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Penalized Maximum Difference Dose - A New Criterion for Phase I/II Dose-Finding Trials

Yuan Ji* Yisheng Li†

Benjamin Bekele‡

*The University of Texas M.D. Anderson Cancer Center, yji@northshore.org

†The University of Texas M.D. Anderson Cancer Center, ysli@mdanderson.org

‡The University of Texas M.D. Anderson Cancer Center, bbekele@mdanderson.org

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Yuan Ji, Yisheng Li, and Benjamin Bekele

Abstract

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Penalized Maximum Difference Dose - A new criterion for phase I/II dose-finding trials

Yuan Ji, Yisheng Li, B. Nebiyou Bekele

Department of Biostatistics and Applied Mathematics, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030.

Email: *yuanji@mdanderson.org.*

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SUMMARY We consider dose-finding in phase I/II clinical trials by accounting for the preferences of both patients and investigators. We propose to search for the dose that maximizes the difference in the probability of response relative to the probability of toxicity, to reflect the patient's preference to be treated at the best dose. We introduce a penalty term in assessing doses to reflect the principal investigator's preference to examine the efficacy and toxicity of various doses and therefore select the best dose for treating future patients. The combined criterion is called the penalized maximum difference dose (pMDD). We develop a flexible probability model that relaxes the usual monotonicity assumption that the probability of toxicity increases with dose. However, in the proposed dose-assignment rules, we restrict escalation to untried doses if the highest tried dose is toxic. Under the new probability model and the new dose-assignment rules, we obtain improved simulation results compared to currently available methods. In addition, we demonstrate that our new method can be directly applied to two different types of trials: one in which the probability increases with dose and the other in which toxicity does not increase with dose.

KEY WORDS: Dose escalation; Dose de-escalation; Efficacy; Maximum tolerated dose; Oncology trials; pMDD.

1 Introduction

Conventional phase I oncology trials often aim to locate the maximum tolerated dose (MTD), the highest dose with tolerable toxicity. Various statistical approaches have been developed to determine the MTD (e.g., Gasparini and Eisele, 2000; Leung and Wang, 2002; O'Quigley, Pepe, and Fisher, 1990; and Storer, 1989, among others). Typically, patients are sequentially assigned to a series of doses and their toxicity events are recorded. Statistical models are then employed to estimate the toxicity probabilities based on these events. The trial continues until the MTD is located or the maximum sample size is reached. The underlying assumption of these phase I trials is that toxicity is positively correlated with efficacy; otherwise they would be unethical and inefficient. Recently, statisticians have proposed monitoring both efficacy and toxicity in phase I clinical trials. Because efficacy is traditionally considered in phase II trials, this new type of trial is named a phase I/II trial. By simultaneously monitoring efficacy and toxicity, investigators no longer need to assume that the MTD is more effective than its lower doses. We should note that the term "phase I/II clinical trials" in oncology also applies to two-stage designs in which the first stage performs dose-finding based on toxicity alone and the second stage assesses efficacy at the dose determined to be the MTD in the first stage. Typically, in these designs there is no way of modifying the dose after the first stage. Thus, if a dose is inappropriately determined to be the MTD in the first stage, there are usually no means of adjusting dose in the second stage. Under the new type of phase I/II trials, the investigators gain an advantage over traditional phase I/II studies in that dose modification can occur at anytime thus adding flexibility to the clinical trial.

New dose-finding algorithms for the phase I/II trials include those of Thall and Russell (1998), Thall and Cheng (1999), O'Quigley, Hughes, and Fenton (2001), Braun (2002), Ivanova (2003), Thall and Cook (2004), Bekele and Shen (2005), and Yin, Li, and Ji (2006). While Bekele and Shen (2005) considered a continuous efficacy response, most researchers modeled a

bivariate binary efficacy and toxicity outcome. Both parametric and nonparametric models have been used to describe the relationship between efficacy outcomes and dose levels and between toxicity outcomes and dose levels. In their recent work, Thall and Cook (2004) proposed a new concept of efficacy-toxicity trade-offs: a set of doses is considered equally desirable if they have the same trade-off values. Yin, Li, and Ji (2005) used an odds-ratio trade-off that has a practical interpretation: the doses are considered equally desirable if they have the same toxicity and efficacy odds ratio. Based on these trade-offs, both methods construct equivalence contours on the two-dimensional probability space of efficacy and toxicity, such that the doses lying along the same contour are considered equally desirable for treating patients. They select the best dose, of which the equivalence contour has the largest desirability.

We propose a new dose-finding method that has two distinct features, which we describe in Sections 1.1 and 1.2.

1.1 Feature one: pMDD

One question that arises when assuming an equivalence contour is whether or not the doses on the same contour are equally desirable to the patients. Since the contours in the methods by Thall and Cook (TC) and Yin, Li and Ji (YLJ) are different, the doses that are equally desirable under TC are not equally desirable under YLJ. In fact, the patients want to be treated at a dose that maximizes the difference between the probability of response and the probability of toxicity at that dose. However, the principal investigators (PIs) want to examine the patients' responses at various doses (including potentially nonoptimal ones) in order to identify the best dose and use it to treat future patients. To incorporate the preferences from both patients and PIs, we develop a dose-finding criterion that has two components.

First, in order to reflect the patient's preference we search for the maximum difference dose (MDD), the dose that has tolerable toxicity and maximizes the difference in the probability of

efficacy relative to the probability of toxicity. Second, in order to reflect the PI's preference, we incorporate a penalty term in our dose-assignment rules for evaluating whether to de-escalate, stay or escalate the dose received by the next cohort of patients. The following example explains why a penalty term is useful in dose assignments. Suppose there are only two doses in the trial, with the true efficacy probability and toxicity probability for the first dose being 0.5 and 0.1, and those for the second dose being 0.5 and 0.3, respectively. Suppose a cohort of three patients is treated at the first dose and neither event, efficacy or toxicity, is observed. A new cohort of three patients is then treated at dose two. Suppose two efficacy events and one toxicity event are then observed. Based on the observed data, dose two is better than dose one, and a reasonable dose-finding algorithm will choose to continue treating patients at dose two. Since dose two has a larger efficacy probability (0.5) than its corresponding toxicity probability (0.3), it is very likely that more patients will experience efficacy than toxicity when they are treated at this dose. If this is the case, based on the observed data, dose two will always be more desirable. At the end of the trial, most patients will have been treated at dose two and the conclusion will be to choose dose two as the best dose. However, dose one is in fact better since it is less toxic and is as efficacious as dose two. Such an incorrect decision of a trial is simply due to the random outcome of zero toxicity and efficacy from the first three patients treated at dose one. Once the outcome was observed, dose one never had a chance to be used again to show its superiority. Although one can argue that it is not likely to observe neither efficacy nor toxicity at dose one (given its probabilities of efficacy and toxicity), in practice, whenever this type of response is indeed observed, the consequence of a misconcluded trial can be destructive to the patients who suffer the disease. Therefore, to minimize the possibility of such an incorrect decision, we introduce a penalty term when assessing the MDD, thus allowing potentially desirable but under-assigned doses to be tried. We call our combined criterion for making dose escalation, stay, or de-escalation decisions the penalized MDD (pMDD), which is one of the two distinct features of our new method.

1.2 Feature two: non-monotonicity

The second feature of the new method is that it automatically accommodates two different types of dose-toxicity relationships: one in which the probability of toxicity increases with dose, and the other in which the probability of toxicity does not increase with dose. In most trials, the probability of toxicity increases with the dose level. However, depending on the definition of toxicity, the probability does not always increase with the dose level. For example, in the trial described by TC, the inclusion of death as a composite outcome of toxicity implies the possibility that when dose levels are higher, the probability of toxicity may be smaller since higher level doses could be more effective hence reducing the probability of death. Obviously, for this type of trial, a model with the monotonicity restriction might not fit. Our probability model does not assume that toxicity increases with dose. Instead, to protect patients from being exposed to excessively toxic doses, we develop dose-assignment rules that restrict escalation to untried doses that may be too toxic based on the probability of toxicity at the highest tried dose. A benefit of not incorporating a monotonicity assumption in the model is that we seem to be able to obtain better estimates of the probabilities of toxicity, which in turn allows us to make better dose assignment decisions. In addition, we do not have to change the model, and, more importantly, make amendments to the study protocol if the monotonicity assumption is incorrect.

The rest of the paper is organized as follows. Section 2 introduces notation and provides a graphical demonstration of the MDD. Section 3 develops the probability model and Section 4 contains the new dose-finding algorithm. The simulation results comparing the new algorithm with the methods of TC and YLJ are presented in Section 5. The article ends with concluding remarks and a discussion in Section 6.

2 Graphical display of MDD

Let d_j denote the level of dose j, $j = 1, \ldots, D$, where D is the total number of candidate doses. Let p_j^E and p_j^T denote the probability of efficacy and the probability of toxicity, respectively, for dose j. Suppose that the dose level d_j increases continuously from 0 to ∞, then the corresponding values of (p_j^E, p_j^T) will induce a curve on the two-dimensional probability space, as shown in Figure 1. In phase I/II trials, a dose is considered acceptable if the percentage of patients who experience toxicity is no more than Q_T and the percentage of patients who experience efficacy is at least Q_E, where Q_T and Q_E are fixed probability cutoffs specified by physicians. Therefore, in Figure 1, only doses in the upper left rectangle are acceptable.

The MDD is a special point on the curve.

DEFINITION: *The MDD is the dose with the largest value of* $(p^E - p^T)$ *among which the value of* $1_{(p^E > Q_E)} 1_{(p^T < Q_T)} = 1$, *where* $1_{()}$ *is the indicator function.*

It is easy to show that in Figure 1, the point corresponding to the MDD on the dose-response curve is the one at which the tangent is the same as the 45-degree line. Any doses to the right of the MDD will have a larger increment in p^T than in p^E; and any doses to the left of the MDD will have more reduction in p^E than in p^T. Therefore, patients will benefit the most if they are treated at the MDD. Here, we are treating a unit reduction in p^T as if it had the same desirability as a unit increment in p^E. This is because toxicities considered in these trials are dose-limiting such that avoiding a toxicity event is as desirable as having an efficacy event. Therefore, the MDD aims at maximizing $(p^E - p^T)$. However, the criterion can be modified easily if one wishes to put different weights on toxicity and efficacy. For example, $(P^E - Kp^T)$ for $K \in (0, 1)$ corresponds to that a K-unit reduction in toxicity is the same desirable as a one-unit increment in efficacy.

3 Probability model

In addition to the notations already introduced, let (E_{ij}, T_{ij}) be the efficacy and toxicity binary response vector for patient i at dose j, $j = 1, \ldots, D$. If patient i experiences an efficacy or toxicity event at dose j, the corresponding E_{ij} or T_{ij} equals 1; otherwise, they equal zero.

Let $p_j^{(ab)} = P(E_{ij} = a, T_{ij} = b)$ be the joint probability mass function of (E_{ij}, T_{ij}), in which $a, b = 0, 1$. Then $p_j^E = P(E_{ij} = 1)$ and $p_j^T = P(T_{ij} = 1)$ are the two previously defined marginal probabilities of efficacy and toxicity associated with dose j. Finally, let

$$\theta_j = \frac{p_j^{(00)} p_j^{(11)}}{p_j^{(01)} p_j^{(10)}}$$

be the association parameter of the joint probabilities. Based on the global cross-ratio model (Dale, 1986) , $p_j^{(ab)}$ can be expressed using the marginal probabilities and the association parameter. Let $\alpha_j = 1 + (p_j^E + p_j^T)(\theta_j - 1)$ and $\beta_j = -4\theta_j(\theta_j - 1)p_j^E p_j^T$, then

$$p_j^{(11)} = \begin{cases} (\alpha_j - \sqrt{(\alpha_j^2 + \beta_j)})/\{2(\theta_j - 1)\} & \text{if } \theta_j \neq 1, \\ p_j^E p_j^T & \text{if } \theta_j = 1, \end{cases}$$

$p_j^{(10)} = p_j^E - p_j^{(11)}$, $p_j^{(01)} = p_j^T - p_j^{(11)}$, and $p_j^{(00)} = 1 - p_j^E - p_j^T + p_j^{(11)}$. Denote $\boldsymbol{p}_E = (p_1^E, \ldots, p_d^E)'$, $\boldsymbol{p}_T = (p_1^T, \ldots, p_d^T)'$, and $\boldsymbol{\theta} = (\theta_1, \ldots, \theta_d)'$. Then the likelihood function is given by

$$L(\boldsymbol{p}_E, \boldsymbol{p}_T, \boldsymbol{\theta}) = \prod_{j=1}^{d} \prod_{i=1}^{n_j} \prod_{a,b=0,1} \left\{ p_j^{(ab)} \right\}^{1(E_{ij}=a, T_{ij}=b)}, \tag{1}$$

where n_j is the number of patients treated at dose j. We propose independent normal priors for $\phi_j = \log\{p_j^E/(1 - p_j^E)\}$ and $\psi_j = \log\{p_j^T/(1 - p_j^T)\}$ with mean 0 and variance σ^2. We take independent and identical log-normal priors for θ_j, which are also independent of the priors of ϕ_j and ψ_j. Denoting $\boldsymbol{\phi} = (\phi_1, \ldots, \phi_d)'$ and $\boldsymbol{\psi} = (\psi_1, \ldots, \psi_d)'$, the joint posterior distribution is given by

$$\pi(\boldsymbol{\phi}, \boldsymbol{\psi}, \boldsymbol{\theta}) \propto L(\boldsymbol{p}_E(\boldsymbol{\phi}), \boldsymbol{p}_T(\boldsymbol{\psi}), \boldsymbol{\theta}) \pi(\boldsymbol{\phi}) \pi(\boldsymbol{\psi}) \pi(\boldsymbol{\theta}),$$

where $\pi(\boldsymbol{\phi})$, $\pi(\boldsymbol{\psi})$, and $\pi(\boldsymbol{\theta})$ are the corresponding prior densities.

4 Dose-finding algorithm

Assume that patients are assigned to doses in cohorts. Each time the current interim data, $\mathcal{X}$, are available, a dose must be assigned to treat future patients. We first define a dose j to be *acceptable* if the posterior probability

$$p(p_j^E > Q_E|\mathcal{X}) > \pi_E \tag{2}$$

and

$$P(p_j^T < Q_T|\mathcal{X}) > \pi_T, \tag{3}$$

where π_E and π_T are fixed probability cutoffs. The chosen dose must be acceptable; if there is no acceptable dose, the trial is terminated.

Suppose the starting dose is somewhere at the beginning of the curve in Figure 1 (lower left corner). A sound dose-finding algorithm should escalate quickly until the toxicity probability p_j^T is larger than Q_T. To achieve fast escalation, if condition (3) is satisfied for the highest tried dose, i.e., it is deemed nontoxic, the next cohort will be treated at the lowest untried dose. Once the highest tried dose becomes unacceptably toxic according to (3), the algorithm should examine all the lower-level acceptable doses and treat patients at the dose with the largest difference of $(p_j^E - p_j^T)$. Mathematically, this requires comparing the posterior quantity $E\{(p_j^E - p_j^T)1_{(p_j^E > Q_E)}1_{(p_j^T < Q_T)}|\mathcal{X}\}$ between doses. This quantity reflects patient's desire to be treated at the best dose.

Next, we introduce the aforementioned penalty term, which reflects the PI's desire in dose-finding trials. The PI wants to examine all the potentially effective and safe doses and select the best one to use for either treating more future patients or for drug development. In order to examine as many potentially desirable doses as possible, we propose to penalize for over-assignment at a given dose (treating a large number of patients at one dose) and under-assignment at another dose. If too few patients are treated at a given dose, its toxicity probability and efficacy

probability might not be accurately estimated, and the dose assignment decisions based on these estimates would not be accurate. Denoting n_j as the number of patients treated at dose j, we compute

$$\Gamma_j = E\{(p_j^E - p_j^T)1_{(p_j^E > Q_E)}1_{(p_j^T < Q_T)}|\mathcal{X}\} + \lambda\left(\frac{1}{n_j}\right)^\tau \tag{4}$$

for each tried dose j, in which $\lambda > 0$ and $\tau > 0$ are tuning parameters. We assign patients to the dose with the largest value of Γ_j. The quantity $\lambda(1/n_j)^\tau$ is the penalty for treating a large n_j number of patients at dose j. The dose with the maximum value of Γ_j is the pMDD. Aiming at maximizing Γ_j, we will have more opportunities to treat patients at doses which have been tried with only a few patients and therefore may not have the chance to show their potential superiority over the other doses. Due to the way in which the penalty is structured, if a dose is much more effective and less toxic than the other doses, even with a large value of n_j (relative to the other doses), the difference in $E\{(p_j^E - p_j^T)1_{(p_j^E > Q_E)}1_{(p_j^T < Q_T)}|\mathcal{X}\}$ will overwhelm the difference in the penalty and that dose will still be chosen to treat future patients. In our simulation studies, we choose $\lambda = 1$ and $\tau = 1/2$. We explain how and why we choose these values in the discussion section.

Based on the criterion Γ_j, we propose a new dose-finding algorithm for phase I/II clinical trials.

1. At any step of the trial, if no dose is acceptable, the trial is terminated.

2. The first cohort of patients is treated at the starting dose level specified by physicians.

3. If patients are treated at dose j and dose $(j+1)$ is an untried dose, then

   - if condition (3) is satisfied, the next cohort of patients will be treated at the next higher dose $(j+1)$;
   - if condition (3) is not satisfied, the next cohort of patients will be treated at the tried acceptable dose with a maximum value of Γ_j.

4. If patients are treated at dose j and dose $(j+1)$ is a tried dose, then the next cohort of patients will be treated at the acceptable dose with a maximum value of Γ_j.

5 Simulation

We conducted two simulation studies to examine the operating characteristics of the new dose-finding algorithm. In one study, we assumed that the probability of toxicity monotonically increases with the dose level and in the other, we relaxed the monotonicity assumption. Similar to the methods of TC and YLJ, we set the maximum sample size at 60 for the simulated trials with five doses. The toxicity and efficacy limits in conditions (2) and (3) were taken to be $Q_E = Q_T = 0.3$, and the probability cutoffs were $\pi_E = 0.1$ and $\pi_T = 0.07$, respectively. The values of Q_E and Q_T were fixed by the physician of the clinical trial and the values of π_E and π_T were calibrated in such a way that the design made the right dose-assignment decisions when the data clearly indicate that the dose is either too toxic or safe, or that the dose is either effective or not effective. The prior variance $\sigma^2 = 10$, resulting in a U-shaped prior for the probabilities p_j^E and p_j^T, is desirable for the binomial data, according to the work of Zhu and Lu (2004). We took $\tau = 0.5$ and $\lambda = 1$, thus the penalty term in (4) took the form $(1/\sqrt{n_j})$. For comparison purposes, we also let $\lambda = 0$ and repeated each simulation. When $\lambda = 0$, the penalty term equals zero and therefore the algorithm does not penalize for dose over-assignment. We simulated trial data according to different scenarios in which the true toxicity probabilities and efficacy probabilities were prespecified. For each scenario, we conducted 1,000 simulated trials.

We used a Gibbs sampler to obtain the posterior samples for the unknown parameters. Sampling from the posterior distributions of the parameters in our model was accomplished using the adaptive rejection Metropolis sampling (ARMS) algorithm (Gilks, Best and Tan, 1995). In implementing this algorithm, we used a burn-in of 1,000 iterations and recorded every fifth sample out of the subsequent 5,000 iterations. Thus, inference was based on these final 1,000 posterior

samples. The Markov chain converged rapidly and mixed well.

5.1 Study one

In this study, for comparison purposes, we adopted 12 scenarios from the YLJ paper with a slight change to their scenario 3. We removed scenario 9 because it was a trivial case in which no dose was either efficacious or toxic. We compared three methods in the simulation. The first method was the approach taken by TC, in which they used a continual ratio model and an equivalence contour based on three equivalent doses elicited by physicians. The second method was the approach taken by YLJ, in which they used the global cross-ratio model and an equivalence contour based on the odds ratio of efficacy and toxicity probabilities. The third method was the algorithm proposed in this paper. For details of the first two methods, refer to Yin, Li, and Ji (2005).

Table 1 summarizes the simulation results. We retained the notation used by YLJ: the criterion used by TC was denoted by δ_j, and the three criteria by YLJ were denoted by $\omega_j^{(2)}$, $\omega_j^{(3)}$, and $\pi_{01}^{(j)}$, respectively, in which $\omega_j^{(2)}$ and $\omega_j^{(3)}$ were the two-dimensional and three-dimensional efficacy and toxicity odds ratios and $\pi_{01}^{(j)}$ was the joint probability of efficacy and no toxicity at dose j. For each scenario, the first row represents the true probabilities (p_j^T, p_j^E) used to generate the trial data, assuming independence between efficacy and toxicity outcomes. The next six rows contain simulation results using these methods: the first four rows are the percentages representing the number of times out of 1,000 simulations each dose is selected as the best dose under the four criteria presented by TC and YLJ, respectively. The numbers in the parentheses represent the average number of patients treated at each dose. The last two rows contain the same results from the proposed method when $\lambda = 0$ and $\lambda = 1$, respectively. The column "None" represents the number of times (in percentages) that no dose is selected, i.e., no dose is acceptable.

Examining Table 1, we make some key observations. First, except for scenario 5, the new method has better operating characteristics than those of YLJ. The new method has a greater chance of selecting the best dose and treating more patients at more desirable doses. Also, the probability of selecting no dose when there is at least one acceptable dose is much smaller under the new method (see scenarios 1 and 8, for example). Second, the operating characteristics are comparable to those of TC. Although our new dose-finding method is better in some scenarios and worse in others, it is, for the scenarios studied, less likely to over-dose patients compared to the TC method. For example, in scenarios 6 through 10, the TC method is more likely to select doses with larger toxicity probability than Q_T. Third, when $\lambda = 0$ resulting in no penalty term in (4), the number of times the best dose is selected (in percentages) is much lower in most scenarios compared to the case when $\lambda = 1$. However, using $\lambda = 0$ allows slightly more patients to be treated at the best dose in many scenarios. We recommend using $\lambda = 1$. That is, by allowing some patients to be treated at what would appear to be non-optimal doses at the time, we learn more about the efficacy and toxicity of each dose and hence are more likely to make the right decision in finding the best dose for future patients.

5.2 Study two

In the second simulation study, we constructed nine scenarios involving five doses in which toxicity does not increase with the dose level. For example, see the trial described by TC where toxicity is a composite event that includes death. Under this condition, if higher level doses are more effective, they may prevent death and thus have lower probabilities of toxicity. We set up three distinct configurations that determined the true toxicity probabilities and efficacy probabilities for all the doses. Specifically, the three configurations for the five toxicity probabilities were $(.05, .10, .25, .15, .10)$, $(.20, .10, .05, .15, .25)$ and $(.10, .11, .12, .11, .10)$; and the three configurations for the efficacy probabilities were $(.52, .62, .72, .82, .92)$, $(.80, .60, .40, .20, .10)$ and

$(.55, .58, .60, .62, .65)$. The combinations of each toxicity and efficacy configuration resulted in nine scenarios. The first toxicity configuration assumes that the probability of toxicity increases and then decreases as the dose level increases; the second assumes that the probability of toxicity decreases first and then increases; and the third assumes that the probability of toxicity remains almost flat as the dose level increases. The three efficacy configurations represent cases in which the dose efficacy increases, decreases, or remains almost unchanged as the dose level increases. Note that in all the nine scenarios, none of the probability of toxicity is above the threshold $Q_T = 0.3$, i.e., all the doses are safe. This is mainly because in practical clinical trials, once a dose is found to be excessively toxic, patients must be treated at lower level doses, regardless of the monotonicity assumption between the probability of toxicity and the dose level. Due to ethical and legal concerns, the PI will never treat patients at a toxic dose or a higher level dose, even if it is assumed that the probability of toxicity does not increase with the dose level. Since study one has already examined the cases in which some doses are excessively toxic, in this study, we are interested in the scenarios in which the monotonicity assumption does not hold and yet the doses are safe.

We simulated 1,000 trials based on the nine scenarios by combining each pair of toxicity and efficacy configurations. We implemented our dose-finding algorithm for each scenario using the same settings given in simulation study one. Both YLJ and TC assume that the probability of toxicity increases with the dose level. We also implemented the TC method for the nine scenarios to compare the operating characteristic of our method (which does not assume monotonicity) relative to those of the TC method (which does assume, a priori, that toxicity increases with dose). Table 2 summarizes the simulation results of the two methods. Our method seems to have a high probability of finding the best dose and treating most patients at that dose in all scenarios. The TC method performs very well in many scenarios where the best dose is the first dose; however, since that method assumes a monotone relationship between the probability of toxicity and the dose level, it performs poorly in scenarios when the best dose is not the first dose.

We recommend using $\lambda = 1$ for our method, because this results in more desirable operating characteristics.

6 Discussion

We have proposed a new dose-finding method for phase I/II clinical trials using a bivariate binary efficacy and toxicity model. Our pMDD criterion is comprehensible for collaborating physicians and is also appealing in its simplicity. It does not require long and potentially difficult elicitation sessions with the principal investigator, which should be particularly appealing to research teams who do not have much experience with such elicitation. The new method uses the global cross-ratio model to account for the correlation in the bivariate response. The prior distributions for the model parameters are simple and vague, thus respecting the trial data in estimating dose efficacy and toxicity probabilities. Although the prior does not obey the usual toxicity monotonicity restriction, we include as part of our dose-assignment rules a criterion for not escalating to a higher dose if the highest tried dose is deemed too toxic; the simulation results from study one have shown that the new method performs very well for simulated trials with such a restriction. In addition, the new method is also applicable for clinical trials in which the probability of toxicity does not increase with the dose level. It is particularly convenient for physicians and statisticians in that nothing extra needs to be done in order to apply the new method to trials with or without the restriction. One can simply implement the proposed dose-finding algorithm and follow the steps until the MDD is located.

We have introduced the idea of penalizing doses at which patients have been over-assigned, and have developed the dose-finding criterion Γ_j for the new algorithm. The simulation results indicate that the method using the penalty performs better than the one without the penalty. In phase I/II trials, there is a trade-off between treating as many patients at the most desirable dose and the probability of selecting the most desirable dose. That is, patients have to be treated

at all the doses so that we can learn which dose is the most desirable. The more patients we treat at every dose, the more precise our estimations of the efficacy and toxicity probabilities, and the more accurate our selection of the most desirable dose. However, it is inevitable that some patients will be treated at inferior doses. For any design, one has to trade off this negative eventuality against the benefit associated with increasing the probability of finding the best dose. For our algorithm, this is realized by carefully choosing the value of λ. We tried several values of λ (0, 1, 2, and 4) and selected the one that yielded the most desirable operating characteristics in the simulations. The value of λ balances the scale of the posterior quantity $E\{(p_j^E - p_j^T)1_{(p_j^E > Q_E)}1_{(p_j^T < Q_T)}|\mathcal{X}\}$ and the penalty term. It is essentially a tuning parameter similar to the one used in other methods, such as the one in the penalized spline.

The parameter value for τ is set at 0.5. Therefore, the penalty in (4) is proportional to the square root of the inverse dose sample size n_j. This penalty has a much larger impact when n_j is relatively small than when it is large. Therefore, the penalty only has a significant impact at the beginning of the trial. This criterion seems reasonable because at the beginning of the trial, each dose is tried with only a few patients and by chance, the trial data may not truly reflect the real toxicity and efficacy of the doses. By using the penalty to force the assignment of patients to different doses, more accurate estimates can be obtained, leading to better dose-assignment decisions. As the number of patients treated at each dose gets larger and the toxicity and efficacy probabilities are more closely estimated, the penalty has less impact on dose assignment, and will thus allow a larger number of patients to be treated at the best dose.

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Table 1: Simulation results when probability of toxicity increases with dose level. The percentage of selection and the average number of patients treated (in parentheses) are presented.

	Selection percentage of dose (# of patients)					
	1	2	3	4	5	None
Scenario 1	(15, 55)	(25, 58)	(35, 60)	(45, 62)	(55, 65)	
δ_j	**51.7** (28.5)	34.9 (20.3)	6.7 (5.5)	1.0 (1.2)	0 (.2)	5.7
$\omega_j^{(2)}$	**57.4** (30.1)	22.1 (13.5)	6.4 (6.0)	1.4 (2.6)	.1 (1.1)	12.6
$\omega_j^{(3)}$	**54.1** (28.5)	25.4 (15.0)	6.4 (6.2)	1.2 (2.7)	.2 (1.0)	12.7
$\pi_{01}^{(j)}$	**53.7** (28.7)	23.4 (14.4)	8.2 (7.0)	2.4 (2.8)	.3 (1.0)	12.0
$\lambda = 0$	**63.6** (30.5)	25.8 (15.8)	6.8 (7.9)	1.0 (3.2)	0.3 (1.5)	1.8
$\lambda = 1$	**63.9** (27.0)	24.2 (15.5)	7.4 (8.9)	1.9 (5.1)	0.5 (2.5)	1.7
Scenario 2	(1, 52)	(1.5, 61)	(2, 71)	(2.5, 82)	(3, 90)	
δ_j	22.1 (16.4)	4.2 (8.9)	5.3 (7.0)	29.6 (17.3)	**38.8** (10.5)	0
$\omega_j^{(2)}$	21.8 (11.5)	11.5 (8.4)	11.5 (8.8)	17.4 (11.9)	**37.5** (19.2)	.3
$\omega_j^{(3)}$	5.8 (6.1)	7.3 (6.8)	12.1 (9.1)	25.1 (14.5)	**49.3** (23.2)	.4
$\pi_{01}^{(j)}$	1.2 (4.4)	1.9 (5.5)	9.5 (8.6)	29.6 (16.8)	**57.8** (24.8)	0
$\lambda = 0$	0.9 (4.1)	4.5 (5.9)	11.2 (8.8)	27.6 (15.3)	**55.8** (25.8)	0
$\lambda = 1$	0.5 (5.5)	1.8 (6.8)	7.7 (9.7)	24.7 (14.3)	**65.3** (23.8)	0
Scenario 3	(10, 10)	(20, 20)	(30, 30)	(40, 40)	(50, 50)	
δ_j	2.7 (7.7)	18.1 (10.6)	**17.6** (10.5)	4.9 (5.7)	.1 (1.4)	56.6
$\omega_j^{(2)}$	3.1 (8.6)	12.8 (9.7)	**11.1** (7.5)	2.1 (2.7)	.2 (1.0)	70.7
$\omega_j^{(3)}$	3.3 (8.3)	14.9 (10.5)	**8.8** (6.9)	2.0 (2.9)	.1 (1.0)	70.9
$\pi_{01}^{(j)}$	4.2 (8.4)	12.9 (9.6)	**10.9** (7.8)	3.9 (3.9)	.1 (1.3)	68.0
$\lambda = 0$	7.0 (8.1)	16.0 (12.8)	**24.0** (14.3)	16.0 (9.4)	2.0 (4.6)	35.0
$\lambda = 1$	5.2 (9.1)	17.2 (12.6)	**23.8** (13.1)	16.0 (9.3)	2.9 (4.7)	34.9
Scenario 4	(1, 5)	(2, 20)	(3, 35)	(4, 60)	(5, 80)	
δ_j	0 (3.4)	0 (3.0)	.2 (3.4)	4.6 (9.4)	**95.2** (40.8)	0
$\omega_j^{(2)}$	0 (3.1)	1.3 (4.2)	6.3 (6.6)	28.0 (16.0)	**61.5** (28.5)	2.9
$\omega_j^{(3)}$	0 (3.1)	.5 (3.7)	5.3 (5.6)	26.4 (14.8)	**65.1** (31.3)	2.7
$\pi_{01}^{(j)}$	0 (3.1)	.3 (3.3)	1.6 (4.4)	17.1 (12.5)	**79.1** (35.7)	1.9
$\lambda = 0$	0 (3.0)	0.1 (3.4)	2.4 (5.0)	21.5 (13.1)	**75.7** (35.4)	0.2
$\lambda = 1$	0 (3.2)	0 (3.9)	0.5 (5.0)	12.4 (12.0)	**86.9** (35.8)	0

Table 1 (*continued*)

	Selection percentage of dose (# of patients)					
	1	2	3	4	5	None
Scenario 5	(30, 5)	(40, 20)	(50, 35)	(60, 50)	(70, 60)	
δ_j	.5 (3.6)	6.0 (5.1)	.4 (3.2)	.1 (1.2)	.1 (.3)	**92.9**
$\omega_j^{(2)}$	0 (3.8)	.4 (2.6)	0 (1.4)	0 (.3)	0 (.1)	**99.6**
$\omega_j^{(3)}$	.3 (3.8)	1.0 (3.2)	.1 (1.7)	0 (.4)	0 (.0)	**98.6**
$\pi_{01}^{(j)}$	0 (4.0)	.8 (3.3)	.1 (1.6)	0 (.4)	0 (.1)	**99.1**
$\lambda = 0$	1.9 (5.3)	4.1 (9.1)	3.8 (5.8)	0.2 (2.2)	0.1 (0.6)	**90.0**
$\lambda = 1$	2.1 (5.8)	5.3 (9.2)	3.7 (6.1)	0.6 (2.3)	0 (0.6)	**88.3**
Scenario 6	(1, 20)	(3, 40)	(4, 60)	(5, 70)	(35, 75)	
δ_j	1.6 (5.7)	.7 (3.8)	2.2 (5.8)	**82.8** (36.0)	12.6 (8.7)	.1
$\omega_j^{(2)}$	4.8 (6.4)	15.2 (10.4)	35.1 (17.2)	**38.5** (18.2)	4.3 (6.6)	2.1
$\omega_j^{(3)}$	2.0 (4.4)	11.6 (8.3)	32.3 (16.4)	**42.9** (20.8)	9.0 (8.8)	2.2
$\pi_{01}^{(j)}$	.5 (3.6)	5.6 (6.4)	30.0 (16.8)	**53.4** (23.3)	9.1 (9.2)	1.4
$\lambda = 0$	2.9 (5.8)	11.1 (9.0)	27.1 (14.8)	**54.9** (24.5)	3.0 (5.8)	0
$\lambda = 1$	0.1 (4.4)	2.8 (7.0)	27.2 (15.8)	**66.7** (26.4)	2.1 (6.3)	0
Scenario 7	(2, 60)	(4, 62)	(6, 64)	(25, 66)	(35, 68)	
δ_j	**41.0** (24.5)	**16.8** (14.0)	**29.9** (14.0)	11.9 (7.2)	.4 (.4)	0
$\omega_j^{(2)}$	**60.5** (28.8)	**24.6** (14.2)	**11.1** (8.3)	2.6 (5.0)	1.0 (3.5)	.2
$\omega_j^{(3)}$	**45.1** (21.9)	**25.8** (14.3)	**20.5** (12.5)	6.4 (6.8)	1.6 (4.2)	.6
$\pi_{01}^{(j)}$	**31.7** (18.0)	**28.1** (15.1)	**26.8** (14.4)	9.5 (7.7)	3.5 (4.6)	.4
$\lambda = 0$	**34.7** (18.2)	**33.2** (17.3)	**28.9** (15.8)	3.0 (5.5)	0.1 (3.2)	0
$\lambda = 1$	**30.9** (16.1)	**32.6** (16.4)	**33.2** (16.3)	2.4 (6.7)	0.8 (4.5)	0
Scenario 8	(8, 15)	(10, 35)	(12, 52)	(45, 65)	(55, 70)	
δ_j	.6 (5.2)	5.8 (5.9)	**72.4** (30.7)	17.6 (15.4)	0.1 (0.9)	3.5
$\omega_j^{(2)}$	2.8 (6.7)	24.9 (13.4)	**47.8** (21.8)	4.5 (6.0)	0.3 (2.0)	19.7
$\omega_j^{(3)}$	1.8 (5.5)	25.5 (13.6)	**50.4** (22.9)	3.6 (6.6)	0.4 (2.0)	18.3
$\pi_{01}^{(j)}$	1.3 (4.9)	19.8 (11.5)	**56.0** (24.9)	5.0 (7.1)	0.6 (2.4)	17.3
$\lambda = 0$	1.2 (5.0)	22.1 (14.2)	**71.0** (31.0)	2.4 (6.1)	0.7 (2.6)	2.6
$\lambda = 1$	1.1 (7.1)	19.0 (13.4)	**73.2** (26.8)	3.7 (7.9)	0.8 (3.9)	2.2

Table 1 (*continued*)

	Selection percentage of dose (# of patients)					
	1	2	3	4	5	None
Scenario 9	(5, 40)	(15, 60)	(40, 50)	(60, 40)	(80, 30)	
δ_j	22.7 (15.7)	**68.9** (34.0)	4.5 (7.6)	.1 (.8)	0 (0)	3.8
$\omega_j^{(2)}$	43.6 (24.8)	**48.6** (25.0)	1.3 (4.6)	0 (1.8)	0 (.5)	6.5
$\omega_j^{(3)}$	38.1 (21.6)	**52.6** (27.2)	2.5 (5.4)	0 (1.9)	0 (.5)	6.8
$\pi_{01}^{(j)}$	28.3 (18.2)	**62.3** (30.2)	1.9 (5.3)	.3 (2.0)	0 (.5)	7.2
$\lambda = 0$	35.2 (21.4)	**62.9** (30.7)	1.7 (5.1)	0 (2.1)	0 (0.6)	0.2
$\lambda = 1$	29.2 (18.6)	**69.6** (30.3)	0.8 (6.9)	0 (3.1)	0 (0.8)	0.4
Scenario 10	(1, 10)	(5, 30)	(10, 50)	(40, 80)	(50, 60)	
δ_j	.1 (3.7)	.6 (3.7)	**65.2** (28.3)	33.0 (23.3)	0 (.4)	1.1
$\omega_j^{(2)}$	1.2 (4.8)	28.1 (15.6)	**47.4** (21.7)	14.2 (12.0)	.1 (2.4)	9.0
$\omega_j^{(3)}$	1.0 (4.2)	22.5 (12.4)	**52.9** (23.5)	14.0 (13.5)	.1 (2.7)	9.5
$\pi_{01}^{(j)}$	0.5 (4.1)	16.5 (10.9)	**54.3** (23.8)	17.9 (14.6)	.4 (2.6)	10.4
$\lambda = 0$	0.8 (4.4)	18.5 (12.8)	**68.0** (28.4)	9.8 (10.8)	1.0 (2.9)	0
$\lambda = 1$	0.1 (6.3)	14.2 (11.4)	**72.9** (26.3)	11.1 (11.3)	0.9 (4.4)	0
Scenario 11	(1.3, 58.9)	(1.5, 66.0)	(1.7, 72.4)	(2, 78.0)	(3.5, 92.2)	
δ_j	25.9 (17.7)	8.1 (11.3)	6.7 (8.4)	24.7 (13.6)	**34.6** (9.0)	0
$\omega_j^{(2)}$	23.8 (12.8)	11.4 (8.9)	9.3 (7.9)	8.3 (8.2)	**46.8** (22.0)	.4
$\omega_j^{(3)}$	10.4 (7.9)	9.6 (8.3)	9.7 (8.5)	15.2 (10.4)	**54.3** (24.4)	.8
$\pi_{01}^{(j)}$	2.3 (5.2)	4.6 (6.6)	8.1 (8.2)	14.5 (10.7)	**70.4** (29.2)	.1
$\lambda = 0$	3.0 (5.0)	5.7 (6.4)	10.6 (8.8)	19.6 (11.7)	**61.2** (28.2)	0
$\lambda = 1$	0.8 (6.0)	3.0 (7.6)	8.6 (9.5)	15.6 (12.2)	**72.1** (24.8)	0
Scenario 12	(2.6, 9.8)	(4.1, 29.7)	(6.4, 53.1)	(9.9, 67.9)	(41.8, 40.2)	
δ_j	.1 (4.0)	.7 (3.4)	6.3 (7.0)	**88.3** (39.8)	2.8 (5.0)	1.8
$\omega_j^{(2)}$	.4 (4.0)	11.3 (9.0)	35.6 (18.1)	**47.0** (22.7)	.3 (3.2)	5.4
$\omega_j^{(3)}$	.1 (3.6)	7.5 (6.9)	33.2 (17.3)	**52.8** (25.5)	.4 (3.5)	6.0
$\pi_{01}^{(j)}$	0.1 (3.3)	4.4 (6.2)	29.0 (16.9)	**61.3** (27.6)	0.4 (3.3)	4.8
$\lambda = 0$	0 (3.3)	4.3 (6.0)	35.1 (19.1)	**60.0** (28.0)	0.1 (3.3)	0.5
$\lambda = 1$	0 (4.3)	2.1 (6.8)	28.1 (17.1)	**69.3** (27.1)	0. (4.3)	0.4

Table 2: Simulation results when probability of toxicity does not increase with dose level. The percentage of selection and the average number of patients treated (in parentheses) are presented.

	Selection percentage of dose (# of patients)					
	1	2	3	4	5	None
Scenario 1	(5, 52)	(10, 62)	(25, 72)	(15, 80)	(10, 85)	
δ_j	24.4 (18.3)	28.0 (15.6)	20.1 (12.5)	14.4 (8.3)	**13.1** (5.2)	0
$\lambda = 0$	17.2 (11.9)	19.1 (12.6)	4.1 (5.9)	19.8 (11.6)	**39.6** (18.0)	0.2
$\lambda = 1$	11.8 (11.1)	17.2 (12.6)	3.6 (7.1)	17.4 (10.7)	**50.1** (18.5)	0
Scenario 2	(5, 55)	(10, 58)	(25, 60)	(15, 62)	(10, 65)	
δ_j	**40.1** (25.2)	23.7 (13.6)	12.9 (9.0)	7.5 (5.3)	15.8 (6.8)	0
$\lambda = 0$	**31.5** (17.3)	24.6 (14.7)	5.2 (6.4)	14.3 (9.1)	24.3 (12.5)	0.1
$\lambda = 1$	**32.3** (17.3)	23.5 (13.9)	3.7 (6.8)	13.8 (9.4)	26.4 (12.5)	0.2
Scenario 3	(5, 80)	(10, 60)	(25, 40)	(15, 20)	(10, 10)	
δ_j	**93.4** (53.5)	6.0 (4.9)	0.6 (1.2)	0 (0.3)	0 (0.1)	0
$\lambda = 0$	**82.0** (39.4)	17.5 (12.0)	0.5 (3.6)	0 (2.6)	0 (2.3)	0
$\lambda = 1$	**91.3** (39.2)	8.5 (11.0)	0.1 (4.1)	0 (3.1)	0 (2.6)	0.1
Scenario 4	(20, 52)	(10, 62)	(5, 72)	(15, 80)	(25, 85)	
δ_j	15.6 (14.1)	5 (6.1)	**13.4** (8.8)	37.9 (17.4)	28.1 (13.5)	0
$\lambda = 0$	4.6 (6.3)	13.2 (9.4)	**44.4** (20.8)	26.2 (13.9)	8.3 (7.8)	2.6
$\lambda = 1$	1.2 (6.2)	10.9 (9.8)	**47.5** (19.4)	28.1 (14.6)	8.5 (7.9)	2.9

Table 2 (*continued*)

	Selection percentage of dose (# of patients)					
	1	2	3	4	5	None
Scenario 5	(20, 55)	(10, 58)	(5, 60)	(15, 62)	(25, 65)	
δ_j	27.7 (19.7)	11.4 (8.8)	**12.0** (7.3)	23.1 (11.3)	25.8 (12.9)	0
$\lambda = 0$	8.1 (8.4)	26.9 (14.7)	**36.3** (17.0)	18.4 (11.3)	6.7 (6.8)	3.1
$\lambda = 1$	5.2 (8.7)	23.7 (12.8)	**43.6** (18.2)	17.9 (10.8)	5.5 (7.3)	3.4
Scenario 6	(20, 80)	(10, 60)	(5, 40)	(15, 20)	(25, 10)	
δ_j	**84.4** (48.0)	15.0 (9.5)	0.5 (1.6)	0 (0.6)	0 (0.3)	0.1
$\lambda = 0$	**46.4** (24.2)	38.3 (19.1)	11.4 (8.9)	0.1 (3.4)	0 (2.7)	3.0
$\lambda = 1$	**45.4** (22.0)	42.5 (19.2)	8.9 (9.4)	0.1 (4.5)	0 (3.4)	2.9
Scenario 7	(10, 52)	(11, 62)	(12, 72)	(11, 80)	(10, 85)	
δ_j	24.4 (18.0)	6.7 (7.4)	12.5 (8.8)	21.5 (12.1)	**34.9** (13.8)	0
$\lambda = 0$	8.4 (7.9)	9.4 (8.5)	15.5 (10.0)	27.2 (14.5)	**38.9** (18.9)	0.6
$\lambda = 1$	3.2 (7.3)	7.7 (8.9)	13.9 (10.4)	29.2 (14.6)	**45.2** (18.4)	0.6
Scenario 8	(10, 55)	(11, 58)	(12, 60)	(11, 62)	(10, 65)	
δ_j	36.3 (23.8)	11.4 (8.7)	9.9 (7.2)	13.8 (7.9)	**28.6** (12.3)	0
$\lambda = 0$	17.4 (12.1)	18.7 (11.7)	17.2 (10.8)	20.0 (11.6)	**26.0** (13.4)	0.5
$\lambda = 1$	15.5 (11.9)	16.9 (11.7)	16.9 (11.2)	21.4 (11.7)	**29.2** (13.2)	0.1
Scenario 9	(10, 80)	(11, 60)	(12, 40)	(11, 20)	(10, 10)	
δ_j	**94.9** (53.8)	4.9 (4.4)	0.1 (1.2)	0 (0.4)	0 (0.2)	0.1
$\lambda = 0$	**73.8** (34.5)	21.9 (13.4)	3.7 (5.9)	0.1 (3.2)	0 (2.8)	0.5
$\lambda = 1$	**85.3** (35.0)	13.8 (12.3)	0.7 (5.7)	0 (3.8)	0 (3.3)	0.1

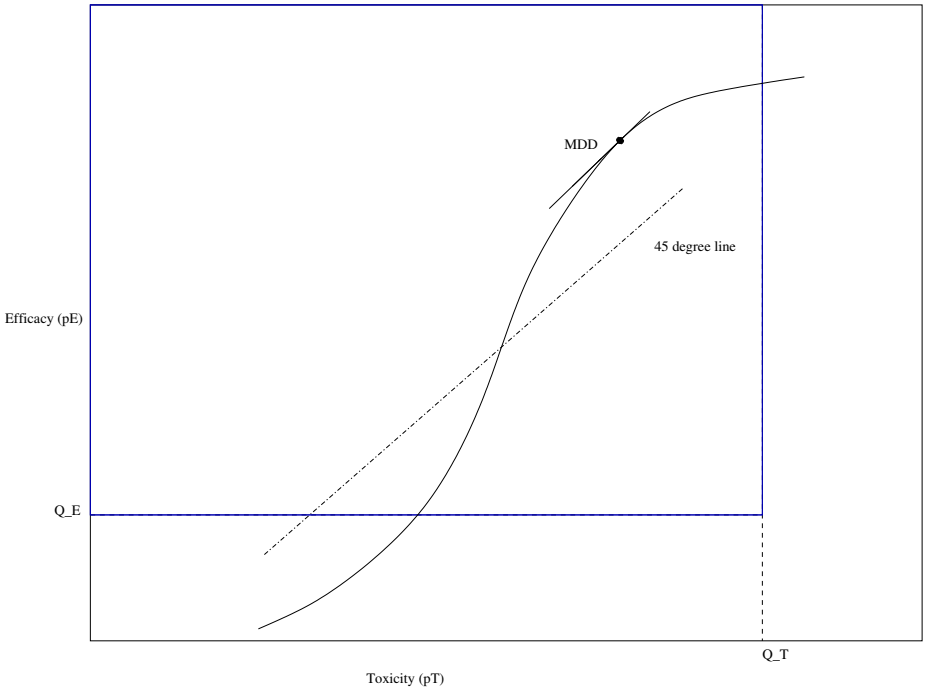

Figure 1: A graphical display of the location of the MDD.