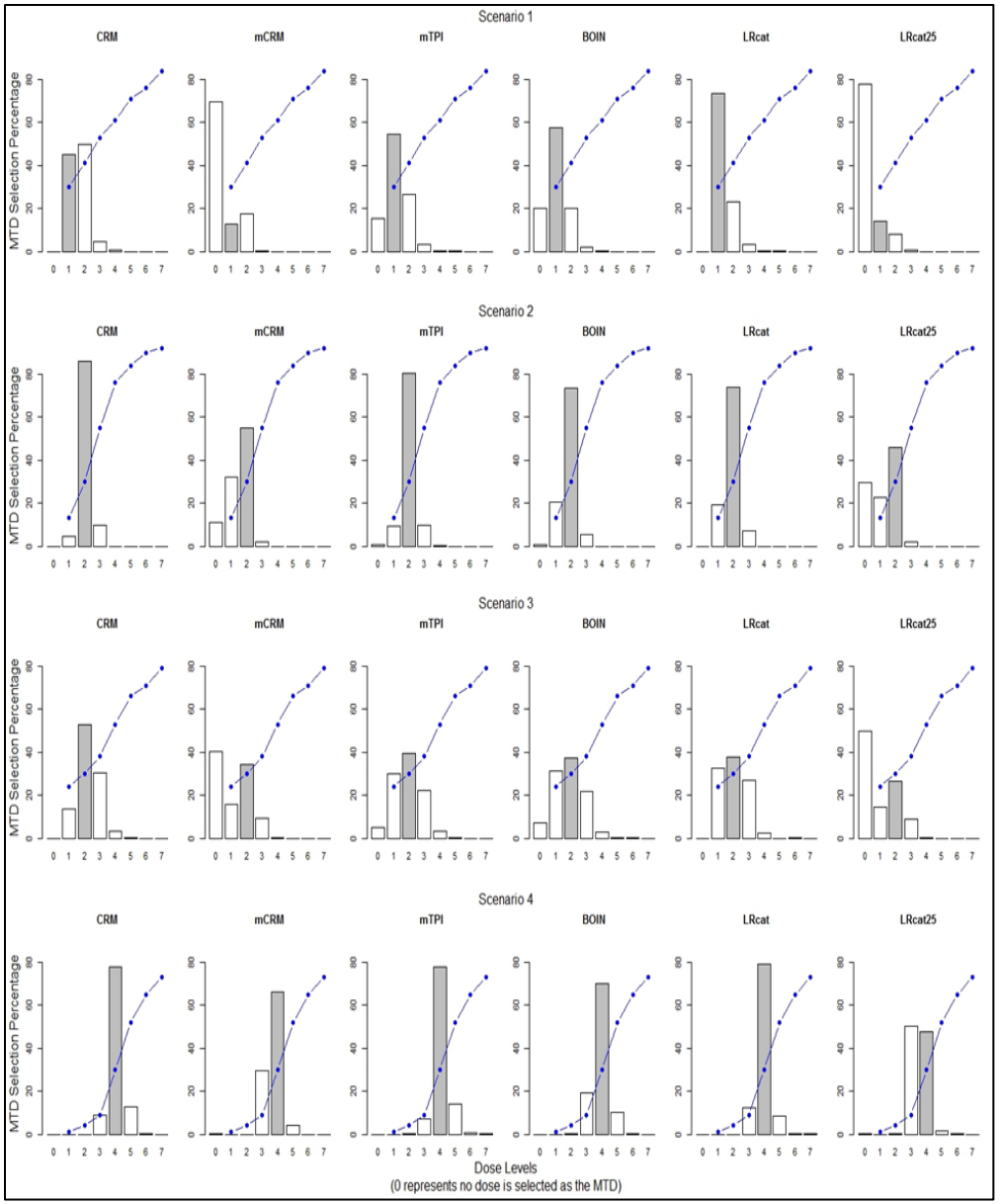
Due to the various levels of conservatism among the explored designs, there is a variation of average sample size. Therefore the commonly used measurement, average number of toxicity, could easily fail to provide accurate information. In this circumstance, a comparison of the average proportion of toxicity is more reasonable.

3.3 RESULTS

3.3.1 Selection percentage of the MTD

When the true MTD is at dose level 2, CRM, mTPI, BOIN and LRcat perform almost identically in selecting the correct MTD regardless of the shape of the underlying dose-toxicity curve. mCRM and LRcat25 behave similarly in selecting MTD at a subtherapeutic dose. Notable differences start to exist among designs when the true MTD is at dose level 4. If the underlying dose-toxicity curve is steep (Scenario 4), CRM and mTPI show higher chance of choosing a dose above the true MTD even though all of the designs give correct prediction of MTD. LRcat25 behaves much more consertively than mCRM as it selects the dose lower than the MTD in more than 40% of the time. When the underlying curve is flat (Scenario 5), only LRcat outperforms other designs. The poor

performance of CRM in Scenarios 5 could be the consequence of a misspecified skeleton. If we apply the skeleton (0.01, 0.02, 0.07, 0.16, 0.30, 0.45, 0.59) with pre-specified MTD at dose level 5, CRM will perform better (result not shown). The sensitivity of CRM and LRcat to prior specifications will be discussed later in Section 4.4. mCRM and LRcat25 start to compensate for their high level of conservatism and perform poorly in this scenario. When the true MTD is at dose level 6 with a flat dose-toxicity curve (Scenario 6), CRM and the three interval-based designs perform similarly and correctly recommend the true MTD. When the toxicity probability increases slowly, CRM, BOIN and LRcat show their potential to give the right recommendation. CRM and LRcat have the best performance in boundary scenarios (Scenario 1 and 8). mCRM performs very poorly if the true MTD is at the highest dose.



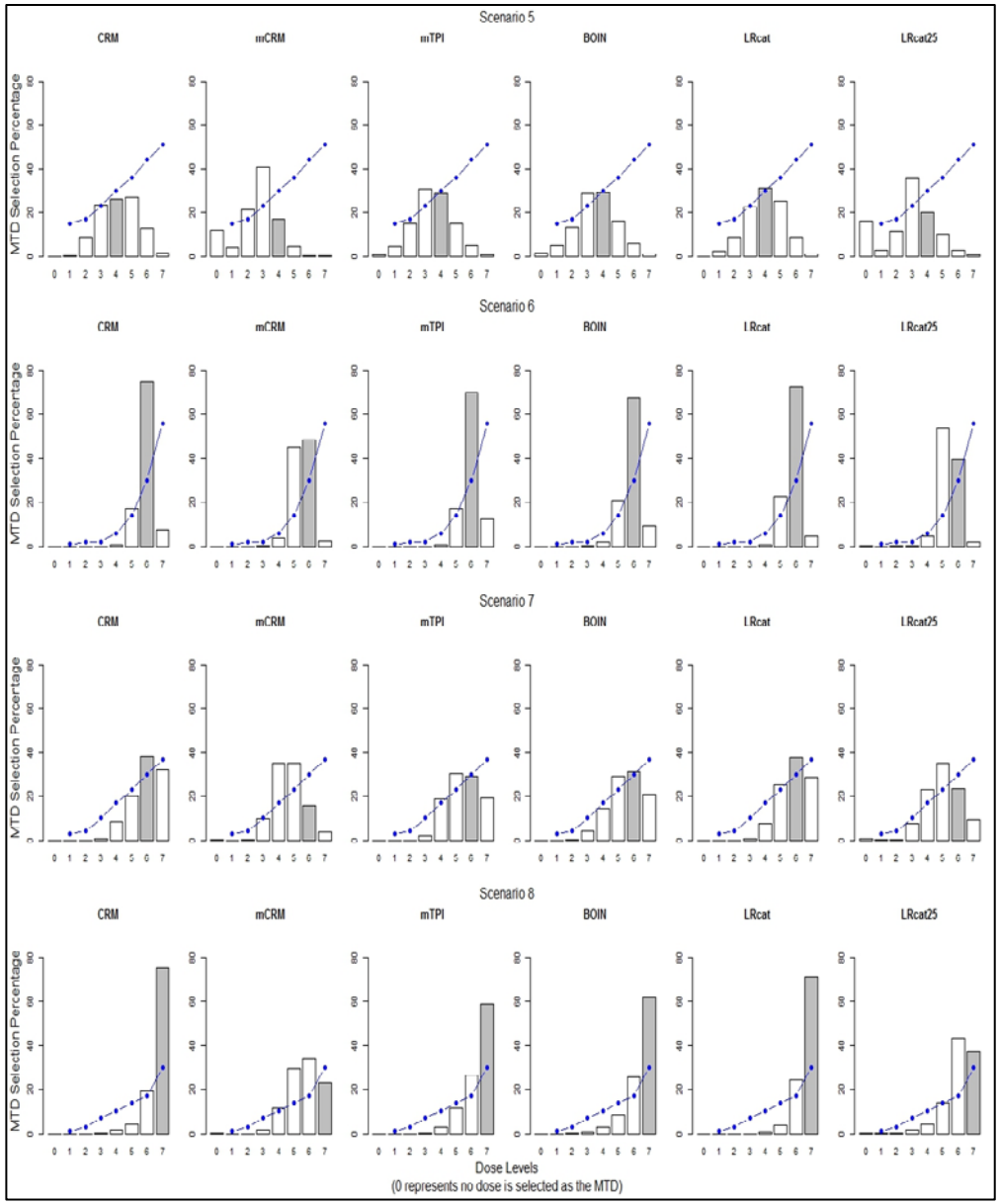


Figure 3. Selection percentage of MTD (Scenario 1 – Scenario 4 in the left panel, Scenario 5 – Scenario 8 in the right panel)
The plots are superimposed by the underlying dose-toxicity curves of the scenario. Shaded bars indicate the true MTD.

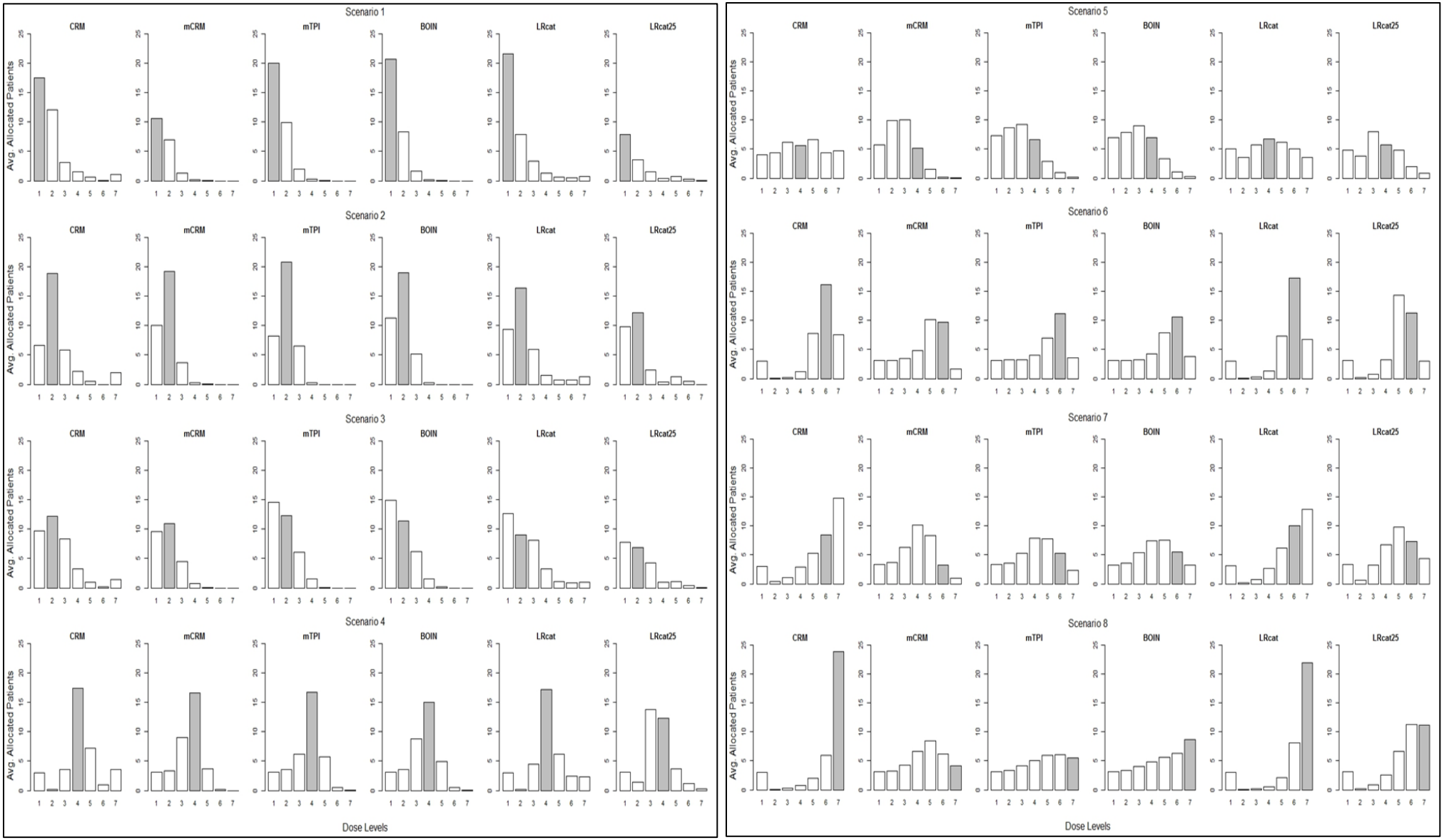


Figure 4. Patient allocation (Scenario 1 – Scenario 4 in the left panel; Scenario 5 – 8 in the right panel)
Greyed bars indicate the true MTD.

3.3.2 Patient allocation, risk of over-dosing and under-dosing

An ideal design should allocate the majority of patients to the level of the true MTD while having a relatively smaller number of patients on suboptimal dose levels. In consideration of safety, we pay extra attention to those designs that tend to assign more patients to overly toxic dose levels. In scenarios where the toxicity of the drug increase rapidly with doses, all designs perform appealingly. By contrast, when the dose-toxicity curve is flat, more conservative designs (mCRM, LRcat25) are likely to have a higher bar on doses below MTD while more aggressive designs (CRM, LRcat) have higher bars above. mTPI and BOIN have a moderate level of conservatism and perform favorably in patient allocation. It is noted that with the true MTD moving to higher dose levels, the level of conservatism further differentiate the performance of designs.

As a complement to the average number of allocated patient, we also examined how likely is a design to assign patients sub-optimally. When the dose level increases, we expect a general decreasing trend in the risk of over-dosing and an increasing trend in the risk of under-dosing. Designs that go against the general trend rise concerns. CRM and LRcat, the most aggressive designs, maintain a high risk of overdosing in all scenarios. The risk even raised 5% for the LRcat design which counteracts the good performance of LRcat in correct selection of MTD. When the differences between adjacent doses are large (dose-toxicity curve is steep), designs are less likely to make implausible decisions which explains the sudden decreases in the heights of bars in the steep-curve scenarios. We also note that designs based on posterior intervals are more sensitive to changes in the distance of adjacent dose. In terms of risk of under-dosing, conservative designs present extremely high bars. The risk of under-dosing even exceeds 80% for mCRM in Scenario 7. The drastic decrease or increase of mTPI design in these two risk measurements is concerning.

It implies that mTPI performance less satisfactorily when the true MTD is not among the intermediate dose levels. BOIN design performs desirably with respect to the two risks and exhibit a good balance between conservativeness and aggressiveness.

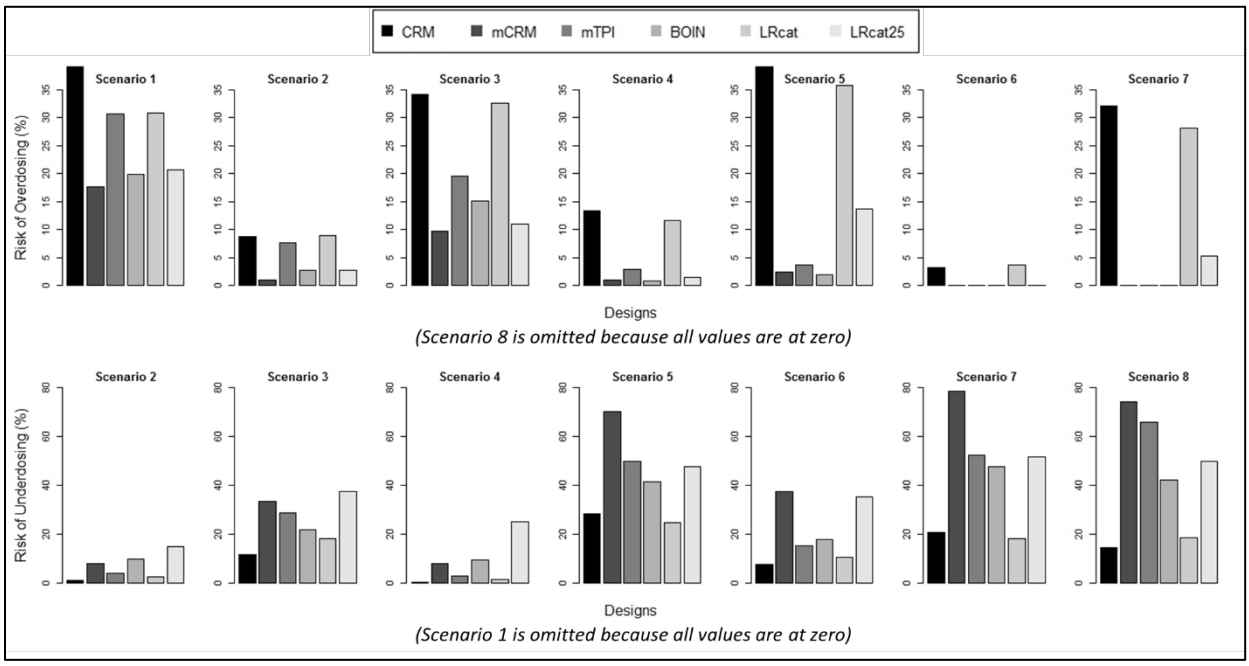


Figure 5. Risk of over-dosing (upper panel) and risk of under-dosing (lower panel)

3.3.3 Toxicity

When the true MTD is at higher doses, it is less likely to observe DLTs. Consequently, we expect an overall decreasing trend in the average proportion of toxicity Scenario 1 through Scenario 8. One thing draw immediate attention is that CRM and LRcat design have substantially higher toxicity proportion in most of the scenarios. It is consistent with previous findings about the aggressiveness of the two designs. Besides, we notice that mCRM and LRcat25 perform no better (even worse) than the more aggressive designs when the MTD is at the lowest dose levels (Scenarios 1 – 3).

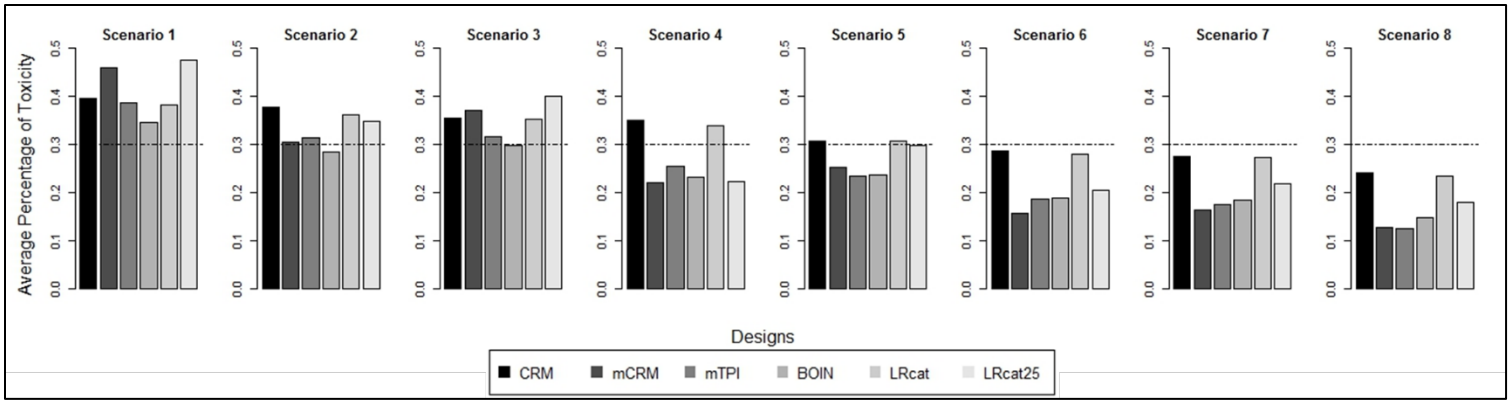


Figure 6. Average proportion of toxicity.

3.4 SENSITIVITY ANALYSIS

3.4.1 Sensitivity to interval width

To conduct an additional sensitivity analysis for the interval-based designs, we compared LRcat, LRcat25, mTPI and BOIN with variations in the target interval width (a deviation of 0.07, 0.1 and 0.15 from the target toxicity of 0.3). We made the following adjustments: for LRcat and LRcat25, we fixed the threshold for an unacceptable toxicity at 0.60 and varied the width of the target toxicity interval; for mTPI, we simply adjusted the width of the equivalence interval; for BOIN, we calibrate the prior guess of the boundaries $\phi_1$and ϕ_2 to get the desired posterior boundaries λ_1 and λ_2. For instance, if the posterior target interval is (0.23, 0.37), we tried several possible pairs of ϕ_1, ϕ_2 to find 0.17 and 0.445 generated λ_1, λ_2 closest to the interval boundaries. Scenario 5 from the previous numeric study was used to represent the underlying dose-toxicity relationship. Most of the interval designs perform poorly in selecting the correct MTD in Scenario 5, and we would like to see if a variation in the interval boundaries could improve or worsen their performance. Designs were compared using the same criteria from the numeric study. The result is shown in the Table 2.

LRcat demonstrates robustness to the changes in interval width. Irrespective of the variations of the boundary values, LRcat keeps accurately predicting the MTD. Also, for LRcat, the percentage of selecting the true MTD is distinguishable from that of selecting the suboptimal doses. The mTPI is also invariant to the changes in interval width when the interval is symmetric. On the other hand, BOIN and LRcat25 are significantly affected by the varying intervals. BOIN selects the true MTD with a percentage only marginally larger than that of selecting a sub-therapeutic dose in the original setting of Scenario 5. With the widening of the target interval, we see the marginal prediction advantage vanishes and BOIN shifts the highest recommendation percentage to the dose lower than the MTD. LRcat25, on the contrary, benefits from the increasing interval width. When the target interval is defined by a 0.15 deviation from the target interval, LRcat25 provides the correct recommendation of the true MTD.

The peril of a wide target interval is also evident. As the interval getting wider, there is an increase in the average toxicity rate and the risk of overdosing. The rise in the risk of overdosing for LRcat and LRcat25 is stunning. The risk of overdosing for LRcat25 is about 10% when the interval boundary deviated from the target by 0.05, but upsurges to over 30% when the deviation expands to 0.15.

Under certain circumstances, the clinical investigator might want to define a target interval with asymmetric distances from the target toxicity. For example, a trial is carried out with target toxicity of 0.25, but previous studies have shown no efficacy under 0.20. Thus, the investigator may suggest a target interval from 0.2 to 0.35. To investigate the effects of asymmetric target intervals, we compared the performance of the interval-based designs with target intervals (0.2, 0.35) and (0.25, 0.4). The results are shown in Table 3. We noted that LRcat consistently gives the correct prediction of the MTD and does not vary notably in the measurements of toxicity and over-

dosing. However, the mTPI design shows unanticipated behaviors by incorrectly predicting the MTD to a higher dose level and displaying much higher level of toxicity and risk of overdosing.

Table 3. Interval-based designs with symmetric target intervals of varying width.

Dose levels		1	2	3	*4*	5	6	7		Toxicity proportion	Average No. of patients	Risk of overdosing (%)
Scenario 5		0.15	0.17	0.23	*0.30*	0.36	0.44	0.51	none			
Target toxicity interval = (0.23, 0.37)												
mTPI	% MTD	5.15	13.90	**29.60**	29.50	15.85	4.30	1.10	0.60	0.23	35.8	2.95
	# Pts	7.4	8.2	**9.2**	6.8	3.1	0.9	0.2				
BOIN	% MTD	5.35	12.90	28.35	**29.05**	16.00	5.80	1.20	1.35	0.24	35.6	2.05
	# Pts	7.0	7.8	9.1	**6.9**	3.4	1.1	0.2				
LRcat	% MTD	1.20	6.85	24.05	**33.95**	24.70	8.00	1.45	0.00	0.27	36	**23.85**
	# Pts	5.5	3.8	7.5	**9.2**	6.3	3.1	0.7				
LRcat25	% MTD	2.00	10.60	**33.05**	23.80	14.00	3.60	1.05	12.00	0.30	32	**17.6**
	# Pts	5.0	4.0	**7.7**	6.1	5.2	2.8	1.1				
Target toxicity interval = (0.20, 0.40)												
mTPI	% MTD	7.30	14.80	**29.60**	28.25	14.90	3.60	0.90	0.65	0.23	35.8	2.85
	# Pts	8.1	8.3	**9.0**	6.5	2.9	0.8	0.2				
BOIN	% MTD	8.15	15.20	**30.55**	27.70	12.15	4.20	0.70	1.35	0.23	35.6	2.3
	# Pts	10.9	9.6	**8.6**	4.6	1.5	0.3	0.1				
LRcat	% MTD	1.45	7.15	25.2	**32.65**	23.35	8.55	1.75	0.00	0.28	36	**27.7**
	# Pts	5.6	3.4	7.3	**8.4**	6.4	3.8	1.1				
LRcat25	% MTD	0.60	6.75	**29.05**	28.1	18.95	6.10	1.0	9.45	0.32	33.2	**23.85**
	# Pts	4.7	2.7	**7.3**	6.8	5.8	4.2	1.5				
Target toxicity interval = (0.15, 0.45)												
mTPI	% MTD	14.00	22.25	**29.35**	23.25	8.20	2.00	0.20	0.75	0.21	35.7	3.70
	# Pts	10.8	9.6	**8.4**	4.7	1.6	0.3	0.0				
BOIN	% MTD	16.60	22.35	**30.15**	20.80	7.20	1.35	0.35	1.20	0.20	35.6	2.65
	# Pts	11.0	9.6	**8.6**	4.6	1.5	0.3	0.1				
LRcat	% MTD	1.55	9.65	24.25	**30.45**	23.25	9.05	1.85	0.00	0.29	36	**30.7**
	# Pts	5.7	3.9	6.2	**7.7**	6.7	4.3	1.4				
LRcat25	% MTD	0.60	4.50	22.75	**28.8**	23.50	9.35	1.05	9.45	0.33	32.9	**32.65**
	# Pts	3.8	2.7	6.2	**6.8**	5.9	6.0	1.7				

NOTE: Important results are in bold face.

Table 4. Interval-based designs with asymmetric target intervals

	Dose levels	1	2	3	*4*	5	6	7		Toxicity proportion	Average No. of patients	Risk of overdosing (%)
	Scenario 5	0.15	0.17	0.23	*0.30*	0.36	0.44	0.51	none			
Target toxicity interval = (0.20, 0.35)												
mTPI	% MTD	0.05	2.1	11.7	34.30	**42.65**	7.95	1.25	0	**0.34**	35.8	**54.15**
	# Pts	0	0.5	3.1	9.9	**17.5**	4.3	0.5				
BOIN	% MTD	8.25	15.35	**30.4**	27.90	11.90	4.15	0.70	1.35	0.22	35.6	2.0
	# Pts	8.3	8.3	**9.1**	6.3	2.7	0.8	0.2				
LRcat	% MTD	2.40	9.30	23.7	**33.05**	20.95	9.20	1.50	0	0.31	36	**34.35**
	# Pts	5.2	3.5	5.7	**7.2**	6.0	4.8	3.6				
LRcat25	% MTD	2.70	11.50	**35.45**	20.10	10.35	3.00	0.55	16.4	0.3	30	**13.7**
	# Pts	4.8	3.8	**8.0**	5.7	4.8	2	0.8				
Target toxicity interval = (0.25, 0.40)												
mTPI	% MTD	0	0.40	4.95	27.55	**52.0**	12.45	2.65	0	**0.36**	35.7	**71.45**
	# Pts	0	0.1	1.3	7.3	**19.0**	6.9	1.1				
BOIN	% MTD	3.45	11.90	27.30	**30.20**	17.60	6.75	1.45	1.35	0.24	35.6	2.4
	# Pts	6.5	7.5	9.1	**7.3**	3.7	1.3	0.3				
LRcat	% MTD	0.60	4.05	19.90	**32.95**	26.65	12.15	3.70	0	0.28	36	**27.3**
	# Pts	5.2	3.2	7.3	**8.7**	6.7	3.6	1.2				
LRcat25	% MTD	0.40	7.10	**28.85**	26.40	17.65	6.95	2.50	10.2	0.31	32.8	**22.35**
	# Pts	4.8	3.0	**7.8**	6.3	5.6	3.7	1.4				

NOTE: Important results are in bold face.

3.4.2 Sensitivity of LRcat and CRM to mis-specified priors

A big challenge for model-based Bayesian designs is the prior specification. Prior studies have demonstrated higher flexibility of two-parameter models than the one-parameter ones [5, 12]. In order to investigate the degree of sensitivity of CRM and LRcat to different priors, we compared the performance of the two designs under prior A and prior B across all eight scenarios. Figure 7 presents the prior distribution of toxicity probability at each dose level for CRM and LRcat under prior A and B approximately matched medians and 95% credible intervals.

We observed that when the toxicity rates of neighboring dose levels are close (flat dose-toxicity curve), both designs are notably influenced by mis-specified priors. For example, in regard to Scenario 7 (true MTD at dose level 6), prior A is more reasonable since it pre-determines the MTD at a dose close to the true MTD. On the contrary, prior B is a misspecification which assumes a MTD much lower than the true case. Therefore, it is not surprising to see an inferior performance

of CRM and LRcat using prior B in prediction percentage of MTD (Table 4). However, it is worth noting that, under both priors, CRM has higher average toxicity rate and higher risk of allocating too many patients to overly-toxic doses.

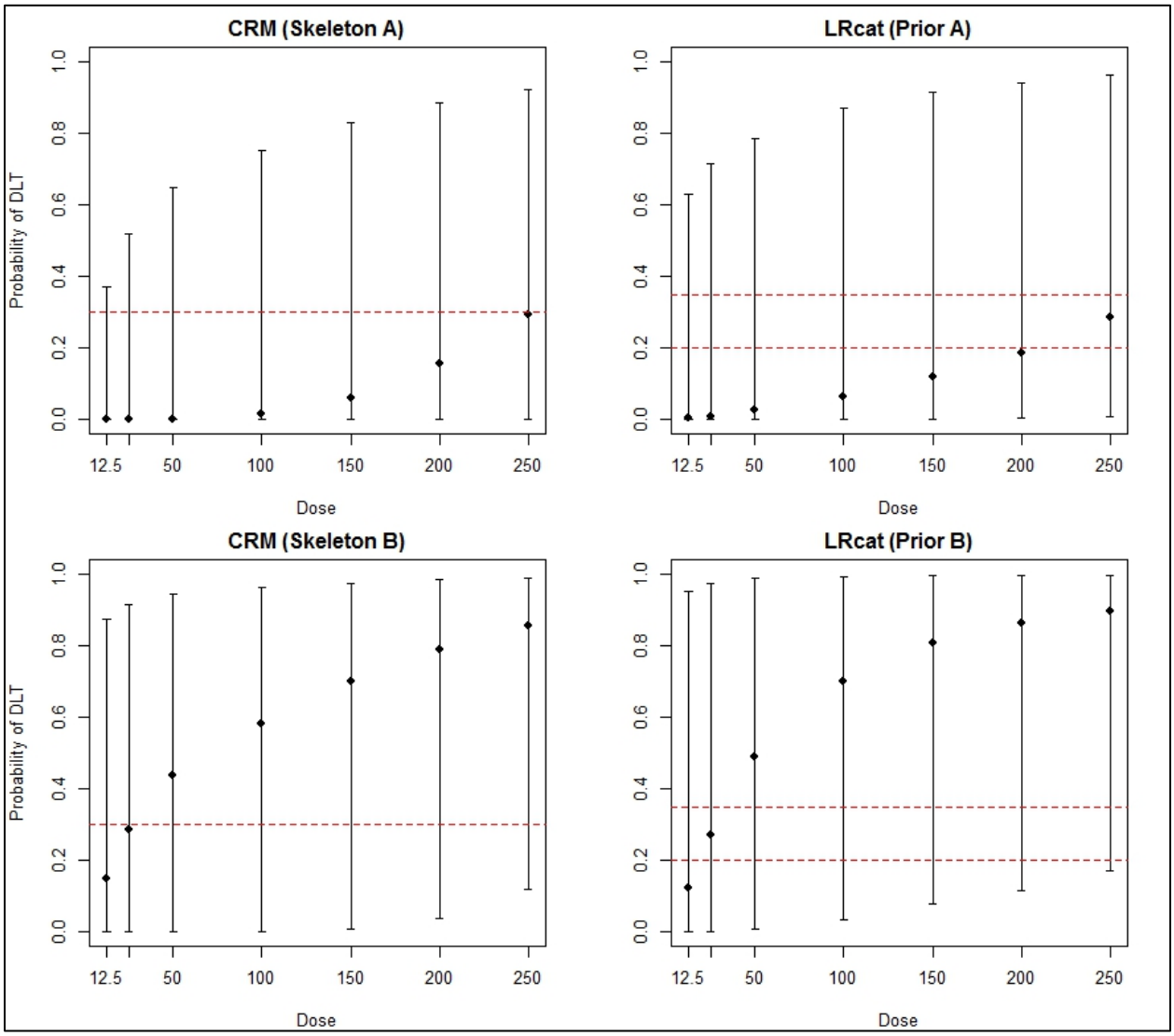


Figure 7. The median and 95% credible interval of prior probability of DLT for CRM and LRcat.
Upper panels: CRM skeleton A and LRcat prior A are used in the simulation study.
Lower panels: CRM skeleton B and LRcat prior B are used in the sensitivity analysis.
Dashed line for CRM indicates target probability of 0.3; dashed lines for LRcat indicate target probability interval.

Table 5. Comparison of CRM and LRcat in Scenario 7 with different priors

	Dose levels	**1**	**2**	**3**	**4**	**5**	***6***	**7**	**Toxicity proportion**	**Risk of overdosing (%)**
	Scenario 7	0.03	0.04	0.10	0.17	0.23	*0.30*	0.37		
(1) CRM (Skeleton A) and LRcat (Prior A)										
CRM	% MTD	0	0	0.85	8.55	20.05	**38.3**	32.25	**0.28**	**32.0**
	# Pts	3	0.4	1.1	2.9	5.2	**8.5**	14.8		
LRcat	% MTD	0	0	0.8	7.75	25.15	**37.55**	28.75	0.27	**28.05**
	# Pts	3.1	0.2	0.8	2.7	6.2	**10.1**	12.9		
(2) CRM (Skeleton B) and LRcat (Prior B)										
CRM	% MTD	0	0	2.65	17.95	**32.85**	30.3	16.25	**0.22**	**8.75**
	# Pts	5.2	3.5	5.7	7.2	**6.0**	4.8	3.6		
LRcat	% MTD	0	0.05	5.1	26.95	**35.15**	22.1	10.75	0.19	**1.75**
	# Pts	4.8	3.8	8.0	5.7	**4.8**	2	0.8		

NOTE: Important results are in bold face.

4.0 REANALYSIS OF A RECENT ONCOLOGICAL CLINICAL TRIAL

We consider a recent phase I cancer clinical trial to serve as a motivating example. The goal of the trial is to identify the MTD of a gamma secretase inhibitor (PF-03084014) with potential antitumor activity for patients with advanced solid malignancies. The open-label study comprised a dose-finding portion and an expansion cohort. A variation of 3+3 design, which targets the MTD with $\leqslant$ two toxicities among six patients (p_T$\leqslant$2⁄6), was implemented in the dose-finding part of the study. The study drug was administered orally at eight prespecified doses 20, 40, 80, 100, 130, 150, 220, and 330 (mg BID). A total of 41 patients were recruited in the dose-finding study. 9 of them were later deemed not evaluable for DLT. The first cohort of patients were treated at the lowest dose without experiencing DLT. The dose escalated sequentially and no DLT were observed for the next two dose levels. At dose 80 mg, one patient experienced DLT in the first cohort of 3, then additional 3 patients were assigned to this level with no DLT observed. The investigator then decided to continue dose escalation. Dose level 6 and 7 had one DLT out of six patients. At the last dose, two DLTs were seen in two patients. The trial was terminated and the MTD was selected to be 220 mg BID [13]. The process of the trial is presented in Table 5.

In this section, the oral gamma-secretase inhibitor trial introduced above was retrospectively analyzed to explore the performance of the novel phase I clinical trial design in real-world application. Based on the number of DLTs at each dose level observed in the study, we assume the underlying dose-toxicity relationship is delineated by the toxicity rates 0, 0, 0, 0.17, 0, 0.17, 0.17, 1.0 (Table 5). The maximum sample size is 33 and the target toxicity rate is 0.3. Since the DLTs were observed at higher doses, we used the prior that pre-determines MTD at dose 7 (prior A) for LRcat/LRcat25 and CRM/mCRM. In this analysis, we kept the default setting of the

toxicity interval boundaries for LRcat/LRcat25, mTPI and BOIN designs. Suppose the trial has not been carried out, we recruit a cohort of 3 patients at each step. Then depending on either a 1000 simulated results (LRcat and its variations) or the prespecified dose-finding spreadsheet for mTPI (Table I-A) and BOIN (Table I-B), we select the dose level for the next cohort. The step repeated until the maximum sample size was reached or the last experimented dose level has a toxicity rate over 95% for CRM. The result of the retrospective analysis is presented in Table 6.

Table 6. The original example trial

	Dose level for 21 days, mg BID							
	20	40	80	100	130	150	220	330
Number of patients	3	3	3	6	3	6	6	2
Number (%) of DLT	0	0	0	1 (16.7)	0	1 (16.7)	1 (16.7)	2 (100)

Table 7. Results of the reanalysis of the example trial

	Doses								Total	Selected MTD (mg/BID)
	20	40	80	100	130	150	*220*	330		
CRM										
No. patient	3	NA	NA	NA	3	NA	6	3	15	220
No. DLT	0	NA	NA	NA	0	NA	1	2	3	
mCRM										
No. patient	3	3	3	6	6	3	NA	NA	24	130
No. DLT	0	0	0	1	0	1	NA	NA	2	
LRcat										
No. patient	3	NA	NA	NA	NA	18	12	NA	33	220
No. DLT	0	NA	NA	NA	NA	3	2	NA	5	
LRcat25										
No. patient	3	NA	3	6	3	18	NA	NA	33	150
No. DLT	0	NA	0	1	0	3	NA	NA	4	
LRcat without dose-skipping										
No. patient	3	3	3	3	3	6	12	NA	33	220
No. DLT	0	0	0	1	0	1	2	NA	4	
LRcat with loss 1-0-1-2										
No. patient	3	NA	3	NA	3	24	NA	NA	33	150
No. DLT	0	NA	0	NA	0	3	NA	NA	3	
LRcat with loss 1-0-2-4										
No. patient	6	3	3	12	6	3	NA	NA	33	150
No. DLT	0	0	0	1	0	1	NA	NA	2	

In this particular trial setting, mTPI and BOIN have the identical dose escalation behavior as the original 3+3 design (results omitted). The only disagreement resides on the highest dose level (330 mg/BID), where 2 DLTs in 2 patients were observed. mTPI, alike 3+3, decides to de-escalate and end the trial. However, BOIN chooses to de-escalate but reserves this dose for future consideration which implies a larger sample size for detecting the true MTD.

A comparison between Table 6 and Table 5 reveals that more aggressive designs perform more efficiently and allocate less proportion of patients to non-therapeutic doses. LRcat skips less therapeutic doses and assigns the majority of patients to doses 150 and 220 mg/BID. CRM escalates fast and detect the MTD with only 15 patients. This type of aggressiveness, however, can easily raise concerns about patient safety. Therefore, we also considered designs with more

constraints like LRcat with no dose-skipping or LRcat applying heavier weights to overly toxic probability intervals. The results show that restrictions can eliminate the risk of abrupt dose escalation but generally undermines the accuracy and efficiency of detecting the MTD. Nevertheless, we want to point out the favorable features of LRcat with constraint on dose-skipping. First, at a dose as low as 100 mg/BID, it chooses to escalate without assigning more patients when one DLT presents (a 2000 simulation over this step validates the consistency of this choice). Secondly, it allocates as many as 12 patients to the dose just below the MTD. Although this design reaches the maximum sample size before properly converges to the true MTD, it could be a good candidate for future implications.

Albeit this reanalysis can be subjective, it still provides evidence that the novel interval-based designs can perform as well as the traditional CRM design. Furthermore, LRcat and its variations are more flexible than mTPI and BOIN in application. Besides, with application of more appropriate safety rules, variants of LRcat are capable of ideal performance.

5.0 COMPUTATION

The previous analysis was programmed in R. The rjags package was used to allow interference to JAGs for implementation of Gibbs sampling algorithm. A sample R code of the LRcat function is provided in Appendix B. The mTPI function and the Excel macro for the spreadsheet were original developed by Ji Yuan and was adapted with a few modifications. Functions for BOIN analysis were adapted from the R package "BOIN" developed by Yuan et al.. (link to CRAN: https://CRAN.R-project.org/package=BOIN)

6.0 DISCUSSION

In this study, we probed the performance of innovative phase I clinical trials which share similar interval-based dose transition schemes. From the simulation study of eight potential scenarios, LRcat, mTPI and BOIN have performance comparable to the CRM design in most scenarios. This observation is consistent with findings in previous simulation studies [10, 11, 13]. However, in certain scenarios, characteristics of these designs are noticeable. LRcat outperforms other designs when the underlying dose-toxicity curve is flat. But this design is criticized for its high probability of toxicity and high risk of overdosing. mTPI is sensitive to the distance of toxicity probability between two adjacent doses, hence does not deal well with scenarios with flat dose-toxicity curve or boundary scenarios. In the original paper of mTPI, Ji et al. only discussed the situations of symmetric target intervals and declared the robustness of mTPI to the choices of $\epsilon's$ [10]. However, we found that mTPI demonstrates sensitivity to EI's when ϵ_1 and ϵ_2 takes different values. Overall, BOIN has the best performance in the numeric study. But in terms of sensitivity to target interval boundaries, BOIN appears to be most sensitive to the varying of target interval width. It is not surprising since BOIN make dose selection decisions simply based on the relative location of the current observed toxicity rate to the pre-determined interval boundaries. Thus, a wide interval increases the risk of retaining a suboptimal dose.

An apparent advantage of mTPI and BOIN over LRcat is their simplicity in application. The rule-based nature of mTPI and BOIN ensures that the dose escalation decisions can be tabulated previewed prior to the conducting of the trial. However, we want to point out that model-based designs also have their merits in application. Firstly, it has been shown in our study that LRcat and CRM perform more flexible and possibly more efficient than the other designs. In

addition, LRcat and CRM can easily accommodate covariates for more complicate clinical analytical purposes like assessing combinations of two drugs or studying of two subpopulations (for phase I-II designs) [12]. From a perspective of promoting closer interdisciplinary collaboration of clinical investigators and biostatisticians, we advocate for a wider application of model-based designs like CRM and LRcat, especially when designs like mTPI and BOIN show no obvious superiority. More specifically, LRcat is more favorable than CRM since it only requires a specification of the prior bivariate normal distribution for model parameters, whereas CRM requires specification of both prior distribution and the skeleton.

On the other hand, it is undeniable that the LRcat design triggers concerns about patient safety. The variant of LRcat with over-dose control proposed in the original paper [11], LRcat25, is proved to be too conservative and compromises the efficacious detection of the true MTD. We briefly investigated other variants of LRcat with different safety and dose selection rules in a retrospective analysis of a recent phase I cancer clinical trial. Although we did not find an optimal design, the considerably good performance of LRcat with no dose skipping is inspiring. Future studies to improve LRcat design can focus on inspecting effects of more suitable safety and dose assignment rules.

Phase I cancer clinical trial is the indispensable step for the development of anticancer therapies. In the two year period from 2012 to 2014 along, there were 272 publications of phase I clinical trial in oncology [8] (needless to say numerous unpublished trials). With such a massive application of phase I clinical trial, researchers and clinical investigators should be supported with up-to-date information about cutting-edge phase I clinical trial methods. Based on our study of head-to-head comparison of novel interval-based dose-finding methods, we provide the following practical implications: (a) LRcat with some proper safety rules can serve as a good alternative for

CRM as it manifest more flexibility and efficiency; (b) BOIN is a well-established dose-finding method but requires cautiousness in defining the boundaries; and (c) mTPI design performs competitively but tends to allocate more patients to suboptimal doses when the true MTD is at the lowest or the highest doses. Besides, before further investigation on the inferior performance of mTPI when the pre-defined target interval is asymmetric, mTPI design might not be a favorable choice in such situations.

APPENDIX A. DOSE-FINDING SPREADSHEETS

A.1 DOSE-FINDING SPREADSHEET OF THE MTPI DESIGN

Number of toxicities	Number of patients treated at current dose																																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		DU	D	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
3			DU	DU	D	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
4				DU	DU	DU	D	D	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E
5					DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E
6						DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E
7							DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S	S	S	S	S	S	S	S	S
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S	S
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S	S	S	S
12												DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S	S	S
13													DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S	S
14														DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S
15															DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
16																DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
17																	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
18																		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
19																			DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
20																				DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
21																					DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
22																						DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
23																							DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
24																								DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
25																									DU	DU	DU	DU	DU	DU	DU	DU	DU
26																										DU	DU	DU	DU	DU	DU	DU	DU
27																											DU	DU	DU	DU	DU	DU	DU
28																												DU	DU	DU	DU	DU	DU
29																													DU	DU	DU	DU	DU
30																														DU	DU	DU	DU
31																															DU	DU	DU
32																																DU	DU
33																																	DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
U = The current dose is unacceptably toxic
MTD = 30%
Sample Size = 33

A.2 DOSE-FINDING SPREADSHEET OF THE BOIN DESIGN

	Number of patients treated at current dose																																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		D	D	D	D	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
3			DU	DU	D	D	D	D	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
4				DU	DU	DU	D	D	D	D	D	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
5					DU	DU	DU	DU	DU	D	D	D	D	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E
6						DU	DU	DU	DU	DU	DU	D	D	D	D	D	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E
7							DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	S	S	S	S	S	S	S	S	S	E	E	E	E	E
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	S	S	S	S	S	S	S	S	S	S	S
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	S	S	S	S	S	S	S	S
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	S	S	S	S	S	S
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	S	S	S
12												DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D
13													DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D
14														DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D
15															DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
16																DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
17																	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
18																		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
19																			DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
20																				DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
21																					DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
22																						DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
23																							DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
24																								DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
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30																														DU	DU	DU	DU
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E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
U = The current dose is unacceptably toxic
MTD = 30%
Sample Size = 33

APPENDIX B: R CODE

B.1 LRCAT FUNCTION

```
LRcat <- function (truep, prior.alpha, ff, sdose, cutpoints, Npat, cohort,
start, loss) {
   ### initialize simulation data
  new.tox <- rep(0, 7)
  new.notox <- rep(0, 7)
  new.npat <- rep(0,7)
  J <- Npat/cohort ## total number of cohorts

  for (j in 1:J) {
    d <- ifelse(j==start,1,d.prior)
    ## generate toxicity indicators for the current cohort
    tox.current <- rbinom(3, 1, truep[d])
    ## non-toxicity indicators per current cohort
    notox.current <- 1- tox.current
    ### update data
    new.tox[d] <- new.tox[d] + sum(tox.current) ## accumulated toxicity
counts
    new.notox[d] <- new.notox[d] + sum(notox.current)
    new.npat <- new.tox + new.notox
    ncurrent <- sum(new.tox + new.notox)

    ### culculate posterior DLT from the prior
    posterior.samples <-
Posterior.rjags(new.tox,new.notox,sdose,ff,prior.alpha,
                                          burnin.itr=2000,production.itr=2000)
    posterior.dlt <- matrix(nrow=2000,ncol=7)
    k <- length(sdose)
    for (m in 1:k) {
      posterior.dlt[,m] <-
exp(log(posterior.samples[,1])+(posterior.samples[,2]*sdose[m]))/

(1+(exp(log(posterior.samples[,1])+(posterior.samples[,2]*sdose[m]))))
    }
    pdlt <- as.data.frame(posterior.dlt)
    cut1 <- cutpoints[1]; cut2 <- cutpoints[2]; cut3 <- cutpoints[3];
    pdlt <- mutate(pdlt,
                   p1=cut(V1,c(0,cut1,cut2,cut3,1),include.lowest=TRUE),
                   p2=cut(V2,c(0,cut1,cut2,cut3,1),include.lowest=TRUE),
                   p3=cut(V3,c(0,cut1,cut2,cut3,1),include.lowest=TRUE),
                   p4=cut(V4,c(0,cut1,cut2,cut3,1),include.lowest=TRUE),
                   p5=cut(V5,c(0,cut1,cut2,cut3,1),include.lowest=TRUE),
                   p6=cut(V6,c(0,cut1,cut2,cut3,1),include.lowest=TRUE),
                   p7=cut(V7,c(0,cut1,cut2,cut3,1),include.lowest=TRUE)
    )

    dose1 <- as.vector(prop.table(table(pdlt$p1)))
    dose2 <- as.vector(prop.table(table(pdlt$p2)))
    dose3 <- as.vector(prop.table(table(pdlt$p3)))
```

```
    dose4 <- as.vector(prop.table(table(pdlt$p4)))
    dose5 <- as.vector(prop.table(table(pdlt$p5)))
    dose6 <- as.vector(prop.table(table(pdlt$p6)))
    dose7 <- as.vector(prop.table(table(pdlt$p7)))

    ### create a data frame containing posterior probability of DLT by
categories
    pdlt.cat <- rbind(dose1,dose2,dose3,dose4,dose5,dose6,dose7)
    colnames(pdlt.cat) <- c("under","target","excess","unaccept")

    ### compute the Bayes risk and overdosing probability
    bayes.risk <- function(loss,d) {
      sum(loss*d)
    }
    risk <- as.vector(apply(pdlt.cat,1,bayes.risk,loss))
    ndose <- seq(1,7,1)
    pdlt.cat <- cbind(ndose,pdlt.cat,risk)
    pdlt.cat <- as.data.frame(pdlt.cat)

    ### select the dose for next level
    ds <- pdlt.cat
    d.prior <- ds$ndose[which(ds$risk==min(ds$risk))]

    ### output the result when all patients are recruited
    if (j==J) {result <- list(d.prior, new.tox, new.npat)}
  }
  return(result)
}
```

B.2 SIMULATION (LRCAT/ LRCAT25)

```
## function to output operation characteristics
oc <- function(mtd,ndlt,npat,target.d,D) {
  d.mtd <- apply(mtd,2,mean)
  d.mtd <- d.mtd*100 # percentage of MTD on each level
  p.tox <- ndlt/npat
  p.tox.mean <- apply(p.tox,2,mean,na.rm=TRUE) # toxicity probability on each
level
  d.pat <- apply(npat,2,mean) # allocation of patients
  avg.n <- mean(rowSums(npat)) # average number of total patients
  avg.dlt <- mean(rowSums(ndlt)) # average number of DLT
  avg.pct.dlt <- mean(rowSums(ndlt)/rowSums(npat)) # average percentage of
dlt
  overrisk <- if(target.d <= (D-1)) {
    xx <- vector(mode="numeric", length=nrow(npat))
    for (i in 1:nrow(npat)) {
      xx[i] <- sum(npat[i,(target.d+1):D])/sum(npat[i,]) # percentage of risk
of overdosing
    }
    (length(xx[which(xx>0.6)])/nrow(npat))*100
  } else 0
  underrisk <- if(target.d >= 2) {
```

```
    xx <- vector(mode="numeric", length=nrow(npat))
    for (i in 1:nrow(npat)) {
      xx[i] <- sum(npat[i,1:(target.d-1)])/sum(npat[i,]) # percentage of risk
of underdosing
    }
    (length(xx[which(xx>0.8)])/nrow(npat))*100
  } else 0
  ocs <-
list(d.mtd,p.tox.mean,d.pat,avg.n,avg.dlt,avg.pct.dlt,overrisk,underrisk)
  ocs <- setNames(ocs, c("PCS","Toxicity probability","Pt. allocation",
                         "Avg. total patient","Avg. DLT","Avg.% of DLT",
                         "Risk of Overdosing","Risk of Underdosing"))
  return(ocs)
}

######################## LRcat25 simulation ########################
LRcat25.sim <- function (truep, nsim) {
  mtd1 <- matrix(nrow=nsim,ncol=8); mtd1[] <- 0L
  ndlt1 <- matrix(nrow=nsim,ncol=7)
  npat1 <- matrix(nrow=nsim,ncol=7)
  for (i in 1:nsim) {
    LRcat25<- LRcat25(truep=truep, prior.alpha=list(4, mu3, Sigma3),
ff="logit2",
                      sdose=sdose, cutpoints=c(0.2,0.35,0.6), Npat=36,
cohort=3, start=1, loss=loss1)
    if (LRcat25[[1]] > 0) {
      mtd1[i,(LRcat25[[1]]+1)] <- 1
    } else {
      mtd1[i,1] <- 1
    }
    ndlt1[i,] <- LRcat25[[2]]
    npat1[i,] <- LRcat25[[3]]
  }
  return(list(mtd1,ndlt1,npat1))
}

LRcat25.1 <- LRcat25.sim(s1, nsim)
lrcat25.1 <- oc(LRcat25.1[[1]],LRcat25.1[[2]],LRcat25.1[[3]],1,7)
LRcat25.2 <- LRcat25.sim(s2, nsim)
lrcat25.2 <- oc(LRcat25.2[[1]],LRcat25.2[[2]],LRcat25.2[[3]],2,7)
LRcat25.3 <- LRcat25.sim(s3, nsim)
lrcat25.3 <- oc(LRcat25.3[[1]],LRcat25.3[[2]],LRcat25.3[[3]],2,7)
LRcat25.4 <- LRcat25.sim(s4, nsim)
lrcat25.4 <- oc(LRcat25.4[[1]],LRcat25.4[[2]],LRcat25.4[[3]],4,7)
LRcat25.5 <- LRcat25.sim(s5, nsim)
lrcat25.5 <- oc(LRcat25.5[[1]],LRcat25.5[[2]],LRcat25.5[[3]],4,7)
LRcat25.6 <- LRcat25.sim(s6, nsim)
lrcat25.6 <- oc(LRcat25.6[[1]],LRcat25.6[[2]],LRcat25.6[[3]],6,7)
LRcat25.7 <- LRcat25.sim(s7, nsim)
lrcat25.7 <- oc(LRcat25.7[[1]],LRcat25.7[[2]],LRcat25.7[[3]],6,7)
LRcat25.8 <- LRcat25.sim(s8, nsim)
lrcat25.8 <- oc(LRcat25.8[[1]],LRcat25.8[[2]],LRcat25.8[[3]],7,7)


######################## LRcat simulation ########################
LRcat.sim <- function (truep, nsim, D) {
  mtd2 <- matrix(nrow=nsim,ncol=D+1); mtd2[] <- 0L
```

```
  ndlt2 <- matrix(nrow=nsim,ncol=D)
  npat2 <- matrix(nrow=nsim,ncol=D)
  for (i in 1:nsim) {
    LRcat <- LRcat(truep=truep, prior.alpha=list(4, mu3, Sigma3),
ff="logit2",
                   sdose=sdose, cutpoints=c(0.2,0.35,0.6), Npat=36,
cohort=3, start=1, loss=loss1)
    if (LRcat[[1]] > 0) {
      mtd2[i,(LRcat[[1]]+1)] <- 1
    } else {
      mtd2[i,1] <- 1
    }
    ndlt2[i,] <- LRcat[[2]]
    npat2[i,] <- LRcat[[3]]
  }
  return(list(mtd2,ndlt2,npat2))
}

LRcat1 <- LRcat.sim(s1, nsim, 7)
lrcat1 <- oc(LRcat1[[1]],LRcat1[[2]],LRcat1[[3]],1,7)
LRcat2 <- LRcat.sim(s2, nsim, 7)
lrcat2 <- oc(LRcat2[[1]],LRcat2[[2]],LRcat2[[3]],2,7)
LRcat3 <- LRcat.sim(s3, nsim, 7)
lrcat3 <- oc(LRcat3[[1]],LRcat3[[2]],LRcat3[[3]],2,7)
LRcat4 <- LRcat.sim(s4, nsim, 7)
lrcat4 <- oc(LRcat4[[1]],LRcat4[[2]],LRcat4[[3]],4,7)
LRcat5 <- LRcat.sim(s5, nsim, 7)
lrcat5 <- oc(LRcat5[[1]],LRcat5[[2]],LRcat5[[3]],4,7)
LRcat6 <- LRcat.sim(s6, nsim, 7)
lrcat6 <- oc(LRcat6[[1]],LRcat6[[2]],LRcat6[[3]],6,7)
LRcat7 <- LRcat.sim(s7, nsim, 7)
lrcat7 <- oc(LRcat7[[1]],LRcat7[[2]],LRcat7[[3]],6,7)
LRcat8 <- LRcat.sim(s8, nsim, 7)
lrcat8 <- oc(LRcat8[[1]],LRcat8[[2]],LRcat8[[3]],7,7)
```

B.3 PLOTS FOR SIMULATION RESULTS

```
############### Percentage of selected MTD on each dose level ###############
bar.mtd <- function(truep,target.d,crm,mcrm,mtpi,lrcat25,lrcat,boin) {
  xaxis <- c('0','1','2','3','4','5','6','7')
  color <- rep(0,8)
  color[(target.d+1)] <- 8
  par(mfrow = c(1, 6), mar=c(4,2.5,2,1), omi=c(0.2,0.2,0.2,0))
  p1 <- barplot(crm[[1]],ylim=c(0,95),main="CRM",names.arg=xaxis,col=color)
  lines(x=p1[2:8], y=truep*100, type="b", pch=16, lty=1, col=4)
  p2 <- barplot(mcrm[[1]],ylim=c(0,95),main="mCRM",names.arg=xaxis,col=color)
  lines(x=p2[2:8], y=truep*100, type="b", pch=16, lty=1, col=4)
  p3 <- barplot(mtpi[[1]],ylim=c(0,95),main="mTPI",names.arg=xaxis,col=color)
  lines(x=p3[2:8], y=truep*100, type="b", pch=16, lty=1, col=4)
  boin.mtd <- c(boin$pctearlystop[1],boin$selpercent)
  p4 <- barplot(boin.mtd,ylim=c(0,95),main="BOIN",names.arg=xaxis,col=color)
```

```
  lines(x=p4[2:8], y=truep*100, type="b", pch=16, lty=1, col=4)
  p5 <-
barplot(lrcat[[1]],ylim=c(0,95),main="LRcat",names.arg=xaxis,col=color)
  lines(x=p5[2:8], y=truep*100, type="b", pch=16, lty=1, col=4)
  p6 <-
barplot(lrcat25[[1]],ylim=c(0,95),main="LRcat25",names.arg=xaxis,col=color)
  lines(x=p6[2:8], y=truep*100, type="b", pch=16, lty=1, col=4)
  mtext("MTD Selection Percentage", side=2, outer=T, at=0.5)

}

## plotting scenarios 1-8
pdf("PCS new.pdf",height=6,width=7)
par(mfrow = c(2, 1))

bar.mtd1(s1,1,crm1,mcrm1,mtpi1,lrcat25.1,lrcat1,boin1)
mtext("Scenario 1", side=3, outer=T, at=0.5)
bar.mtd1(s2,2,crm2,mcrm2,mtpi2,lrcat25.2,lrcat2,boin2)
mtext("Scenario 2", side=3, outer=T, at=0.5)
bar.mtd1(s3,2,crm3,mcrm3,mtpi3,lrcat25.3,lrcat3,boin3)
mtext("Scenario 3", side=3, outer=T, at=0.5)
bar.mtd1(s4,4,crm4,mcrm4,mtpi4,lrcat25.4,lrcat4,boin4)
mtext("Scenario 4", side=3, outer=T, at=0.5)
bar.mtd1(s5,4,crm5,mcrm5,mtpi5,lrcat25.5,lrcat5,boin5)
mtext("Scenario 5", side=3, outer=T, at=0.5)
bar.mtd1(s6,6,crm6,mcrm6,mtpi6,lrcat25.6,lrcat6,boin6)
mtext("Scenario 6", side=3, outer=T, at=0.5)
bar.mtd1(s7,6,crm7,mcrm7,mtpi7,lrcat25.7,lrcat7,boin7)
mtext("Scenario 7", side=3, outer=T, at=0.5)
bar.mtd2(s8,7,crm8,mcrm8,mtpi8,lrcat25.8,lrcat8,boin8)
mtext("Scenario 8", side=3, outer=T, at=0.5)

dev.off()



####################### Patient allocation ##############################
bar.pat1 <- function(target.d,crm,mcrm,mtpi,lrcat25,lrcat,boin) {
  xaxis <- c('1','2','3','4','5','6','7')
  color <- rep(0,7)
  color[target.d] <- 8
  par(mfrow = c(1, 6), omi=c(0.2,0.2,0.2,0), par(mar=c(4,2.5,2,1)))
  p1 <- barplot(crm[[3]],ylim=c(0,25),main="CRM",names.arg=xaxis,col=color)
  p2 <- barplot(mcrm[[3]],ylim=c(0,25),main="mCRM",names.arg=xaxis,col=color)
  p3 <- barplot(mtpi[[3]],ylim=c(0,25),main="mTPI",names.arg=xaxis,col=color)
  p4 <-
barplot(boin$nptsdose,ylim=c(0,25),main="BOIN",names.arg=xaxis,col=color)
  p5 <-
barplot(lrcat[[3]],ylim=c(0,25),main="LRcat",names.arg=xaxis,col=color)
  p6 <-
barplot(lrcat25[[3]],ylim=c(0,25),main="LRcat25",names.arg=xaxis,col=color)

    mtext("Avg. Allocated Patients", side=2, outer=T, at=0.5)
}

## plotting scenarios 1-8
bar.pat1(1,crm1,mcrm1,mtpi1,lrcat25.1,lrcat1,boin1)
```

```
mtext("Scenario 1", side=3, outer=T, at=0.5)
bar.pat1(2,crm2,mcrm2,mtpi2,lrcat25.2,lrcat2,boin2)
mtext("Scenario 2", side=3, outer=T, at=0.5)
bar.pat1(2,crm3,mcrm3,mtpi3,lrcat25.3,lrcat3,boin3)
mtext("Scenario 3", side=3, outer=T, at=0.5)
bar.pat2(4,crm4,mcrm4,mtpi4,lrcat25.4,lrcat4,boin4)
mtext("Scenario 4", side=3, outer=T, at=0.5)
bar.pat1(4,crm5,mcrm5,mtpi5,lrcat25.5,lrcat5,boin5)
mtext("Scenario 5", side=3, outer=T, at=0.5)
bar.pat1(6,crm6,mcrm6,mtpi6,lrcat25.6,lrcat6,boin6)
mtext("Scenario 6", side=3, outer=T, at=0.5)
bar.pat1(6,crm7,mcrm7,mtpi7,lrcat25.7,lrcat7,boin7)
mtext("Scenario 7", side=3, outer=T, at=0.5)
bar.pat2(7,crm8,mcrm8,mtpi8,lrcat25.8,lrcat8,boin8)
mtext("Scenario 8", side=3, outer=T, at=0.5)

################ Average Percentage of Toxicity#########################
bar.tox <- function(crm,mcrm,mtpi,boin,lrcat,lrcat25,title) {
  crm.tox <- crm[[6]]
  mcrm.tox <- mcrm[[6]]
  mtpi.tox <- mtpi[[6]]
  boin.tox <- (boin$totaltox[1]/boin$totaln[1])
  lrcat.tox <- lrcat[[6]]
  lrcat25.tox <- lrcat25[[6]]
  tox <- c(crm.tox,mcrm.tox,mtpi.tox,boin.tox,lrcat.tox,lrcat25.tox)
  barplot(tox, ylim=c(0,0.50), main=title,
          col=c('#66c2a5','#fc8d62','#8da0cb','#e78ac3','#a6d854','#ffd92f')
          )

  abline(h=0.30,lty=4) #,col="#FFC300"
}

## plotting toxicity rate
par(mfrow = c(1, 8), family="", oma=c(3,2,1,1), mar=c(3,3,2,1))

bar.tox(crm1,mcrm1,mtpi1,boin1,lrcat1,lrcat25.1,"Scenario 1")
bar.tox(crm2,mcrm2,mtpi2,boin2,lrcat2,lrcat25.2,"Scenario 2")
bar.tox(crm3,mcrm3,mtpi3,boin3,lrcat3,lrcat25.3,"Scenario 3")
bar.tox(crm4,mcrm4,mtpi4,boin4,lrcat4,lrcat25.4,"Scenario 4")
bar.tox(crm5,mcrm5,mtpi5,boin5,lrcat5,lrcat25.5,"Scenario 5")
bar.tox(crm6,mcrm6,mtpi6,boin6,lrcat6,lrcat25.6,"Scenario 6")
bar.tox(crm7,mcrm7,mtpi7,boin7,lrcat7,lrcat25.7,"Scenario 7")
bar.tox(crm8,mcrm8,mtpi8,boin8,lrcat8,lrcat25.8,"Scenario 8")

mtext("Designs", side=1, outer=T, at=0.5)
mtext("Average Toxicity Rate", side=2, outer=T, at=0.5)

legend(x=-45,y=-0.10,legend=c('CRM','mCRM','mTPI','BOIN','LRcat','LRcat25'),
       #col=c('#66c2a5','#fc8d62','#8da0cb','#e78ac3','#a6d854','#ffd92f'),
       col=c('#000000','#4c4c4c','#7f7f7f','#b2b2b2','#cccccc','#e5e5e5'),
       #angle=angle1, density=density1,
       horiz=T, pch=15,bty="0",xpd=NA,cex=1.2,pt.cex=2)

dev.off()

######################### Risk of overdosing ########################
bar.over <- function(crm,mcrm,mtpi,boin,lrcat,lrcat25,ylim,title) {
```

```
  #xaxis <- c('3+3','CRM','mTPI','LRcat25','LRcat','BOIN')
  mtpi.over <- mtpi[[7]]
  boin.over <- boin$overdose60[1]
  crm.over <- crm[[7]]
  mcrm.over <- mcrm[[7]]
  lrcat.over <- lrcat[[7]]
  lrcat25.over <- lrcat25[[7]]
  over <- c(crm.over,mcrm.over,mtpi.over,boin.over,lrcat.over,lrcat25.over)
  barplot(over, ylim=c(0,ylim), main=title,
}

## plotting percentage of overdosing
par(mfrow = c(1, 7), family="", oma=c(4,2,1,1), mar=c(2,3,2,1))

bar.over(crm1,mcrm1,mtpi1,boin1,lrcat1,lrcat25.1,35,"Scenario 1")
bar.over(crm2,mcrm2,mtpi2,boin2,lrcat2,lrcat25.2,35,"Scenario 2")
bar.over(crm3,mcrm3,mtpi3,boin3,lrcat3,lrcat25.3,35,"Scenario 3")
bar.over(crm4,mcrm4,mtpi4,boin4,lrcat4,lrcat25.4,35,"Scenario 4")
bar.over(crm5,mcrm5,mtpi5,boin5,lrcat5,lrcat25.5,35,"Scenario 5")
bar.over(crm6,mcrm6,mtpi6,boin6,lrcat6,lrcat25.6,35,"Scenario 6")
bar.over(crm7,mcrm7,mtpi7,boin7,lrcat7,lrcat25.7,35,"Scenario 7")
#bar.over(three8,mtpi8,boin8,crm8,lrcat8,lrcat25.8,"Scenario 8")

mtext("Designs", side=1, outer=T, at=0.5)
mtext("Risk of Overdosing (%)", side=2, outer=T, at=0.5)

legend(x=10,y=25,legend=c('CRM','mCRM','mTPI','BOIN','LRcat','LRcat25'),
       #col=c('#66c2a5','#fc8d62','#8da0cb','#e78ac3','#a6d854','#ffd92f'),
       col=c('#000000','#4c4c4c','#7f7f7f','#b2b2b2','#cccccc','#e5e5e5'),
       #angle=angle1, density=density1,
       horiz=F, pch=15,bty="o",xpd=NA,cex=2,pt.cex=3)
dev.off()
######################## Risk of Underdosing ############################
bar.under <- function(crm,mcrm,mtpi,boin,lrcat,lrcat25,ylim,title) {
  mtpi.under <- mtpi[[8]]
  boin.under <- boin$underdose80[1]
  crm.under <- crm[[8]]
  mcrm.under <- mcrm[[8]]
  lrcat.under <- lrcat[[8]]
  lrcat25.under <- lrcat25[[8]]
  under <-
c(crm.under,mcrm.under,mtpi.under,boin.under,lrcat.under,lrcat25.under)
  barplot(under, ylim=c(0,ylim), main=title,
          col=c('#000000','#4c4c4c','#7f7f7f','#b2b2b2','#cccccc','#e5e5e5')
          )
}

## Plot percentage of overdosing
par(mfrow = c(1, 7), family="", oma=c(4,2,1,1), mar=c(2,3,2,1))

bar.under(crm2,mcrm2,mtpi2,boin2,lrcat2,lrcat25.2,80,"Scenario 2")
bar.under(crm3,mcrm3,mtpi3,boin3,lrcat3,lrcat25.3,80,"Scenario 3")
bar.under(crm4,mcrm4,mtpi4,boin4,lrcat4,lrcat25.4,80,"Scenario 4")
bar.under(crm5,mcrm5,mtpi5,boin5,lrcat5,lrcat25.5,80,"Scenario 5")
bar.under(crm6,mcrm6,mtpi6,boin6,lrcat6,lrcat25.6,80,"Scenario 6")
bar.under(crm7,mcrm7,mtpi7,boin7,lrcat7,lrcat25.7,80,"Scenario 7")
bar.under(crm8,mcrm8,mtpi8,boin8,lrcat8,lrcat25.8,80,"Scenario 8")
```

```
mtext("Designs", side=1, outer=T, at=0.5)
mtext("Risk of Underdosing (%)", side=2, outer=T, at=0.5)

legend(x=10,y=25,legend=c('CRM','mCRM','mTPI','BOIN','LRcat','LRcat25'),
       col=c('#000000','#4c4c4c','#7f7f7f','#b2b2b2','#cccccc','#e5e5e5'),
       horiz=F, pch=15,bty="o",xpd=NA,cex=2,pt.cex=3)

dev.off()
```

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