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On the consistency of the continual reassessment method with multiple toxicity constraints

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ABSTRACT

Conventional dose finding methods require the dichotomization of toxicity outcome measures generally collected in an ordinal scale. To improve efficiency and include more information on the gradation of toxicities, a sequential likelihood procedure that accounts for multiple toxicity constraints is proposed to differentiate the tolerance for toxicity of various degrees of severity under a novel class of multiplicative models, and the asymptotic properties of the procedure under certain model misspecification are established.

1. Introduction

The main objective of dose finding clinical trials is to estimate the maximum tolerated dose, defined as the dose level associated with a pre-specified probability of dose limiting toxicity. Therefore, the objective is posed as a quantile estimation problem based on a binary outcome. Numerous methods have been proposed under this framework. Among the earliest publications in this area, we have Storer (1989), O'Quigley et al. (1990), Durham et al. (1997), and Babb et al. (1998). To implement any of these methods, the toxicity outcome measured must be dichotomized given that it is collected on an ordinal scale from 0 to 5 based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (National Cancer Institute, 2003). To improve efficiency, several methods have been proposed to allow for ordinal toxicity outcomes. Several of these improved methods incorporate gradations of toxicity, while controlling only the rate of dose limiting toxicity in the objective Simon et al. (1997), Wang et al. (2000), Iasonos et al. (2011), Van Meter et al. (2011, 2012). Others reformulate the problem to find the dose associated with a pre-specified value of the outcome Bekele and Thall (2004), Yuan et al. (2007), and Ivanova and Kim (2009). The method of Lee et al. (2011) retains the quantile estimation objective while controlling the rate of higher toxicities as well to ensure that the identified dose is safe in terms of both dose limiting toxicity and other higher toxicities. This method generalizes the definition of the maximum tolerated dose by imposing multiple constraints on toxicities and proposes a generalized version of the continual reassessment method under the Bayesian framework.

Among the above dose finding methods, the continual reassessment method originally proposed by O'Quigley et al. (1990) is one of the few methods whose theoretical properties have been rigorously investigated. This paper aims to establish the theoretical properties of the multi-parameter models under the multiple toxicity constraint framework. Specifically,

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we investigate the large sample properties of the likelihood procedure for the continual reassessment method with multiple constraints and investigate its asymptotic behaviors. The paper is organized as follows. In Section 2, we describe the probability model, the objective under multiple constraints, and the dose-finding algorithm. In Section 3, we establish the large sample properties of the likelihood procedure under a class of multiplicative models. In Section 4, we conduct a simulation study comparing the proposed method with the Bayesian approach and the likelihood based continual reassessment method that considers only the constraint for dose limiting toxicity. Some discussions are provided in Section 5.

2. Methods

Let $D = \{d_1, \ldots, d_K\}$ be the K test doses of ascending dosage $d_1 < \cdots < d_K$. Let Y^* be an ordinal or continuous toxicity outcome such as the NCI-CTCAE or the toxicity burden score Lee et al. (2012). Let Y be the re-defined ordinal toxicity outcome which takes on values $0, 1, \ldots, L$ based on the desired constraints, such that L is less than or equal to the number of possible toxicity outcomes in Y^*. For example, suppose the raw outcome Y^* is the NCI-CTCAE, which assumes values 0, 1, 2, 3, 4, 5, and we are interested in only two constraints (i.e. $L = 2$), one on $\text{pr}(Y^* \geq 3)$ and the other on $\text{pr}(Y^* \geq 4)$. In that case, the variable Y is defined as $Y = 0$ if and only if $Y^* = 0, 1, 2$, $Y = 1$ if and only if $Y^* = 3$, and $Y = 2$ if and only if $Y^* \geq 4$. Denote $\text{pr}(Y \geq l|d_k) = R_l(d_k)$, $k = 1, \ldots, K$, $l = 1, \ldots, L$. The unknown toxicity probabilities $R_l(d_k)$ satisfy $0 < R_l(d_1) < \cdots < R_l(d_K) < 1$ for $l = 1, \ldots, L$, and $R_{l_1}(d_k) > R_{l_2}(d_k)$ for any $l_1 < l_2$ and fixed k. Thus, it is implicitly assumed that there are L toxicity constraints, where constraint on $\text{pr}(Y \geq l)$ corresponds to the non-zero value $Y = l$, $l = 1, \ldots, L$.

Consider a pre-specified targeting toxicity vector $\theta = (\theta_1, \ldots, \theta_L)^T$ such that $1 > \theta_1 > \cdots > \theta_L > 0$. For each $l = 1, \ldots, L$, we define the optimal dose associated with the lth toxicity constraint as

$$d_{v_l} = \underset{x \in D}{\text{argmin}} \, |R_l(x) - \theta_l|.$$

When $l = 1$, $Y \geq 1$ corresponds to the dose limiting toxicity and d_{v_1} corresponds to the original definition for the maximum tolerated dose.

The maximum tolerated dose under multiple toxicity constraints is defined as

$$d_v = \min\{d_{v_1}, \ldots, d_{v_L}\},$$

which is seen as a generalization of definition for the maximum tolerated dose. In this paper, we assume that d_v is uniquely defined.

We note that the objective of the CRM with multiple constraints is the same as the original CRM when a single constraint is specified, that is, it identifies the dose associated with a single target probability of dose limiting toxicity. However, when more than one constraint is specified, the objective differs from that of the original CRM. Previously proposed methods by Iasonos et al. (2011), Van Meter et al. (2011, 2012) have incorporated information on grades of toxicity by including the additional information in the modeling, but keeping the objective the same as the original CRM. Their extensive simulations conclude that only including the grade information in the modeling does not generally improve the accuracy of identification of the MTD. By contrast, our proposed method changes the objective by including toxicity thresholds for the various grades of toxicity.

To estimate the maximum tolerated dose d_v, consider a generic working model

$$\text{pr}(Y \geq l) = \psi_l(x, \beta), \quad l = 1, \ldots, L, \tag{1}$$

where $\beta = (\beta_1, \ldots, \beta_L)^T$ is the unknown parameter. We assume that the above model is rich enough in the sense that for any fixed dose x and any given targeting toxicity θ, there exists a β such that $\psi_l(x, \beta) = \theta_l$, $l = 1, \ldots, L$. The choice of such models will be discussed in Section 3.1.

We propose to use the maximum likelihood method to estimate the model parameters instead of the Markov chain Monte Carlo method used in Lee et al. (2011). Specifically, the maximum likelihood estimate $\hat{\beta}_n$ based on the toxicity outcomes of the first n subjects is a value maximizing the likelihood

$$L(\beta) = \prod_{i=1}^{n} \psi_L\{x(i), \beta\}^{I(Y_i=L)} \, [1 - \psi_1\{x(i), \beta\}]^{I(Y_i=0)} \prod_{l=1}^{L-1} [\psi_l\{x(i), \beta\} - \psi_{l+1}\{x(i), \beta\}]^{I(Y_i=l)}.$$

If $\hat{\beta}_n$ exists, the recommended dose for the $(n+1)$th patient is

$$x(n+1) = \min\{\underset{x \in D}{\text{argmin}} \, |\psi_l(x, \hat{\beta}_n) - \theta_l|, l = 1, \ldots, L\}.$$

The likelihood approach does not require the specification of priors. In addition, the determination of the maximum likelihood estimator $\hat{\beta}_n$ is much easier to compute as it does not require the Markov chain Monte Carlo method. However, $\hat{\beta}_n$ may not exist, particularly when n is small. In fact, Pratt (1981) indicated that under certain condition on $\psi_l(x, \beta)$, the maximum likelihood estimate $\hat{\beta}_n$ exists when all the $(L+1)$ possible values of Y are observed. Therefore, to make use of all the L constraints, all the $L+1$ possible values of Y must be observed, which we call "full heterogeneity". However, we emphasize that our procedure can be used as long as two or more distinct values are observed, which we call "partial heterogeneity",

with the understanding that under partial heterogeneity, some of the constraints may not be invoked. For implementation of the method, we take a staged approach which depends on the extent of heterogeneity observed. At the start of a trial, we propose to use a rule based design that starts at the lowest dose and escalates after every patient (1 + 1) or escalates in cohorts of 3 (3+3). Once partial heterogeneity is achieved, the design switches to the proposed procedure invoking as many constraints as distinct values of outcomes are observed. For example, suppose Y takes on three possible values: 0 (no toxicity), 1 (dose limiting toxicity), and 2 (life-threatening toxicity), and we are interested in two constraints: $\text{pr}(Y \geq 1) \leq \theta_1$ and $\text{pr}(Y \geq 2) \leq \theta_2$. In the first stage, we will use a rule-based design. If the first toxicity we observe is $Y = 2$, then we proceed by considering only the constraint $\text{pr}(Y \geq 2) \leq \theta_2$. We invoke the constraint $\text{pr}(Y \geq 1) \leq \theta_1$ once $Y = 1$ is observed. This is different from the regular CRM in that the constraint $\text{pr}(Y \geq 1) \leq \theta_1$ is always used disregarding whether $Y = 1$ or $Y = 2$ is first observed. In the situation where $Y = 1$ is not observed and all toxicities are $Y = 2$, the CRM will recommend the dose with a toxicity probability of θ_1 while the proposed method will recommend the dose with a toxicity probability of θ_2.

3. Asymptotic properties

3.1. Continual reassessment method with single constraint

The asymptotic properties of the likelihood approach to continual reassessment method for single constraint (i.e., $L = 1$) have been established in Shen and O'Quigley (1996). In this section, we briefly review their results in order to make comparison with our main results for multiple constraints.

With $L = 1$ we observe a binary toxicity outcome Y with $Y = 1$ indicating dose limiting toxicity and $Y = 0$ otherwise. Using the notation of the previous section, the maximum tolerated dose is defined as

$$d_\nu = \underset{x \in D}{\text{argmin}} |R_1(x) - \theta_1|,$$

where θ_1 is a pre-specified target toxicity rate and $R_1(d_k)$, $k = 1, \ldots, K$, are totally unknown except that they are nondecreasing with respect to dosage d_k. They proposed to estimate the maximum tolerated dose when $\text{pr}(Y = 1) = \psi(x, \beta)$. Specifically, let $\hat{\beta}_n$ be the maximum likelihood estimator based on data from the first n subjects, then the proposed dosage for the $(n + 1)$th subject would be

$$x(n + 1) = \underset{x \in D}{\text{argmin}} |\psi(x, \hat{\beta}_n) - \theta_1|,$$

which would also be the estimate of the maximum tolerated dose d_ν at the $(n + 1)$th step.

Shen and O'Quigley (1996) showed that $x(n)$ is asymptotically consistent, that is $x(n) \to d_\nu$ almost surely, provided that $\text{pr}(Y = 1) = \psi(x, \beta)$ satisfies the following conditions

Condition C1: For each β, $\psi(x, \beta)$ is strictly increasing in x.

Condition C2: Function $\psi(x, \beta)$ is continuous and strictly monotone in β in the same direction for all x.

Condition C3: For each $0 < t < 1$ and each x,

$$t\frac{\psi'}{\psi}(x, \beta) + (1 - t)\frac{-\psi'}{1 - \psi}(x, \beta)$$

is continuous and strictly monotone in β.

More important, they pointed out that their consistency result may still hold even if the model specified is not the true model. Specifically, define β_k such that $\psi(d_k, \beta_k) = R_1(d_k)$, $k = 1, \ldots, K$ and

$$S = \{\beta : |\psi(d_\nu, \beta) - \theta_1| \leq |\psi(d_k, \beta) - \theta_1|, k \neq \nu\}.$$

They proved that $x(n)$ is consistent provided that in addition to Conditions C1–C3, the following condition also holds:

Condition C4: For $k = 1, \ldots, K$, $\beta_k \in S$.

It is easily seen that this condition is trivially satisfied when $\psi(x, \beta)$ is indeed the true model. Therefore, Condition C4 can be viewed as a robustness condition for a working model $\psi(x, \beta)$.

3.2. Continual reassessment method with multiple constraints

In this section, we investigate the asymptotic properties of the proposed likelihood approach when multiple constraints are imposed for an ordinal toxicity outcome. Before embarking on the proof of consistency, we first point out that the maximum likelihood estimator $\hat{\beta}_n$ exists when n is large enough by establishing the following lemma.

Lemma 1. *Define*

$$n_0 = \inf\left\{n : \sum_{i=1}^{n} I(Y_i = l) > 0, l = 0, 1, \ldots, L\right\},$$

the first time that all L possible values of Y are observed. Then, $\text{pr}(n_0 < \infty) = 1$.

Proof. Consider the multivariate martingale

$$W_n = \left[\sum_{i=1}^{n} I(Y_i \geq 1) - R_1\{x(i)\}, \ldots, \sum_{i=1}^{n} I(Y_i \geq L) - R_L\{x(i)\} \right]^T.$$

The martingale limit theorem implies that $W_n/n \to 0$ almost surely. Since

$$0 < R_l(d_1) \leq \frac{1}{n} \sum_{i=1}^{n} R_l\{x(i)\} \leq R_l(d_K) < 1, \quad l = 1, \ldots, L,$$

we conclude that when n is large enough, $1 \leq \sum_{i=1}^{n} I(Y_i \geq l) \leq n-1$ almost surely for $l = 1, \ldots, L$, which implies that $\mathrm{pr}(n_0 < \infty) = 1$. This result indicates that the maximum likelihood estimate $\hat{\beta}_n$ exists almost surely when n is large enough. □

It is important to note that not all generic models (1) can yield a consistent dose sequence in a multiple constraints case. Therefore, to obtain a consistent dose sequence $x(n)$ and the maximum likelihood estimate $\hat{\beta}_n$, we first need to choose a working model wisely.

Let $\mathcal{M}$ be the collection of parametric models satisfying Conditions C1–C3. We propose to use the following multiplicative model as the working model for Y when multiple constraints are used

$$\mathrm{pr}(Y \geq l) = \psi_l(x, \beta) = \prod_{i=1}^{l} \varphi_i(x, \beta_i), \quad l = 1, \ldots, L, \tag{2}$$

where $\varphi_1, \ldots, \varphi_L \in \mathcal{M}$.

Some remarks on the proposed multiplicative model (2) are in order. First, model (2) is equivalent to the following model

$$\mathrm{pr}(Y \geq l+1 | Y \geq l) = \varphi_{l+1}(x, \beta_{l+1}), \quad l = 1, \ldots, L-1.$$

Second, model (2) is flexible because the φ_ls could be in different analytic forms. In practice, however, it is convenient to choose $\varphi_1 = \cdots = \varphi_L = \varphi$. In our simulation, we chose the empiric model $\varphi(x, \beta) = x^{\beta}$. Third, although in general we do not have $R_l(d_v) = \theta_l$, $l = 1, \ldots, L$, model (2) is rich enough such that for any fixed x and any target toxicity θ, we can find β such that $\psi_l(x, \beta) = \theta_l$, $l = 1, \ldots, L$.

To formulate the condition for consistency of the dose sequence using the proposed procedure, we define the "good parameter" set as

$$\Omega = \left[\beta : d_v = \min \left\{ \operatorname*{argmin}_{x \in D} |\psi_l(x, \beta) - \theta_l|, l = 1, \ldots, L \right\} \right].$$

The set Ω is obviously non-empty since it contains β_0, where $\psi_l(d_v, \beta_0) = \theta_l$, $l = 1, \ldots, L$. However, unlike the single constraint case considered in Shen and O'Quigley (1996), Ω is usually not a convex set. As an example, consider a toxicity outcome Y whose possible values are 0, 1, 2 and the following working model

$$\mathrm{pr}(Y \geq 1) = x^{\beta_1}, \qquad \mathrm{pr}(Y = 2) = x^{\beta_1 + \beta_2}.$$

Proposition 1 shows that Ω is not a convex set.

Proposition 1. *Assume $L = 2$, $\psi_1(x, \beta) = x^{\beta_1}$, $\psi_2(x, \beta) = x^{\beta_1+\beta_2}$, $\beta = (\beta_1, \beta_2)^T$. Denote b_k as the unique solution to $d_k^{b_k} + d_{k+1}^{b_k} = 2\theta_1$ and c_k as the unique solution to $d_k^{c_k} + d_{k+1}^{c_k} = 2\theta_2$, for $k = 1, \ldots, K-1$ and set $b_0 = c_0 = 0$, $b_K = c_K = \infty$. Define*

$$\Omega_+ = \{\beta : b_{v-1} \leq \beta_1 \leq b_v, \beta_2 + \beta_1 \geq c_{v-1}, \beta_2 \geq 0\}$$

and

$$\Omega_- = \{\beta : \beta_1 \geq b_{v-1}, c_{v-1} \leq \beta_2 + \beta_1 \leq c_v, \beta_2 \geq 0\}.$$

Then, $\Omega = \Omega_+ \cup \Omega_-$.

Proof. For any i, j such that $1 \leq i, j \leq K$. Define

$$\Omega_{ij} = \left\{ \beta : |\psi_1(d_i, \beta) - \theta_1| \leq |\psi_1(d_k, \beta) - \theta_1|, k \neq i, |\psi_2(d_j, \beta) - \theta_1| \leq |\psi_2(d_{k'}, \beta) - \theta_2|, k' \neq j \right\}.$$

The set Ω_{ij} consists of parameters that yield $v_1 = i$ and $v_2 = j$, that is, d_i is the optimal dose for the first constraint and d_j is the optimal dose for the second constraint. By Cheung and Chappell (2002),

$$\Omega_{ij} = \left\{ \beta : b_{i-1} \leq \beta_1 \leq b_i, h_{j-1}(\beta_1) \leq \beta_2 \leq h_j(\beta_2), \beta_2 \geq 0 \right\},$$

where b_i's are defined in Proposition 1 and for any fixed $\beta_1 \in [b_{i-1}, b_i]$, $h_j(\beta_1)$ is the solution to

$$d_j^{\beta_1 + h_j(\beta_1)} + d_{j+1}^{\beta_1 + h_j(\beta_1)} = 2\theta_2.$$

Taking the derivative of the above implicit function, we conclude that $\frac{\partial h_j(\beta_1)}{\partial \beta_1} = -1$ hence $h_j(\beta_1) = -\beta_1 + c_j$ for some constant c_j. Plugging the expression of $h_j(\beta_1)$ back into the above equation, we conclude that c_j is determined in Proposition 1.

It is straightforward to check that

$$\Omega_+ = \bigcup_{j=v}^{K} \Omega_{v,j} = \{\beta : b_{v-1} \le \beta_1 \le b_v, \beta_2 + \beta_1 \ge c_{v-1}, \beta_2 \ge 0\},$$

$$\Omega_- = \bigcup_{i=v}^{K} \Omega_{i,v} = \{\beta : \beta_1 \ge b_{v-1}, c_{v-1} \le \beta_2 + \beta_1 \le c_v, \beta_2 \ge 0\},$$

and both sets are convex and $\Omega = \Omega_+ \cup \Omega_-$. □

Let $\beta(k) = \{\beta_1(k), \ldots, \beta_L(k)\}^T$ be such that $\psi_l(d_k, \beta(k)) = R_l(d_k), l = 1, \ldots, L, k = 1, \ldots, K$. Denote set $B = \{\beta(1), \ldots, \beta(K)\}$ and its convex hull B^*. Let

$$\beta_l^- = \min\{\beta_l(1), \ldots, \beta_l(K)\}, \qquad \beta_l^+ = \max\{\beta_l(1), \ldots, \beta_l(K)\}, \quad l = 1, \ldots, L.$$

The *rectangular envelope* of a set B is defined as

$$B^{\#} = \prod_{l=1}^{L} [\beta_l^-, \beta_l^+],$$

the Cartesian product of the L close intervals $[\beta_l^-, \beta_l^+], l = 1, \ldots, L$. It is clear that $B \subset B^* \subset B^{\#}$. For example, suppose $L = 2, K = 3, \beta(1) = (1, 2), \beta(2) = (3, 1), \beta(3) = (2, 4)$. Then, $B = \{(1, 2), (3, 1), (2, 4)\}$ which consists of 3 points in the two-dimensional Euclidean space, and its convex hull B^* consists of all the points in the triangle formed by the 3 points in B, while the rectangular envelope $B^{\#} = [1, 3] \times [1, 4] = \{(x, y) : 1 \le x \le 3, 1 \le y \le 4\}$.

Theorem 1. *Assume a working multiplicative model (2). Suppose that the rectangular envelope $B^{\#}$ is a subset of Ω^o, the interior of Ω. Then, $\hat{\beta}_n \to \beta_0$ and $x(n) \to d_v$ almost surely.*

Proof. Define the average score

$$S_n(\beta) = \frac{1}{n} \sum_{i=1}^{n} \left[\sum_{l=1}^{L-1} I(Y_i = l) \frac{\nabla\psi_l - \nabla\psi_{l+1}}{\psi_l - \psi_{l+1}}\{x(i), \beta\} + I(Y_i = L) \frac{\nabla\psi_L}{\psi_L}\{x(i), \beta\} + I(Y_i = 0) \frac{-\nabla\psi_1}{1 - \psi_1}\{x(i), \beta\} \right]$$

and its expectation

$$\begin{aligned} \tilde{S}_n(\beta) &= E\{S_n(\beta)\} \\ &= \frac{1}{n} \sum_{i=1}^{n} \left(\sum_{l=1}^{L-1} [R_l\{x(i)\} - R_{l+1}\{x(i)\}] \frac{\nabla\psi_l - \nabla\psi_{l+1}}{\psi_l - \psi_{l+1}}\{x(i), \beta\} \right. \\ &\quad \left. + R_L(x(i)) \frac{\nabla\psi_L}{\psi_L}\{x(i), \beta\} + [1 - R_1(x(i))] \frac{-\nabla\psi_1}{1 - \psi_1}\{x(i), \beta\} \right). \end{aligned}$$

By an argument similar to Shen and O'Quigley (1996), the martingale family $S_n(\beta) - \tilde{S}_n(\beta)$ converges to 0 almost surely and uniformly with respect to $\beta \in A$ for any compact set A. That is,

$$\sup_{\beta \in A} |S_n(\beta) - \tilde{S}_n(\beta)| \to 0 \tag{3}$$

almost surely. Rewrite

$$\tilde{S}_n(\beta) = \sum_{k=1}^{K} \hat{p}_k \left[\sum_{l=1}^{L-1} \{R_l(d_k) - R_{l+1}(d_k)\} \frac{\nabla\psi_l - \nabla\psi_{l+1}}{\psi_l - \psi_{l+1}}(d_k, \beta) + R_L(d_k) \frac{\nabla\psi_L}{\psi_L}(d_k, \beta) + \{1 - R_1(d_k)\} \frac{-\nabla\psi_1}{1 - \psi_1}(d_k, \beta) \right],$$

where $\hat{p}_k$ is the proportion of subjects assigned to dose d_k out of the first n subjects. For model (2), $\tilde{S}_n(\beta) = 0$ is simplified as the following system of equations

$$\sum_{k=1}^{K} \hat{p}_k \left[R_1(d_k) \frac{\varphi_1'}{\varphi_1}(d_k, \beta_1) + \{1 - R_1(d_k)\} \frac{-\varphi_1'}{1 - \varphi_1}(d_k, \beta_1) \right] = 0;$$

$$\sum_{k=1}^{K} \hat{p}_k R_1(d_k) \left[\frac{R_2(d_k)}{R_1(d_k)} \frac{\varphi_2'}{\varphi_2}(d_k, \beta_2) + \left\{ 1 - \frac{R_2(d_k)}{R_1(d_k)} \right\} \frac{-\varphi_2'}{1 - \varphi_2}(d_k, \beta_2) \right] = 0;$$

$$\vdots$$

$$\sum_{k=1}^{K} \hat{p}_k R_{L-1}(d_k) \left[\frac{R_L(d_k)}{R_{L-1}(d_k)} \frac{\varphi_L'}{\varphi_L}(d_k, \beta_L) + \left\{ 1 - \frac{R_L(d_k)}{R_{L-1}(d_k)} \right\} \frac{-\varphi_L'}{1 - \varphi_L}(d_k, \beta_L) \right] = 0.$$

Denote the solution to $\tilde{S}_n(\beta) = 0$ as $\tilde{\beta}_n$. Since by Condition C3, the left hand sides of the above L equations are monotone in $\beta_1, \ldots, \beta_L$, respectively, we conclude that $\tilde{\beta}_n \in B^{\#} \subset \Omega^o$. Choosing $A = B^{\#}$ in (3) and by the openness of Ω^o, $\hat{\beta}_n \in \Omega$ eventually. By the definition of Ω, $x(n+1) = d_\nu$ eventually. Now, as $n \to \infty$, $\hat{p}_k \to 0$ for $k \neq \nu$. Therefore, $\tilde{\beta}_n$, and hence $\hat{\beta}_n$, approaches β_0, the unique solution to the following system of equations

$$\sum_{l=1}^{L-1} \{R_l(d_\nu) - R_{l+1}(d_\nu)\} \frac{\nabla\psi_l - \nabla\psi_{l+1}}{\psi_l - \psi_{l+1}}(d_\nu, \beta) + R_L(d_\nu)\frac{\nabla\psi_L}{\psi_L}(d_\nu, \beta) + \{1 - R_1(d_\nu)\}\frac{-\nabla\psi_1}{1-\psi_1}(d_\nu, \beta) = 0.$$

This proves the consistency of $\hat{\beta}_n$. □

Once the consistency of $\hat{\beta}_n$ is obtained, we can establish its asymptotical distribution.

Theorem 2. *Under the same assumptions of Theorem 1, we have, as* $n \to \infty$,

$$\sqrt{n}(\hat{\beta}_n - \beta_0) \to_d N_L\{0, \Sigma(d_\nu, \beta_0)\},$$

where $\Sigma(d_\nu, \beta_0)$ *is an* $L \times L$ *positive definite diagonal matrix whose* l*th diagonal entry is* $\theta_l(\theta_{l-1} - \theta_l)/[\theta_{l-1}^3\{\varphi_l'(d_\nu, \beta_{0,l})\}^2]$, $l = 1, \ldots, L$, *and* $\theta_0 \equiv 1$.

The proof of Theorem 2 is straightforward and hence is omitted.

3.3. Comparison of assumptions for single versus multiple constraints

The robust condition we proposed for the asymptotic result under multiple constraints is $B^{\#} \subset \Omega^o$. In this section, we provide some discussions of this assumption and contrast it with the one made in Shen and O'Quigley (1996) for single constraint (i.e., Condition 4 in Section 3.1).

When the working model (2) is indeed the true model, $B^{\#} = \{\beta_0\} \subset \Omega^o$, hence this assumption is trivially satisfied. If the model is misspecified, the procedure could still be consistent as long as $B^{\#} \subset \Omega^o$, and in that case the robustness of the procedure is reflected by the geometric shape and volume of the rectangular envelope $B^{\#}$. That is, the bigger the volume of $B^{\#}$, the more robust the result against violation of model assumption.

Using our notations, the Condition C4 is $B \subset \Omega^o$, which implies that the convex hull $B^* \subset \Omega^o$ since the good parameter set Ω in the single constraint case is a convex set. They showed that $B^* \subset \Omega^o$ implies that $\tilde{\beta}_n \in \Omega^o$ (so does $\hat{\beta}_n$ when n is large enough). This claim is based on the mathematical fact that the maximum point of a positive linear combination of univariate non-monotone concave down functions lies in the convex hull spanned by the individual maximum points of these concave down functions. Unfortunately, there is no similar fact for multivariate convex functions. Therefore, the assumption $B^* \subset \Omega^o$ is not enough for the multiple constraints problem. Our proposed assumption $B^{\#} \subset \Omega^o$ is stronger than $B^* \subset \Omega^o$ since the convex hull B^* is always a subset of the rectangular envelope $B^{\#}$.

Although we have shown that assumption $B^{\#} \subset \Omega^o$ implies $\tilde{\beta}_n \in \Omega^o$, we must emphasize that the claim is confirmed only for the proposed multiplicative model (2) and may not be true for a non-multiplicative model. This signifies a drastic technical difference between a single constraint dose finding problem and a multiple constraint dose finding problem. From a practical point of view, we argue that our multiplicative model, which allows for different analytical forms for $\varphi_l(x, \beta_l)$, $l = 1, \ldots, L$, should be flexible enough to serve the purpose of most toxicity outcome modeling.

4. Simulation study

In the simulation study, we compare the performance of two versions of the proposed likelihood procedure for multiple toxicity constraints using different rule based designs in the first stage with its Bayesian counterpart (CRM-MC-B), one with dose escalation in cohorts of three (CRM-MC-L-3 + 3) and the other with dose escalation after every patient (CRM-MC-L-1+1). For reference purpose, we also include the two versions of the likelihood procedure for single constraint (CRM-L-3+3 and CRM-L-1 + 1).

Using the general setting of the bortezomib trial (Leonard et al., 2005) in Lee et al. (2011), we assume five dose levels (i.e., $K = 5$) with the third dose level being the prior guess of the maximum tolerated dose. The ordinal toxicity outcome has three possible values $Y = 0, 1, 2$, where $Y = 1, 2$ denotes dose limiting toxicity and $Y = 2$ a severe or life threatening toxicity. Two toxicity constraints are imposed, i.e., $L = 2$. The primary constraint requires that the probability of dose limiting toxicity $\text{pr}(Y \geq 1|x) \leq \theta_1 = 0.25$ and the secondary constraint requires the probability of severe toxicity $\text{pr}(Y = 2|x) \leq \theta_2 = 0.10$. We consider sample sizes of 21 and 39 with the corresponding scaled doses (0.02, 0.09, 0.25, 0.44, 0.62) and (0.06, 0.14, 0.25, 0.38, 0.50). These scaled doses are obtained using Lee and Cheung (2009) and assuming only the primary constraint. The empiric working models as specified in Proposition 1 are used. Dose skipping and dose escalation are not allowed immediately after $Y \geq 1$ is observed.

Two thousand simulations are performed for each of the five scenarios considered (Tables 1 and 2). For each method the percentage of times a dose is recommended as the maximum tolerated dose is reported. In Scenario 1, the optimal

Table 1
Operating characteristics of CRM-L, CRM-MC-L, and CRM-MC-B methods with $N = 21$.

	Dose level				
	1	2	3	4	5
Scenario 1					
Probability of DLT	0.05	0.05	**0.25**	0.45	0.55
Probability of severe toxicity	0.01	0.01	**0.10**	0.24	0.35
% recommended by CRM-L-3+3	1	13	**63**	21	2
% recommended by CRM-L-1+1	0	12	**67**	20	1
% recommended by CRM-MC-L-3+3	5	29	**57**	9	0
% recommended by CRM-MC-L-1+1	3	23	**62**	11	1
% recommended by CRM-MC-B	1	23	**70**	6	0
Scenario 2					
Probability of DLT	0.05	0.05	**0.25**	0.45	0.55
Probability of severe toxicity	0.00	0.01	0.05	**0.10**	0.20
% recommended by CRM-L 3+3	1	13	**63**	21	2
% recommended by CRM-L 1+1	0	12	**67**	20	1
% recommended by CRM-MC-L-3+3	2	20	**61**	15	1
% recommended by CRM-MC-L-1+1	1	17	**64**	17	1
% recommended by CRM-MC-B	1	17	**71**	11	0
Scenario 3					
Probability of DLT	0.05	**0.25**	0.45	0.55	0.70
Probability of severe toxicity	0.00	0.01	0.05	**0.10**	0.20
% recommended by CRM-L-3+3	7	**70**	21	1	0
% recommended by CRM-L-1+1	9	**69**	20	2	0
% recommended by CRM-MC-L-3+3	10	**70**	19	1	0
% recommended by CRM-MC-L-1+1	12	**68**	19	2	0
% recommended by CRM-MC-B	16	**67**	15	1	0
Scenario 4					
Probability of DLT	0.05	0.10	0.16	**0.25**	0.45
Probability of severe toxicity	0.01	0.03	**0.10**	0.23	0.35
% recommended by CRM-L-3+3	1	14	**37**	35	14
% recommended by CRM-L-1+1	1	10	**30**	45	15
% recommended by CRM-MC-L-3+3	6	33	**44**	14	3
% recommended by CRM-MC-L-1+1	5	28	**44**	20	3
% recommended by CRM-MC-B	2	22	**54**	21	1
Scenario 5					
Probability of DLT	0.05	0.12	0.20	**0.25**	0.45
Probability of severe toxicity	0.01	**0.10**	0.18	0.23	0.35
% recommended by CRM-L-3+3	1	**20**	39	29	11
% recommended by CRM-L-1+1	1	**15**	32	38	14
% recommended by CRM-MC-L-3+3	23	**47**	20	8	2
% recommended by CRM-MC-L-1+1	17	**42**	27	11	2
% recommended by CRM-MC-B	9	**39**	37	15	1

dose for the primary constraint agrees with the one for the secondary constraint. In Scenarios 2 and 3, the optimal dose for the secondary constraint is either one level (Scenario 2) or two levels (Scenario 3) higher than the one for the primary constraint. These three scenarios are chosen to simulate scenarios when multiple constraints are not needed because the primary constraint is the limiting constraint. The purpose is to evaluate the efficiency of the proposed method in comparison with the original CRM. In Scenarios 4 and 5, the optimal dose for secondary constraint is either one level (Scenario 4) or two levels (Scenario 5) lower than the one for the primary constraint. As the result, in both these cases the maximum tolerated dose for multiple constraints is lower than the optimal dose for the single primary constraint. The 4th and 5th scenarios are chosen to simulate scenarios when multiple constraints are useful because the secondary constraint is the limiting constraint. Here we point out that in these scenarios, the objective of CRM with multiple constraints is different from that of the original CRM which is only based on the primary constraint. Therefore, it is expected that the two methods will choose different MTDs.

When the maximum tolerated dose under multiple constraints agrees with the optimal dose for the primary constraint (Scenarios 1, 2, and 3), the likelihood based continual reassessment method with multiple constraints performs similarly (Scenarios 2 and 3) or slightly worse (Scenario 1). In these cases, imposing the secondary constraint does not improve the ability to identify the maximum tolerated dose and may worsen the performance for small sample sizes. With larger sample sizes, the performance of the likelihood based continual reassessment method with multiple constraints improved and was comparable to the likelihood methods with a single constraint (Table 2). When the maximum tolerated dose under multiple constraints does not agree with the optimal dose for the primary constraint (Scenarios 4 and 5), both the Bayesian and likelihood methods that take into account of the multiple constraints performed much better than the original likelihood based continual reassessment methods which recommended a wrong dose with high probability. The likelihood based

Table 2
Operating characteristics of CRM-L and CRM-MC-L methods with $N = 39$.

	Dose level				
	1	2	3	4	5
Scenario 1					
Probability of DLT	0.05	0.05	**0.25**	0.45	0.55
Probability of severe toxicity	0.01	0.01	**0.10**	0.24	0.35
% recommended by CRM-L-3+3	0	9	**76**	15	0
% recommended by CRM-L-1+1	0	8	**79**	13	0
% recommended by CRM-MC-L-3+3	1	19	**73**	7	0
% recommended by CRM-MC-L-1+1	0	18	**75**	7	0
Scenario 2					
Probability of DLT	0.05	0.05	**0.25**	0.45	0.55
Probability of severe toxicity	0.00	0.01	0.05	**0.10**	0.20
% recommended by CRM-L-3+3	0	9	**76**	15	0
% recommended by CRM-L-1+1	0	8	**79**	13	0
% recommended by CRM-MC-L-3+3	0	8	**77**	14	0
% recommended by CRM-MC-L-1+1	0	9	**78**	13	0
Scenario 3					
Probability of DLT	0.05	**0.25**	0.45	0.55	0.70
Probability of severe toxicity	0.00	0.01	0.05	**0.10**	0.20
% recommended by CRM-L-3+3	8	**78**	14	0	0
% recommended by CRM-L-1+1	8	**80**	12	0	0
% recommended by CRM-MC-L-3+3	7	**79**	14	0	0
% recommended by CRM-MC-L-1+1	8	**79**	13	0	0
Scenario 4					
Probability of DLT	0.05	0.10	0.16	**0.25**	0.45
Probability of severe toxicity	0.01	0.03	**0.10**	0.23	0.35
% recommended by CRM-L-3+3	0	3	**28**	58	11
% recommended by CRM-L-1+1	0	3	**29**	59	10
% recommended by CRM-MC-L-3+3	1	25	**60**	13	1
% recommended by CRM-MC-L-1+1	1	25	**61**	12	0
Scenario 5					
Probability of DLT	0.05	0.12	0.20	**0.25**	0.45
Probability of severe toxicity	0.01	**0.10**	0.18	0.23	0.35
% recommended by CRM-L-3+3	0	**8**	35	48	9
% recommended by CRM-L-1+1	0	**7**	35	50	9
% recommended by CRM-MC-L-3+3	13	**59**	22	5	0
% recommended by CRM-MC-L-1+1	12	**59**	24	5	0

methods for multiple constraints had comparable performance across all the five scenarios with their Bayesian counterpart, but dramatically reduced the computing time (from 24 h to 15 min). This confirmed our initial conjecture about the two methods and supported our preference to the likelihood methods for their computational convenience. This conclusion was further supported by additional simulations with 60 subjects for each simulation (data not shown). The performance of the likelihood based methods improved as the sample size increased but the computational burden made it impractical to use the Bayesian method.

In comparison to the CRM, the simulations indicate that in the scenarios where the objective matches that of the CRM, the CRM performs slightly better than the proposed method, suggesting a small loss of efficiency due to the additional constraint. In scenarios where the objectives are different, the methods select the dose associated with their corresponding objectives. That is, the CRM selects the MTD associated with the primary constraint and the CRM with multiple constraints selects the MTD that satisfies both constraints. Therefore, if at the planning stage, with or without knowledge of the relative composition of toxicity grades, the investigators are interested in controlling the probabilities of toxicity for the various gradations of toxicities, they could use the proposed method to ensure that the MTD selected satisfies the prespecified multiple constraints. For example, if the investigators suspect that a substantial number of the DLTs would be grade 4 or higher toxicities and are not willing to tolerate a 25% rate of these severe toxicities, they can specify a lower tolerance for these severe toxicities in addition to the DLT threshold and use the proposed method. However, if there is not such prior concern, then the original CRM is the method of choice.

5. Discussion

In this paper, we investigate the asymptotic properties of the generalized continual reassessment method under multiple toxicity constraints and give the first rigorous proof of the consistency of the procedure under a class of potentially misspecified models. One of the critical steps of the proof involves characterizing the location of the maximum likelihood estimator, which is much harder in a multiple constrain problem. To overcome this difficulty, we propose a class of multiplicative

models and show that under these models the score function can be drastically simplified and hence it becomes easier to characterize the location of its solutions.

We have established the consistency of the sequential dosing procedure under condition $B^{\#} \subset \Omega^{o}$. When this condition is violated, it is generally unclear whether the dosing procedure remains consistent. It is of theoretical interest to investigate whether the condition can be weakened. In addition, the consistency result is obtained using a multiplicative model (2) as the working model. The consistency of dosing procedure under non-multiplicative models requires further study. Therefore, although clinicians have flexibility to choose their own working models, it is recommended that a multiplicative model be used for its clear clinical interpretation and confirmed theoretical properties if the trials involve multiple toxicity constraints.

It must be noted that in order to make use of all L constraints, full heterogeneity in Y must be observed. Otherwise, some of the constraints will never be invoked. Depending on the number of constraints specified, observing full heterogeneity may require large sample sizes. Given the small sample sizes in most phase I studies, we do not recommend many toxicity constraints, although the procedure remains theoretically justified. From the practical point of view, we believe that in most phase I studies using two constraints, one constraint on DLT and one additional constraint, will be sufficient.

The findings in Iasonos et al. (2011), Van Meter et al. (2011, 2012) indicate that incorporating the additional grade information in the modeling does not generally improve the accuracy of identification of the MTD as long as the objective remains the same as the original CRM. The proposed method complements the above findings by showing that incorporating the grade information could be helpful if the objective is modified to include additional constraints on the various levels. In practice, the proposed method can be applied to situations where the investigators are interested in setting thresholds for various gradations of toxicity and seeking for an MTD that satisfies multiple toxicity criteria.

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