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A Study of the Probit Model with Latent Variables in Phase I Clinical Trials

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SUMMARY

Maximum tolerated dose (MTD) finding is an important problem in Phase I & II clinical trials. Based on the continual reassessment method (CRM) that is used to find MTD, a new dose-escalation strategy is presented. The suggested strategy relies on a probit model. By introducing latent variables, Markov chain Monte Carlo (MCMC) methods are employed to estimate the model parameters. Compared with the widely used CRM in simulation studies, the new dose-escalation strategy is superior to or at least as good as the original dose-escalation strategy used in CRM for most of the considered scenarios.

KEY WORDS: phase I clinical trial; dose finding; continual reassessment method (CRM); probit model; latent variable; Markov chain Monte Carlo (MCMC)

JEL Classification: C11, C13, C15

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1 Introduction

The primary goal of a phase I clinical trial is to determine the dose of a candidate drug for use in the subsequent phase II trial. This is traditionally achieved by exposing patients to dose levels that adaptively selected based on cumulative toxicity measurements. The most widely used approaches in phase I clinical trial, such as "3+3" design and CRM, classify safety events into two categories: dose-limiting toxicity (DLT) and non-DLT, with the aim of finding the dose with probability of DLT closed to a target probability, usually 25 to 30 percent. More precisely, the goal is to find the maximum tolerated dose (MTD), defined as the dose for which the probability of DLT is equal to a specified value θ:

$$\Pr\{\text{DLT}|\text{Dose} = \text{MTD}\} = \theta, \tag{1}$$

where θ is set relatively high when DLT is a non-fatal condition, and low when it is life threatening.

There are two different philosophies in MTD definition. The first treats the risk of toxicity as a sample statistic identified by the doses studied, and hence defines the MTD as a statistic computed from the data. In this situation, the MTD is identified, rather than estimated. The second treats the risk of toxicity as a parameter of a dose-response model and hence defines the MTD as a parameter or a function of the parameter(s) of a monotonic dose-response curve, and thus it is estimated. Implementing the different definitions of MTD, phase I trial designs can be divided into two divergent categories: rule-based design and model-based design, which result in different dose escalating strategies.

From rule-based design to model-based design, various designs for phase I clinical trials have been discussed in the literature. In practice, the rule-based designs, which only need a dose-escalation rule with no complicated statistical modeling, still dominate in phase I trials since they are simple to understand, easy to implement, and the decision rule is intuitive and does not involve complicated calculations. However, the poor operating characteristics of the traditional design has been criticized recently (see [2, 3, 5, 7, 8, 9, 11, 13]). The major criticism of the standard design is that it has no intrinsic property producing accurate estimates of a target quantile and many patients are treated at low, possibly ineffective dose levels when the initial dose level falls far below the true MTD.

Despite the wide use of rule-based schemes in applications, model-based clinical trial

designs have drawn much attention from the biostatistical community since 1990 when O'Quigley *et al.* [9] proposed the Continual Reassessment Method (CRM), which is most prominent among all model-based approaches. Denoted by Y the toxic response for a patient at dose level x, then Y is a binary random variable, taking value 1 when DLT is observed, 0 otherwise. O'Quigley *et al.* [9] proposed a simple dose-response function, $\psi(x, a)$, such that

$$\Pr\{\text{DLT}|\text{Dose} = x\} = E(Y = 1|x, a) = \psi(x, a),$$

where a is(are) the parameter(s) which will be modified sequentially according to the accrued data under the Bayesian framework and $\psi(x, a)$ is monotone in both x and a. They also assume that the model is rich enough so that for any dose, say $\tilde{x}$, and the target probability of DLT, say $\tilde{\theta}$, there exists a unique parameter, say $\tilde{a}$, such that $\psi(\tilde{x}, \tilde{a}) = \tilde{\theta}$. Suppose that the parameter a has a prior $\pi(a)$. One can find the posterior of a, $\pi(a|\text{Data})$, according to the accumulated information on the first $j-1$ patients. Next, O'Quigley gave two estimates of the probability of toxic response at dose level x, denoted by θ_{xj} where

$$\theta_{xj} = E^{\pi(a|\text{Data})}[\psi(x, a)], \text{ or } \theta'_{xj} = \psi(x, \hat{a}),$$

where $\hat{a} = E^{\pi(a|\text{Data})}(a)$. Finally, let $\Delta(v, w)$ denote a measure of distance between v and w, for example $\Delta(v, w) = (v - w)^2$. Then for the jth entered patient in the trial, one chooses dose level x_j^* such that $\Delta(\theta_{xj}, \theta)$, $\Delta(\theta'_{xj}, \theta)$ or $\Delta(x, \psi^{-1}_{a=\hat{a}}(\theta))$ is minimized. After n patients, the estimate of the MTD is taken to be x^*_{n+1}. It has been shown that x^*_{n+1} converges to the unknown MTD.

In the mid-1990s, several variants of the CRM (see [3, 5, 7]) were proposed, addressing some of the safety concerns raised regarding O'Quigley *et al.*'s [9] original design. Although the dose escalation strategies are different from each other, all these modified CRMs are based on the dose-response function, $\psi(x, a)$, including the original CRM. The most frequently used one-parameter $\psi(x, a)$ are:

$$\psi(x, a) = \{(\tanh(x) + 1)/2\}^a; \tag{2}$$

$$\psi(x, a) = p_x^a, \quad \text{where } 0 < p_x < 1 \text{ and increasing in } x; \tag{3}$$

$$\psi(x, a) = \exp\{c + ax\}/(1 + \exp\{c + ax\}), \quad \text{where } c \text{ is a constant.} \tag{4}$$

Dose-response function (2) used in the original CRM is a special case of (3), which is com-

monly called power model [10].

One-parameter dose-response model performs, in general, remarkably well and there has been no hesitation in recommending its use. However O'Quigley *et al.* [9] still warned that its lack of flexibility has proven to be something of a handicap in trying to find a good fit to data. Two-parameter logistic models are introduced and well discussed for dose-finding in Phase I clinical trials recently (see [4, 14, 15]). Shu and O'Quigley [12] argued that, for two-parameter model, the parameter estimates are inconsistent and no statistical properties appear to have been studied. Despite the argument, two-parameter model, stemming from its greater flexibility, is welcomed in practice since it provides a good fit to data for the large sample size.

But in phase I clinical trial, the sample size n is relatively small. Usually, n takes value from 20 to 40. The accuracy of the parameters estimation for the two-parameter model is questionable for small sample size. From a non-Bayesian viewpoints, Griffiths *et al.* [6] pointed out that the MLE of the parameter has significant bias for small samples. From a Bayesian approach, Zellner *et al.* [16] also commented on the inaccuracy of the approximation for small n. Hence, stemming from its greater flexibility, using two-parameter model in dose-finding clinical trials is criticized for having been the greater rapidity with which it changes dose levels early in the experiment.

Albert and Chib [1] propose a Bayesian computational method which allows one to perform exact inference for binary regression models and is preferable to ML methods for small samples. The general approach can be summarized as follows. The probit regression model for binary outcomes is seen to have an underlying normal regression structure on latent continuous data. Values of the latent data can be simulated from suitable truncated normal distributions. If the latent data are known, then the posterior distribution of the parameters can be computed using standard results for normal linear models. Draws from this posterior are used to sample new latent data, and the process is iterated with Gibbs sampling.

In this research, we propose a two-parameter probit model with latent variables to extend the CRM for the cases of dichotomous toxicity responses. In next section, we introduce the probit model with latent variables and the full conditional distributions are given. The dose allocation rule will be discussed in Section 3. In Section 4, a simulation study exploring operating characteristics of this escalation strategy is presented. Finally, in Section 5, a brief

discussion is provided and we also draw some conclusions.

2 Probit Model with Latent Variables

In this section, Albert and Chib's method [1] will be modified since there is a positive constraint on the slope parameter which will lead to the probability of toxic response increasing monotonically in dosage x. In Section 2.1, the probit model with latent variable is introduced and the MTD is obtained analytically. In Section 2.2, The full conditional distributions of the parameters and the latent variables are given, which will serve as the base in the Gibbs sampling method (See Gelfand & Smith, 1990).

2.1 The Model

Denoted by $Y = 1$ a severe toxic response (or dose limiting toxicity, DLT) at dosage x and by $Y = 0$ a nontoxic response at dosage x. Assume that, at dosage x, there exists an underlying normal latent variable

$$Z|x \sim N(\beta_0 + \beta_1 x, \sigma^2), \tag{5}$$

where $\beta_1 > 0$, such that,

$$Y = \begin{cases} 1 & \text{if } Z > 0, \\ 0 & \text{if } Z \leq 0. \end{cases} \tag{6}$$

Then,

$$\begin{aligned} P(Y = 1|x) = P(Z > 0|x) &= \Phi\left(\frac{\beta_0 + \beta_1 x}{\sigma}\right) \\ &= \Phi(\beta_0^* + \beta_1^* x), \end{aligned} \tag{7}$$

where $\Phi(t)$ is the cumulative density function of the standard normal random variable, $\beta_0^* = \beta_0/\sigma$ and $\beta_1^* = \beta_1/\sigma$. Define $Z^* = Z/\sigma$, then $Z^*|x \sim N(\beta_0^* + \beta_1^* x, 1)$. Since $Z > 0$ if and only if $Z^* > 0$, one can simply assume that $Z|x \sim N(\beta_0 + \beta_1 x, 1)$ without loss of generality and hence

$$P(Y = 1|x) = \Phi(\beta_0 + \beta_1 x), \tag{8}$$

which is a probit model. Essentially, by introducing the normal latent variable, we assume that the dose-response follows a probit model. According to the MTD definition (1) and the dose-response model (8), the MTD can be determined, analytically, as

$$\text{MTD} = \frac{\beta_0 - \Phi^{-1}(\theta)}{\beta_1}. \tag{9}$$

2.2 The Full Conditional Distributions

Denote by $\mathscr{F}_j = \{(x_1, y_1), \ldots, (x_j, y_j)\}$ the history of the first j dose assignments and toxicity responses, where y_l is the observed toxicity response taking value either 0 for non-DLT or 1 for DLT and $x_l \in \mathbb{X}$ (the set of all doses for the drug under investigation, usually, $\mathbb{X} = \{d_1, \ldots, d_K\}$), $l = 1, \ldots, j$. Since the sample size is relatively small in phase I clinical trials, we fit the probit model (8) by introducing the normal latent variables. Assume that $Z_1, Z_2, \ldots, Z_j$ are j independent latent variables, where $Z_l \sim N(\beta_0 + \beta_1 x_l, 1)$, such that,

$$Y_l = \begin{cases} 1 & \text{if } Z_l > 0, \\ 0 & \text{if } Z_l \leq 0, \end{cases} \qquad \text{for } l = 1, \ldots, j,$$

where x_l is the dose level at which the lth patient is assigned (that is $x_l \in \{d_1, \ldots, d_K\}$). Then, the toxicity probability at dose level x_l is

$$P(Y_l = 1|x_l) = P(Z_l > 0|x_l) = \Phi(\beta_0 + \beta_1 x_l),$$

where $\beta_1 > 0$ is a constraint since the toxicity probability is increasing as the dose level increases.

Accruing data up to $\mathscr{F}_j = \{(x_1, y_1), \ldots, (x_j, y_j)\}$, the joint posterior density of the parameters (β_0, β_1) and unobserved latent variables $\mathbf{Z} = (Z_1, Z_2, \ldots, Z_j)$ is given by

$$\begin{aligned} &\pi(\beta_0, \beta_1, \mathbf{Z}|\mathscr{F}_j) \\ \propto\ &\pi(\beta_0, \beta_1) \prod_{l=1}^{j} [I(Z_l > 0)I(y_l = 1) + I(Z_l \leq 0)I(y_l = 0)]\phi(Z_l; \beta_0 + \beta_1 x_l, 1), \end{aligned} \tag{10}$$

where $\phi(t; \mu, \sigma^2)$ is the probability density function of $N(\mu, \sigma^2)$ and $I(A)$ is the indicator function, taking value 1 if A is true and 0 otherwise.

Note that this joint posterior distribution is intractable in the sense that it is difficult to normalize and to sample from directly. However, the computation of the marginal posterior distribution of (β_0, β_1) using the Gibbs sampling algorithm requires only the posterior distribution of β_0 conditional on $(\beta_1, \mathbf{Z})$, the posterior distribution of β_1 conditional on $(\beta_0, \mathbf{Z})$ and the posterior distribution of $\mathbf{Z}$ conditional on (β_0, β_1), and these full conditional posterior distributions are easy to obtained and easy to sample from as shown follows.

Based on (10), the full conditional posterior distributions can be calculated and are given by the following formulas.

- $\pi(\beta_0|\beta_1, \mathbf{Z}, \mathscr{F}_j)$

Denoted by $\pi(\beta_0)$ the prior density of β_0. Regardless of the proportion constant, the posterior density of β_0 is given as

$$\begin{aligned}\pi(\beta_0|\beta_1, \mathbf{Z}, \mathscr{F}_j) &\propto \pi(\beta_0) \prod_{l=1}^{j} \phi(Z_l; \beta_0 + \beta_1 x_l, 1) \propto \pi(\beta_0) \exp\{-\sum_{l=1}^{j} (Z_l - \beta_0 - \beta_1 x_l)^2/2\} \\ &\propto \pi(\beta_0) \exp\left\{ -\frac{1}{2} \frac{\left(\beta_0 - \sum_{l=1}^{j}(z_l - \beta_1 x_l)/j\right)^2}{1/j} \right\}.\end{aligned}$$

If a flat prior $\pi(\beta_0) \propto 1$ is assigned, then,

$$\pi(\beta_0|\beta_1, \mathbf{Z}, \mathscr{F}_j) \propto \exp\left\{ -\frac{1}{2} \frac{\left(\beta_0 - \sum_{l=1}^{j}(z_l - \beta_1 x_l)/j\right)^2}{1/j} \right\},$$

which implies that

$$\beta_0|\beta_1, \mathbf{Z}, \mathscr{F}_j \sim N\left(\frac{\sum_{l=1}^{j}(z_l - \beta_1 x_l)}{j}, \frac{1}{j} \right). \tag{11}$$

If a proper conjugate prior $N(\bar{\beta}_0, \bar{\sigma}_0^2)$ is assigned, then,

$$\beta_0|\beta_1, \mathbf{Z}, \mathscr{F}_j \sim N\left(\frac{\bar{\sigma}_0^2 \sum_{l=1}^{j}(z_l - \beta_1 x_l) + \bar{\beta}_0}{1 + \bar{\sigma}_0^2 j}, \frac{\bar{\sigma}_0^2}{1 + \bar{\sigma}_0^2 j} \right). \tag{12}$$

- $\pi(\beta_1|\beta_0, \mathbf{Z}, \mathscr{F}_j)$

Denoted by $\pi(\beta_1)$ the prior density of β_1. Regardless of the proportion constant, the posterior density of β_1 is given as

$$\pi(\beta_1|\beta_0, \mathbf{Z}, \mathscr{F}_j) \propto \pi(\beta_1) \prod_{l=1}^{j} \phi(Z_l; \beta_0 + \beta_1 x_l, 1) \propto \pi(\beta_1) \exp\{-\sum_{l=1}^{j} (Z_l - \beta_0 - \beta_1 x_l)^2/2\}$$
$$\propto \pi(\beta_1) \exp\left\{ -\frac{1}{2} \frac{\left(\beta_1 - \sum_{l=1}^{j}(z_l - \beta_0)x_l / \sum_{l=1}^{j} x_l^2\right)^2}{1/\sum_{l=1}^{j} x_l^2} \right\}.$$

If a flat prior $\pi(\beta_1) \propto I(\beta_1 > 0)$ is assigned, then,

$$\beta_1|\beta_0, \mathbf{Z}, \mathscr{F}_j \sim N\left(\frac{\sum_{l=1}^{j}(z_l - \beta_0)x_l}{\sum_{l=1}^{j} x_l^2}, \frac{1}{\sum_{l=1}^{j} x_l^2} \right) I(\beta_1 > 0), \tag{13}$$

which is a left truncated normal random variable.

If a proper conjugate truncated normal prior $N(\bar{\beta}_1, \bar{\sigma}_1^2)I(\beta_1 > 0)$ is assigned, then,

$$\beta_1|\beta_0, \mathbf{Z}, \mathscr{F}_j \sim N\left(\frac{\bar{\sigma}_1^2 \sum_{l=1}^{j}(z_l - \beta_0)x_l + \bar{\beta}_1}{1 + \bar{\sigma}_1^2 \sum_{l=1}^{j} x_l^2}, \frac{\bar{\sigma}_1^2}{1 + \bar{\sigma}_1^2 \sum_{l=1}^{j} x_l^2} \right) I(\beta_1 > 0), \tag{14}$$

which is also a left truncated normal random variable.

If a proper, but non-conjugate exponential prior $\exp\{-\beta_1\}I(\beta_1 > 0)$ is assigned, then,

$$\pi(\beta_1|\beta_0, \mathbf{Z}, \mathscr{F}_j) \propto \exp\{-\beta_1\} \exp\left\{ -\frac{1}{2} \frac{\left(\beta_1 - \sum_{l=1}^{j}(z_l - \beta_0)x_l / \sum_{l=1}^{j} x_l^2\right)^2}{1/\sum_{l=1}^{j} x_l^2} \right\} I(\beta_1 > 0)$$
$$\propto \exp\left\{ -\frac{1}{2} \frac{\left(\beta_1 - \left[\sum_{l=1}^{j}(z_l - \beta_0)x_l - 1\right] / \sum_{l=1}^{j} x_l^2\right)^2}{1/\sum_{l=1}^{j} x_l^2} \right\} I(\beta_1 > 0),$$

which implies that $\beta_1|\beta_0, \mathbf{Z}, \mathscr{F}_j$ is left truncated normal distributed, i.e.,

$$\beta_1|\beta_0, \mathbf{Z}, \mathscr{F}_j \sim N\left(\frac{\sum_{l=1}^{j}(z_l - \beta_0)x_l - 1}{\sum_{l=1}^{j} x_l^2}, \frac{1}{\sum_{l=1}^{j} x_l^2} \right) I(\beta_1 > 0). \tag{15}$$

- $\pi(Z_l|\beta_0, \beta_1, \mathscr{F}_j)$, $l = 1, \ldots, j$

Refer to the posterior distribution of $\mathbf{Z}$ conditional on $\boldsymbol{\beta} = (\beta_0, \beta_1)$, based on (10), we find that the random variables $Z_1, Z_2, \ldots, Z_j$ are independent with

$$Z_l|\beta_0, \beta_1, \mathscr{F}_j \sim \begin{cases} N(\beta_0 + \beta_1 x_l, 1)I(Z_l > 0) & \text{if } y_l = 1, \\ N(\beta_0 + \beta_1 x_l, 1)I(Z_l \leq 0) & \text{if } y_l = 0, \end{cases} \qquad \text{for } l = 1, \ldots, j \tag{16}$$

Based on the Gibbs samplers, estimates of β_0, β_1 and $\mathbf{Z}$ can be produced from those full conditional posterior distributions.

3 Dose Allocation Rules

After drawing the samples from the joint marginal posterior distribution

$$\pi(\boldsymbol{\beta}|\mathscr{F}_j) = \pi(\beta_0, \beta_1|\mathscr{F}_j),$$

one can find the dose $x_{j+1} \in \{d_1, \ldots, d_K\}$ such that the corresponding probability of DLT is "closest" to the target probability of DLT θ, i.e. one of the following criteria (which are similar as those in the original CRM [9]) is minimized:

$$\textbf{Criterion 1} \quad l_1(\psi(x, \boldsymbol{\beta}), \theta) = \Delta(\psi(x, E^{\pi(\boldsymbol{\beta}|\mathscr{F}_j)}\boldsymbol{\beta}), \theta), \tag{17}$$

$$\textbf{Criterion 2} \quad l_2(\psi(x, \boldsymbol{\beta}), \theta) = \Delta(E^{\pi(\boldsymbol{\beta}|\mathscr{F}_j)}\psi(x, \boldsymbol{\beta}), \theta), \tag{18}$$

where $\Delta(v, w) = (v - w)^2$. The estimates of the expectations in (17) and (18) can be obtained based on the simulation by using the Monte Carlo method. Suppose one has generated N pairs of $\boldsymbol{\beta} = (\beta_0, \beta_1)$, denoted by $\boldsymbol{\beta}^{(i)} = (\beta_0^{(i)}, \beta_1^{(i)}), i = 1, 2, \ldots, N$, then,

$$\hat{E}^{\pi(\boldsymbol{\beta}|\mathscr{F}_j)}\boldsymbol{\beta} = \frac{1}{N}\sum_{i=1}^{N}\boldsymbol{\beta}^{(i)}, \quad \text{and}$$

$$\hat{E}^{\pi(\boldsymbol{\beta}|\mathscr{F}_j)}\psi(x, \boldsymbol{\beta}) = \frac{1}{N}\sum_{i=1}^{N}\psi(x, \boldsymbol{\beta}^{(i)}).$$

Table 1 is an example of the simulated trial based on criterion 1. In this example, six levels $\{d_1, \ldots, d_6\}$ are chosen for experimentation. We recruit 30 patients in 10 cohorts

with 3 patients per cohort. At stage j, 3 toxicity responses is simulated independently from Bernoulli distribution with success probability $P(Y = 1|x_j) = [(1 + \tanh x_j)/2]^{2.2}$, where $x_j \in \{d_1, \ldots, d_6\}$. The data is fitted using two-parameter probit model, i.e. $P(Y = 1|x) = \Phi(\beta_0 + \beta_1 x)$. Assume that the true toxicity probability at each dose level is as follows

Dose Level	d_1	d_2	d_3	d_4	d_5	d_6
Probability	0.03	0.11	0.30	0.49	0.87	0.93

In addition, we start from the lowest dose level x_1 and for any dose escalation more than one does level is not allowed.

Table 1: Simulated trial: True model is $P(Y = 1|x) = [(1 + \tanh x)/2]^{2.2}$; Total 10 cohorts with 3 patients per cohort.

		Response			$l_1(\psi(x, \boldsymbol{\beta}), \theta)$					
Cohort	x_i	1	2	3	x_1	x_2	x_3	x_4	x_5	x_6
1	x_1	0	1	0	**0.01**	0.02	0.08	0.16	0.38	0.42
2	x_1	0	0	0	0.03	**0.00**	0.01	0.04	0.28	0.35
3	x_2	0	0	0	0.05	0.03	0.01	**0.00**	0.07	0.11
4	x_3	0	0	0	0.06	0.05	0.04	0.03	0.01	**0.00**
5	x_4	1	0	0	0.05	0.04	0.02	0.01	**0.00**	0.02
6	x_5	1	1	1	0.06	0.03	0.01	**0.00**	0.26	0.34
7	x_4	1	1	0	0.06	0.02	**0.00**	0.02	0.30	0.38
8	x_3	0	1	0	0.05	0.02	**0.00**	0.03	0.31	0.39
9	x_3	0	0	0	0.06	0.03	**0.00**	0.02	0.30	0.38
10	x_3	1	0	0	0.06	0.03	**0.00**	0.01	0.26	0.35
11	x_3									

To check the feasibility of the proposed method, simulation scenarios and results are presented in the following section.

4 Simulation Studies

In order to assess the operating characteristics of the dose escalation strategy based on criteria (17) and (18) and to compare the performance of one-parameter power model with two-parameter probit model, a simulation study is performed.

In this simulation study, we consider a variety of situations. We suppose there are six ordered dose levels, $x_1, \ldots, x_6$, and that the probability of toxic response at each level is generated in one of the following four ways:

(1) Power Model $\psi(x; a) = [(\tanh(x) + 1)/2]^a$,

(2) Probit Model $\psi(x; \beta_0, \beta_1) = \Phi(\beta_0 + \beta_1 x)$,

(3) Logistic Model $\psi(x; a, b) = \exp(a + bx)/(1 + \exp(a + bx))$,

(4) General Situation $p(x_i) \leq p(x_j), i < j$, where $p(x)$ is the toxicity probability at x.

For the working model, we always use prior $\pi(a) = \exp(-a), a > 0$, as in O'Quigley *et al.* [9], on power model and $\pi(\beta_0, \beta_1) \propto \exp(-\beta_1), \beta_1 > 0$ on probit model. We start the first cohort of patients at the lowest of the preselected dose levels and the next cohort is required to be treated no more than one dose level higher than the previous cohort.

In each duplication, we recruit 30 patients in 10 cohorts with 3 patients per cohort. Recruiting 3 patients, instead of 1 patient (which is the case of the original CRM. See [9]), per cohort is similar as in the standard "3+3"design in phase I clinical trial, which will increase the accuracy of estimation for the unknown parameter(s), especially during the early period of the clinical trial. For each of the total 30 stages in each duplication, we simulated 1000 samples after burn-in the first 1000 samples and thinning every 10 samples. The parameters used in the simulation are shown in Table 2.

Each of the Tables 3 through 6 is based on estimates from 200 duplications as in the original paper of O'Quigley *et al.* [9]. The first row in each of the Tables 3 through 6 gives the true probabilities generating the data. There are 8 entries in each table. The first 4 and the last 4 entries are the simulation results based on two different true models. For both the first 4 and the last 4 entries, the first 2 entries of them are the simulation results of Criterion 1 and Criterion 2, respectively, under the power model and the the second 2 entries are the simulation results of Criterion 1 and Criterion 2, respectively, under the probit model. Each of the 8 entries have 2 rows. The first row gives the frequency at which that dose level was the

Table 2: Setting of simulation study for the dichotomized response model.

Number of cohorts in one trial	10						
Number of patients in each cohort	3						
Number of patients in one trial	30						
Number of duplications	200						
Number of dose levels	6						
Target response probability	0.3						
True toxic response		x_1	x_2	x_3	x_4	x_5	x_6
Power model	H1:	0.16	0.30	0.52	0.68	0.93	0.96
	H2:	0.03	0.11	0.30	0.49	0.87	0.92
Probit model	N1:	0.05	0.10	0.20	0.30	0.65	0.75
	N2:	0.00	0.001	0.01	0.03	0.30	0.46
Logistic model	L1:	0.06	0.08	0.14	0.30	0.53	0.84
	L2:	0.06	0.11	0.30	0.75	0.95	0.99
General Situation	G1:	0.05	0.10	0.15	0.30	0.45	0.60
	G2:	0.30	0.90	0.90	0.90	0.90	0.90
Working Model							
Power model							
	$\psi(x;a) = [(\tanh(x)+1)/2]^a$						
	$\pi(a) = e^{-a}, a > 0$						
Probit model							
	$\psi(x;\beta_0,\beta_1) = \Phi(\beta_0 + \beta_1 x)$						
	$\pi(\beta_0,\beta_1) \propto e^{-\beta_1}, \beta_1 > 0$						

one finally recommended as the MTD, the second the frequency at which experimentation was performed at that level. In each table, the last 3 columns give the average, maximum and minimum number of toxic responses over the 200 duplications.

The true model for Table 3 is the power model. Table 3 shows both working model, power model or probit model, provide the similar simulation results under the true toxicity probability setting H1. All the criteria provide about 70 percent correct recommendations. For scenario H2, the probit model is slightly better than the power model under criterion 2. The power model recommends the MTD correctly with about 73 percent chances and the probit model with about 80 percent.

The true model for Table 4 is the probit model. Under both true toxicity probability settings, N1 and N2, it is shown that the power model underestimate the MTD. Under N1, it is more than 50 percent chances that the power model recommends the dose level having 0.2 toxic response probability which is one level below the true MTD. Under N2, the power model even recommended the dose level having 0.03 toxic response probability with more than 95 percent chances. However, under both N1 and N2, the probit model has more chance to recommend the MTD correctly then to recommend the other doses. Under N1, the probit model has more than 70 percent chances to recommend the MTD and more than 60 percent under N2.

Table 5 uses the logistic model as the true model. Under the toxicity probability setting L1, the probit model is superior to the power model. By using criterion 1, it is about 50 percent chances for the power model to recommend the MTD and about 60 percent for probit model. By using criterion 2, the MTD is underestimated by the power model. Under L2, the power model is slightly better than the probit model. The recommendation rate for power model is close to 90 percent and for probit model is above 85 percent.

The true model for Table 6 under the general situation. Under the toxicity probability setting G1, the probit model is superior to the power model for all there criteria. Under G2, the true toxicity probabilities are set to look at what happens when all toxic probabilities are extremely high (90%) apart from the very lowest one which is at the appropriate level. Under this toxicity probability setting, not surprisingly, both the power model and the probit model recommend the lowest dose level over 95% of the time. And what is rather more encouraging is that only about 10% of the patients are ever tried at a level other than the lowest.

The simulation results summarized in all the tables show that the probit model is

Table 3: Result of simulation study under scenario H1 and H2. The true model is power model, $\psi(x;a) = [(\tanh(x)+1)/2]^a$. MTD is at does level 2 for scenario H1 and dose level 3 for H2.

								# of toxic reponses		
True toxicity prob.	H1:	0.16	0.30	0.52	0.68	0.93	0.96	Mean	Max	Min
Power model										
Criterion 1	Rec.	19.5	**70.5**	10.0						
	Exp.	31.2	58.1	10.7	0.1			8.9	14	4
Criterion 2	Rec.	22.0	**71.0**	7.0						
	Exp.	36.0	54.3	9.6	0.1			8.5	14	4
Probit model										
Criterion 1	Rec.	16.0	**71.0**	12.0	1.0					
	Exp.	28.5	48.7	19.4	3.3	0.1		9.8	15	5
Criterion 2	Rec.	19.0	**71.0**	9.5	0.5					
	Exp.	31.2	48.6	17.4	2.7	0.1		9.4	14	5
True toxicity prob.	H2:	0.00	0.02	0.13	0.30	0.80	0.88			
Power model										
Criterion 1	Rec.			18.5	**81.5**					
	Exp.	10.1	11.2	36.4	40.1	2.2		6.0	11	2
Criterion 2	Rec.			26.3	**73.5**					
	Exp.	10.2	11.5	40.2	35.9	2.2		5.7	11	2
Probit model										
Criterion 1	Rec.			14.0	**84.5**	1.5				
	Exp.	10.0	10.4	21.2	51.9	6.3	0.2	7.6	12	4
Criterion 2	Rec.			18.5	**80.5**	1.5				
	Exp.	10.1	10.8	22.5	50.4	6.1	0.1	7.4	12	4

Table 4: Result of simulation study under scenario N1 and N2. The true model is probit model, $\psi(x; \beta_0, \beta_1) = \Phi(\beta_0 + \beta_1 x)$. MTD is at does level 4 for scenario N1 and dose level 5 for N2.

								# of toxic reponses		
True toxicity prob.	N1:	0.05	0.10	0.20	0.30	0.65	0.75	Mean	Max	Min
Power model										
Criterion 1	Rec.		5.0	**54.0**	41.0					
	Exp.	11.9	21.5	41.4	23.9	1.2	10.1	6.1	11	2
Criterion 2	Rec.		7.0	**59.0**	34.0					
	Exp.	12.6	25.7	40.6	19.8	1.2	0.1	5.8	11	2
Probit model										
Criterion 1	Rec.		1.5	22.0	**72.5**	4.0				
	Exp.	13.1	13.3	22.9	42.7	7.5	0.5	7.8	13	4
Criterion 2	Rec.		3.0	24.5	**70.5**	2.0				
	Exp.	13.6	15.2	23.1	40.6	7.0	0.5	7.5	13	4
True toxicity prob.	N2:	0.00	0.001	0.01	0.03	0.30	0.46			
Power model										
Criterion 1	Rec.				**98.5**	1.5				
	Exp.	10.0	10.1	11.1	53.4	11.8	3.6	2.3	6	1
Criterion 2	Rec.				**99.0**	1.0				
	Exp.	10.0	10.1	11.6	53.0	11.7	3.6	2.2	6	1
Probit model										
Criterion 1	Rec.				3.0	**68.5**	28.5			
	Exp.	10.0	10.0	10.1	12.7	36.2	21.0	6.8	11	3
Criterion 2	Rec.				4.5	**72.5**	23.0			
	Exp.	10.0	10.0	10.1	13.9	37.6	18.4	6.5	11	3

Table 5: Result of simulation study under scenario L1 and L2. The true model is logistic model, $\psi(x; a, b) = \exp(a + bx)/(1 + \exp(a + bx))$. MTD is at dose level 4 for scenario L1 and dose level 3 for L2.

								# of toxic reponses		
True toxicity prob.	L1:	0.06	0.08	0.14	0.30	0.53	0.84	Mean	Max	Min
Power model										
Criterion 1	Rec.			47.5	**51.5**	1.0				
	Exp.	10.2	11.7	45.1	30.5	2.3	0.2	5.8	11	2
Criterion 2	Rec.		1.0	**53.5**	45.5					
	Exp.	12.7	12.2	45.5	27.4	2.0	0.2	5.5	11	2
Probit model										
Criterion 1	Rec.		0.5	26.0	**60.0**	13.0	0.5			
	Exp.	12.4	13.4	29.4	33.9	10.4	0.5	6.8	12	3
Criterion 2	Rec.		0.5	27.5	**61.5**	10.0	0.5			
	Exp.	12.5	14.0	31.2	32.9	8.9	0.5	6.6	12	3
True toxicity prob.	L2:	0.06	0.11	0.30	0.75	0.95	0.99			
Power model										
Criterion 1	Rec.		9.5	**90.0**	0.5					
	Exp.	10.3	18.3	65.9	5.5			8.6	13	4
Criterion 2	Rec.		11.5	**88.5**						
	Exp.	13.1	19.1	63.4	4.4			8.2	13	4
Probit model										
Criterion 1	Rec.		9.5	**88.5**	2.0					
	Exp.	13.1	20.0	60.0	6.8	0.1		8.2	14	4
Criterion 2	Rec.		12.5	**86.0**	1.5					
	Exp.	13.3	23.0	57.0	6.5	0.2		7.9	13	4

Table 6: Result of simulation study under scenario G1 and G2. The true model is under a general situation $p(x_i) \leq p(x_j), i < j$, where $p(x)$ is the toxicity probability at x. MTD is at dose level 4 for scenario G1 and dose level 1 for G2.

								# of toxic reponses		
True toxicity prob.	G1:	0.05	0.10	0.15	0.30	0.45	0.60	Mean	Max	Min
Power model										
Criterion 1	Rec.		4.5	44.5	**51.0**					
	Exp.	12.2	19.6	37.5	29.1	1.5	0.1	5.7	11	2
Criterion 2	Rec.		6.5	**48.0**	45.5					
	Exp.	12.6	22.4	38.4	24.9	1.6	0.1	5.4	10	1
Probit model										
Criterion 1	Rec.		0.5	18.0	**62.5**	16.5	2.5			
	Exp.	12.2	13.2	22.0	38.5	11.3	2.8	7.4	12	4
Criterion 2	Rec.		0.5	18.5	**64.5**	15.0	1.5			
	Exp.	12.3	14.5	23.2	36.8	10.8	2.3	7.2	12	4
True toxicity prob.	G2:	0.30	0.90	0.90	0.90	0.90	0.90			
Power model										
Criterion 1	Rec.	**99.5**	0.5							
	Exp.	90.3	9.7					10.8	16	7
Criterion 2	Rec.	**98.5**	1.5							
	Exp.	92.2	7.8					10.5	15	7
Probit model										
Criterion 1	Rec.	**99.5**	0.5							
	Exp.	91.2	8.6	0.2				10.6	17	6
Criterion 2	Rec.	**99.5**	0.5							
	Exp.	91.7	8.3					10.5	17	5

superior to or at least as good as the power model in most cases. Meanwhile, the simulation results also show that the Bayesian method to fit the probit model wokes well in the clinical phase I trials even there is a relatively small samples.

5 Concluding Remarks

We have presented a two-parameter probit model with normal distributed latent variables for dose-finding in Phase I clinical trials. Our simulation study shows that on average the two-parameter probit model performs well and is superior to the one-parameter power model under a wide variety of circumstances. We also compare the performance of two dose allocation criteria, which are expressed in (17) and (18), under both two-parameter and one-parameter models. The simulation study shows that the criterion 2 is slightly more conservative than the criterion 1 in the sense of the total percentage of recommending the MTD and one level below the MTD.

Introducing different latent variables, the method is much easier to generate in the case of the two-parameter logistic model or in the case of a more general situation. The general procedure is briefly presented as follows. Assume that, at dosage x, there exists a latent variable Z with the probability density function $f_Z(z; x, \boldsymbol{\beta})$, such that,

$$Y = \begin{cases} 1 & \text{if } Z > z_0, \\ 0 & \text{if } Z \leq z_0, \end{cases} \tag{19}$$

where Y is the toxicity response, $\boldsymbol{\beta}$ and z_0 are unknown parameters. Under certain situations, such as in the normally distributed latent variable case presented in Section 2, the unknown parameter z_0 can be absorbed in $\boldsymbol{\beta}$ and hence, in (19), z_0 is set to be zero or a known constant. Then, the dose-response model is given as

$$\begin{aligned} P(Y = 1|x) = P(Z > z_0|x) &= \int_{z_0}^{\infty} f_Z(z; x, \boldsymbol{\beta}) dz \\ &= 1 - F_Z(z_0; x, \boldsymbol{\beta}), \qquad \text{for } x \text{ in the dose range } \mathbb{X}, \end{aligned} \tag{20}$$

where $F_Z(z_0; x, \boldsymbol{\beta})$ is the cumulative density function of the latent variable Z. As a special case of (20), if the latent variable Z is logistic distributed, (20) is reduced to the logistic

model. Furthermore, accruing data up to $\mathscr{F}_j = \{(x_1, y_1), \ldots, (x_j, y_j)\}$, the joint posterior density of the parameters $\boldsymbol{\beta}$, z_0 and unobserved latent variables $\mathbf{Z} = (Z_1, Z_2, \ldots, Z_j)$ is given by

$$\pi(\boldsymbol{\beta}, z_0, \mathbf{Z}|\mathscr{F}_j) \propto \pi(\boldsymbol{\beta}, z_0) \prod_{l=1}^{j} [I(Z_l > z_0) I(y_l = 1) + I(Z_l \leq z_0) I(y_l = 0)] f_Z(Z_l; x, \boldsymbol{\beta}), \quad (21)$$

where $\pi(\boldsymbol{\beta}, z_0)$ is the prior on model parameters $(\boldsymbol{\beta}, z_0)$. For sampling from (21), the Markov chain Monte Carlo method can be applied.

General model (20) is very flexible and can be used to describe a wide variety of dose response curves. Under the Bayesian framework, introducing the latent variables allow one to perform exact inference for the model parameter(s) and is preferable to the ML method for small samples which is the case in Phase I clinical trials. In addition, introducing the latent variables makes it a nature generation of the dichotomous toxicity responses when the ploychotomous toxicity responses is accounted. Introducing the latent variables, the ploychotomous toxicity responses will be discussed in a separated paper.

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