Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Statistical Planning and Inference 136 (2006) 1765–1780
journal of statistical planning and inference
www.elsevier.com/locate/jspi

Theoretical study of the continual reassessment method

John O'Quigley

Institut Curie, 26 rue d'Ulm, 75005 Paris, France

Available online 28 September 2005

Abstract

The continual reassessment method (CRM) was first introduced by O'Quigley et al. [1990. Continual reassessment method: a practical design for Phase I clinical trials in cancer. Biometrics 46, 33–48]. Many articles followed adding to the original ideas, among which are articles by Babb et al. [1998. Cancer Phase I clinical trials: efficient dose escalation with overdose control. Statist. Med. 17, 1103–1120], Braun [2002. The bivariate-continual reassessment method. Extending the CRM to phase I trials of two competing outcomes. Controlled Clin. Trials 23, 240–256], Chevret [1993. The continual reassessment method in cancer phase I clinical trials: a simulation study. Statist. Med. 12, 1093–1108], Faries [1994. Practical modifications of the continual reassessment method for phase I cancer clinical trials. J. Biopharm. Statist. 4, 147–164], Goodman et al. [1995. Some practical improvements in the continual reassessment method for phase I studies. Statist. Med. 14, 1149–1161], Ishizuka and Ohashi [2001. The continual reassessment method and its applications: a Bayesian methodology for phase I cancer clinical trials. Statist. Med. 20, 2661–2681], Legedeza and Ibrahim [2002. Longitudinal design for phase I trials using the continual reassessment method. Controlled Clin. Trials 21, 578–588], Mahmood [2001. Application of preclinical data to initiate the modified continual reassessment method for maximum tolerated dose-finding trial. J. Clin. Pharmacol. 41, 19–24], Moller [1995. An extension of the continual reassessment method using a preliminary up and down design in a dose finding study in cancer patients in order to investigate a greater number of dose levels. Statist. Med. 14, 911–922], O'Quigley [1992. Estimating the probability of toxicity at the recommended dose following a Phase I clinical trial in cancer. Biometrics 48, 853–862], O'Quigley and Shen [1996. Continual reassessment method: a likelihood approach. Biometrics 52, 163–174], O'Quigley et al. (1999), O'Quigley et al. [2002. Non-parametric optimal design in dose finding studies. Biostatistics 3, 51–56], O'Quigley and Paoletti [2003. Continual reassessment method for ordered groups. Biometrics 59, 429–439], Piantodosi et al., 1998. [1998 Practical implementation of a modified continual reassessment method for dose-finding trials. Cancer Chemother. Pharmacol. 41, 429–436] and Whitehead and Williamson [1998. Bayesian decision procedures based on logistic regression models for dose-finding studies. J. Biopharm. Statist. 8, 445–467]. The method is broadly described by Storer [1989. Design and analysis of Phase I clinical trials. Biometrics 45, 925–937]. Whether likelihood or Bayesian based, inference poses particular theoretical difficulties in view of working models being under-parameterized. Nonetheless CRM models have proven themselves to be of practical use and, in this work, the aim is to turn the spotlight on the main theoretical ideas underpinning the approach, obtaining

E-mail address: oquigley@math.ucsd.edu.

0378-3758/$ - see front matter © 2005 Published by Elsevier B.V.
doi:10.1016/j.jspi.2005.08.003

results which can provide guidance in practice. Stemming from this theoretical framework are a number of results and some further development, in particular the way to structure a randomized allocation of subjects as well as a more robust approach to the problem of dealing with patient heterogeneity.

Keywords: Clinical trial; Continual reassessment method; Dose escalation; Dose finding studies; Maximum likelihood; Maximum tolerated dose; Phase 1 trial; Toxicity

1. Introduction

In this work we carry out a study of the theoretical properties of the continual reassessment method (CRM), introduced by O'Quigley et al. (1990). The following section, divided into two subsections, summarizes the main features underlying the method, features which have been described in a number of published papers. The main focus of this current work is in Section 3 where we investigate the theoretical underpinnings to the method. This work has not appeared elsewhere, apart from parts of the subsections headed "Consistency" and "Efficiency" which are included here for completeness. Section 4, headed "Randomization and two parameter models" and Section 5, headed "Subject heterogeneity" present new material.

2. Background

2.1. Continual reassessment method

The CRM, was proposed as a statistical design to meet the requirements of a dose finding study in which, aside from the usual requirements of statistical efficiency, it is necessary, for ethical reasons, to attempt, for every included subject, to allocate to our current best estimate of some acceptable target dose. Many developments and innovations have followed, the basic method and variants having found a number of other potential applications. We assume that we have available k doses; $d_1, \ldots, d_k$, possibly multi dimensional and ordered in terms of the probabilities, $R(d_i)$, for toxicity at each of the levels, i.e. $R(d_i) \leqslant R(d_j)$ whenever $i < j$. The most appropriate dose, the 'target' dose in any study and the dose defined to be the "maximum tolerated dose (MTD)", denoted $d_0 \in \{d_1, \ldots, d_k\}$ is that dose having an associated probability of toxicity, $R(d_0)$, as close as we can get to some target "acceptable" toxicity rate θ. Specifically we define $d_0 \in \{d_1, \ldots, d_k\}$ such that

$$|R(d_0) - \theta| < |R(d_\ell) - \theta|, \quad \ell = 1, \ldots, k; \;\; d_\ell \neq d_0. \tag{1}$$

The binary indicator Y_j takes the value 1 in the case of a toxic response for the jth entered subject ($j = 1, \ldots, n$) and 0 otherwise. The dose for the jth entered subject, X_j is viewed as random taking values $x_j \in \{d_1, \ldots, d_k\}$; $j = 1, \ldots, n$. Thus $Pr(Y_j = 1 | X_j = x_j) = R(x_j)$.

Little is known about $R(\cdot)$ and, given the n observations, the main goal is to identify d_0. The patients included in the Phase I design must, themselves, be treated "optimally", the notion optimal now implying for these patients a requirement to treat at the best dose level, this being defined as the one as close as we can get to d_0. Of course if we knew d_0 the problem no longer exists and, in practice, we can only hope to treat at the level we believe, in the light of all available information, to be our best bet of being d_0. We then have two statistical goals; (1) estimate d_0 consistently and

efficiently and, (2) during the course of the study, concentrate as many experiments as possible around d_0, more precisely treat the jth included patient at the same level we would have estimated as being d_0 had the study ended after the inclusion of $j-1$ patients. We model $R(x_j)$, the true probability of toxic response at $X_j = x_j$; $x_j \in \{d_1, \ldots, d_k\}$ by

$$R(x_j) = Pr(Y_j = 1 | X_j = x_j) = E(Y_j | x_j) = \psi(x_j, a)$$

for some one parameter model $\psi(x_j, a)$ and a defined on the set $\mathscr{A}$. For every a, $\psi(x, a)$ should be monotone increasing in x and, for any x, $\psi(x, a)$ should be monotone in a. For every d_i there exists some $a_i \in \mathscr{A}$ such that $R(d_i) = \psi(d_i, a_i)$, i.e. the one parameter model is rich enough, at each dose, to exactly reproduce the true probability of toxicity at that dose. We have a lot of flexibility in our choice for $\psi(x, a)$, the simple choice:

$$\psi(d_i, a) = \alpha_i^{\exp(a)}, \quad (i = 1, \ldots, k), \tag{2}$$

where $0 < \alpha_1 < \cdots < \alpha_k < 1$ and $-\infty < a < \infty$, having worked well in our experience. The true mechanism generating the observations can be quite removed from our working model overall, but, close to our target, the true situation and our working model coincide. For the six levels studied in the simulations by O'Quigley et al. (1990) the working model had $\alpha_1 = 0.05$, $\alpha_2 = 0.10$, $\alpha_3 = 0.20$, $\alpha_4 = 0.30$, $\alpha_5 = 0.50$ and $\alpha_6 = 0.70$. Once a model has been chosen and we have data in the form of the set $\Omega_j = \{y_1, x_1, \ldots, y_j, x_j\}$, the outcomes of the first j experiments we obtain estimates $\hat{R}(d_i)$, $(i = 1, \ldots, k)$ of the true unknown probabilities $R(d_i)$, $(i = 1, \ldots, k)$ at the k dose levels (see below). The target dose level is that level having associated with it a probability of toxicity as close as we can get to θ. The dose or dose level x_j assigned to the jth included patient is such that

$$|\hat{R}(x_j) - \theta| < |\hat{R}(d_\ell) - \theta|, \quad \ell = 1, \ldots, k; \ d_\ell \neq x_j. \tag{3}$$

This equation should be compared to Eq. (1). It translates the idea that the overall goal of the study is also the goal for each included patient.

The CRM is then an iterative sequential design, the level chosen for the $n+1$th patient, who is hypothetical, being also our estimate of d_0. After having included j subjects, we require some estimate of the unknown parameter a in order to implement the algorithm (Fig. 1).

2.2. Inference

After the inclusion of the first j patients, the log-likelihood can be written as

$$\mathscr{L}_j(a) = \sum_{\ell=1}^{j} y_\ell \log \psi(x_\ell, a) + \sum_{\ell=1}^{j} (1 - y_\ell) \log(1 - \psi(x_\ell, a)) \tag{4}$$

and is maximized at $a = \hat{a}_j$. Once we have calculated $\hat{a}_j$ we can next obtain an estimate of the probability of toxicity at each dose level d_i via: $\hat{R}(d_i) = \psi(d_i, \hat{a}_j)$, $(i = 1, \ldots, k)$. On the basis of this formula the dose to be given to the $(j+1)$th patient, x_{j+1} is determined.

In order to be able to maximize the log-likelihood on the interior of the parameter space we require heterogeneity among the responses, i.e. at least one toxic and one non-toxic response. This condition is slightly weaker than that of Silvapulle (1981) which required that the responses be intermixed, that is that there be at least one toxic response occurring below a non-toxic response or at least one non-toxic response occurring above a toxic response. The condition is needed in

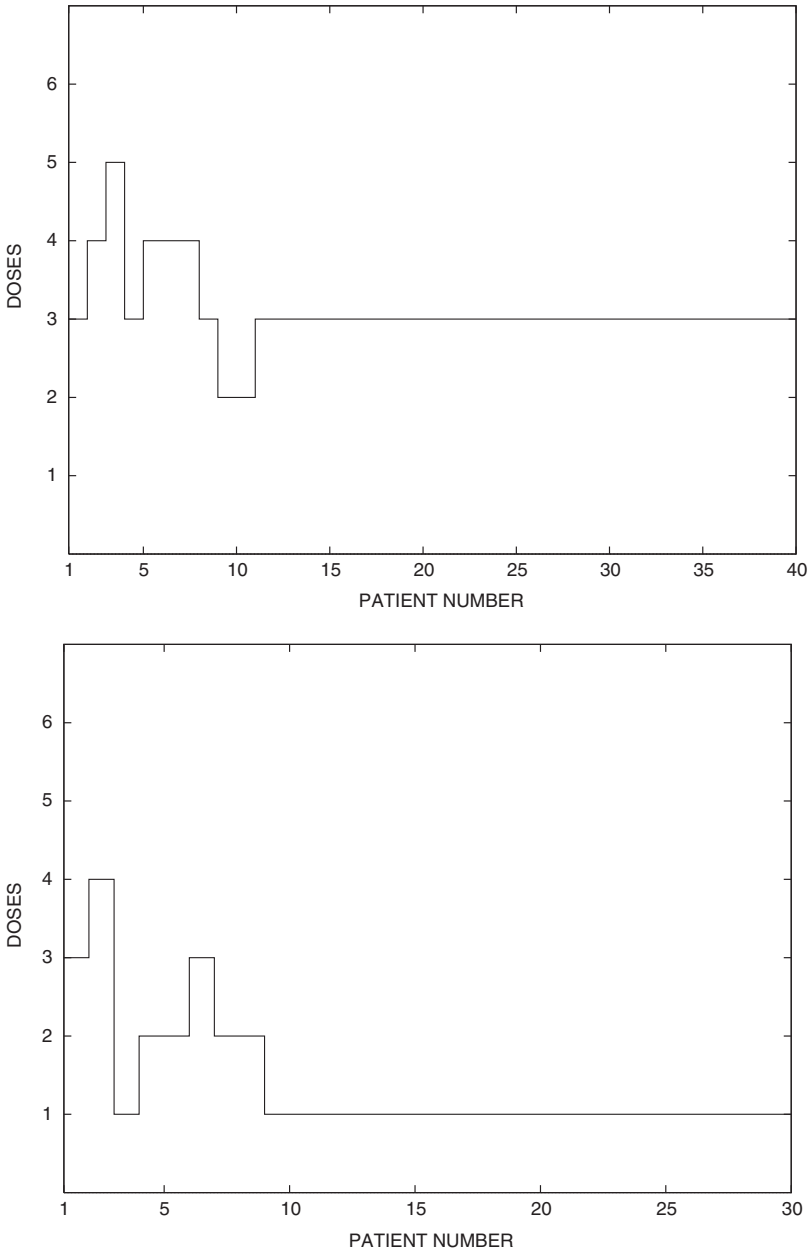

Fig. 1. CRM simulations; upper figure: target level 3; lower figure: target level 1.

order for the likelihood not to be maximized on the boundary of the parameter space leading to estimates of $R(d_i)$, $(i = 1, \ldots, k)$ which are trivially either zero, one, or, depending on the model we are working with, may not even be defined. Thus the experiment is considered as not being fully underway until we have some heterogeneity in the responses. These could arise in a variety of

different ways, use of the up and down approach, use of an initial Bayesian CRM as outlined below or use of a design believed to be more appropriate by the investigator. Once we have achieved heterogeneity, the model kicks in and we continue as prescribed above (estimation–allocation).

Getting the trial underway, i.e. achieving the necessary heterogeneity to carry out the above prescription, is largely arbitrary. This feature is specific to the maximum likelihood implementation and is avoided, although somewhat artificially, if we use Bayes' formula and introduce some prior. It is common then to split the design into 2 stages; an initial exploratory escalation followed by a more refined homing in on the target. Such an idea was first proposed by Storer (1989) in the context of the more classical up and down schemes. Moller (1995) was the first to use this idea in the context of CRM designs. Her idea was to allow the first stage to be based on a randomly stopped up and down procedure. In the context of sequential likelihood estimation, the necessity of an initial stage was pointed out by O'Quigley and Shen (1996) since the likelihood equation is monotone in the unknown parameter until heterogeneity occurs. Their suggestion was to work with any initial scheme, Bayesian CRM or up and down, and, for any reasonable scheme, the operating characteristics appear relatively insensitive to this choice.

3. Theoretical properties

Extensive simulations (O'Quigley et al., 1990; O'Quigley and Shen, 1996; O'Quigley, 1992), over wide choices of possible true unknown dose-toxicity situations, show the method to behave in a mostly satisfactory way, recommending the right level or close levels in a high percentage of situations and treating in the study itself a high percentage of included patients, again, at the right level or levels close by. Here we consider some theoretical results which not only provide some confidence in using the method but can also provide guidance in the choice and structure of working models.

Convergence arguments obtain from considerations of the likelihood. The same arguments apply to Bayesian estimation as long as the prior is other than degenerate i.e. all the probability mass is not put on a single point. Usual likelihood arguments break down since our models are misspecified. We need to define

$$I_n(a) = \frac{1}{n}\sum_{j=1}^{n}\left[y_j\,\frac{\psi'}{\psi}\,\{x_j,a\} + (1-y_j)\,\frac{-\psi'}{1-\psi}\,\{x_j,a\}\right]$$

and

$$\tilde{I}_n(a) = \frac{1}{n}\sum_{j=1}^{n}\left(R\{x_j\}\,\frac{\psi'}{\psi}\,\{x_j,a\} + [1-R\{x_j\}]\,\frac{-\psi'}{1-\psi}\,\{x_j,a\}\right).$$

The maximum likelihood estimate, $\hat{R}(d_i) = \psi(d_i, \hat{a}_j)$ exists as soon as the equation $I_n(a) = 0$ has a solution. We need assume the dose toxicity function $\psi(x,a)$ satisfies some simple conditions in order to prove some useful properties. These are made explicit below.

Condition 1. *The parameter a belongs to a finite interval* $[A, B]$.

This is not really a practical restriction and enables us to avoid dealing with degenerate cases (probability of toxicity equaling zero or one) when the value of a lies on the boundary of the parameter space.

Condition 2. *The probabilities of toxicity satisfy*: $0 < R(d_1) < , \cdots , < R(d_k) < 1$.

This condition translates the idea that the function $R(\cdot)$ is invertible on the interval (0,1).

Condition 3. *For fixed* a, $\psi(x, a)$ *is continuous and strictly increasing in* x.

Condition 4. *For fixed* x, $\psi(x, a)$ *is continuous and strictly decreasing in* a.

Condition 5. *There exist* k *constants* $a_1, \ldots, a_k \in [A, B]$ *such that for* $1 \leqslant i \leqslant k$

(i) $\psi(d_i, a_i) = R_i$.
(ii) $\psi(d_i, B) < \theta < \psi(d_i, A)$.
(iii) *For a unique* $a_0 \in (a_1, \ldots, a_k)$, $\psi(d_0, a_0) = R(d_0) = \theta_0$.

The above conditions restrict our choice of the working model $\psi(x, a)$. The third condition is simply a definition of a_0 and θ_0. Note that, generally, $\theta_0 \neq \theta$ although we expect the two to be close. We also require that;

Condition 6. *For each* $0 < t < 1$ *and each* x, *the function*

$$s(t, x, a) := t\,\frac{\psi'}{\psi}\,(x, a) + (1 - t)\,\frac{-\psi'}{1 - \psi}\,(x, a),$$

is continuous and is strictly monotone in a.

A usual requirement in order for estimating equations to have unique solutions. These conditions, verifiable for $\psi(x, a)$, and generally plausible, although non verifiable, for $R(x)$ are all that is required for many results. Under some weak additional assumptions we can show that convergence can be guaranteed to a level close if not exactly the target level. Under a non verifiable condition, by virtue of its dependence on the unknown a_i, we can demonstrate convergence to the target level. This condition follows. Before writing it down note that, since our model is misspecified, it will generally not be true that $\psi(d_i, a_0) \equiv R(d_i)$ for $i = 1, \ldots, k$. The condition expresses the idea that the working model be not "too distant" from the true underlying dose toxicity curve and this is made precise with the help of the set

$$S(a_0) = \{a : |\psi(d_0, a) - \theta| < |\psi(d_i, a) - \theta| \text{ for all } d_i \neq d_0\}. \tag{5}$$

The condition we require is

Condition 7. *For* $i = 1, \ldots, k$, $a_i \in S(a_0)$.

The condition is not particularly transparent and is a formal way of expressing the idea that the true mechanism generating the observations is not too far removed from the working model. In fact, even when the difference between the two models is great, we will often (although less than 100% of the time) recommend the correct level and, otherwise, we anticipate recommending a level close to that. The condition, whether valid or invalid, can be useful in the context of theoretical study or simulations. We now use the above conditions to establish some useful results.

Theorem 1. *For each* $1 \leqslant i \leqslant k-1$, *there exists a unique constant* κ_i *such that*

$$\theta - \psi(x_i, \kappa_i) = \psi(x_{i+1}, \kappa_i) - \theta > 0.$$

Proof. First set $f_i(a) = \psi(x_i, a) + \psi(x_{i+1}, a)$. By Condition 4, $f_i(a)$ is continuous and strictly decreasing on $[A, B]$. For $1 \leqslant i \leqslant m$, let $L_j = \psi(x_j, A)$ and $U_j = \psi(x_j, B)$. With this notation we have that $f_i(a) : [A, B] \to [L_i + L_{i+1}, U_i + U_{i+1}]$ is invertible. Furthermore, since Condition 5 yields $2\theta \in [L_i + L_{i+1}, U_i + U_{i+1}]$, there exists a unique $\kappa_i \in [A, B]$ such that $f_i(\kappa_i) = 2\theta$. Thus $\psi(x_i, \kappa_i) + \psi(x_{i+1}, \kappa_i) = 2\theta$ and the theorem is proved. □

The constants κ_i naturally give rise to a partitioning of the parameter space $[A, B]$. More precisely we can write the interval $[A, B]$ as a union of non overlapping intervals whereby

$$[A, B] = \bigcup_{i=1}^{m} S_i,$$

where

$$S_1 = [A, \kappa_1), S_2 = [\kappa_1, \kappa_2), \ldots, S_m = (\kappa_{m-1}, B].$$

Example. Let $\psi(x, a) = x^a$, and $x_1 = 0.04, x_2 = 0.07, x_3 = 0.20, x_4 = 0.35, x_5 = 0.5, x_6 = 0.7$. The interval $[A, B] = [0, 5]$ will satisfy condition (C3) for any reality such that $1^{-7} < R_1 < \cdots < R_6 \leqslant 1$. Using the Newton–Raphson method we obtain the following partition: $S_1 = [0, .55)$, $S_2 = [.55, .79)$, $S_3 = [.79, 1.26)$, $S_4 = [1.26, 2.08)$, $S_5 = [2.08, 3.56)$, $S_6 = [3.56, 5]$.

Note that this breakdown enables the construction of a vague prior, very simply by putting a piecewise uniform on each segment so that the prior probability associated with each interval is just $1/k$. The importance of this partition of the parameter space is reflected in the following corollary.

Corollary 1. *Suppose that* $\hat{a}_j$ *is the estimate of the parameter a after the inclusion of j patients. If* $\hat{a}_j \in S_i$ *then* d_i *is the level recommended to patient* $j + 1$.

Proof. It suffices to show that $|\psi(x_j, \hat{a}_j) - \theta| > |\psi(d_i, \hat{a}_j) - \theta|$ for $x_j \neq d_i$. We show this for $x_j < d_i$ but the proof is analogous when $d_i < x_j$. There are two possible cases:

Case 1: $\psi(d_i, \hat{a}_j) \geqslant \theta$.

Using the facts that $\psi(x, a)$ is monotonically decreasing in a and increasing in x together with $\hat{a}_j > \kappa_{i-1}$ and $d_\ell \leqslant d_{i-1} < d_i$ we get $\psi(d_i, \hat{a}_j) < \psi(d_i, \kappa_{i-1})$ and $\psi(d_\ell, \hat{a}_j) \leqslant \psi(d_{i-1}, \hat{a}_j) < \psi(d_{i-1}, \kappa_{i-1}) < \theta$. With this, we can write

$$\psi(d_i, \hat{a}_j) - \theta = (\psi(d_i, \kappa_{i-1}) - \theta) - (\psi(d_i, \kappa_{i-1}) - \psi(d_i, \hat{a}_j)) \tag{6}$$

and

$$\begin{aligned}\theta - \psi(d_\ell, \hat{a}_j) = {} & (\theta - \psi(d_{i-1}, \kappa_{i-1})) + (\psi(d_{i-1}, \kappa_{i-1}) - \psi(d_{i-1}, \hat{a}_j)) \\ & + (\psi(d_{i-1}, \hat{a}_j) - \psi(d_\ell, \hat{a}_j)).\end{aligned} \tag{7}$$

By Eq. (6), $\psi(d_i, \hat{a}_j) - \theta < \psi(d_i, \kappa_{i-1}) - \theta$. On the other hand, Eq. (7) combined with Theorem 1 gives $\psi(d_\ell, \hat{a}_j) - \theta > \theta - \psi(x_{d+1}, \kappa_{i-1}) = \psi(d_i, \kappa_{i-1}) - \theta$.

Case 2: $\psi(d_i, \hat{a}_j) < \theta$.

Since $\psi(x,a)$ is strictly increasing in x we have $\psi(x_d,\hat{a}_j) > \psi(d_{i-1},\hat{a}_j) \geqslant \psi(d_\ell,\hat{a}_j)$. Thus, $\psi(d_\ell,\hat{a}_j) < \psi(d_i,\hat{a}_j) < \theta$. □

Theorem 2. *For each $\varepsilon > 0$ and for every $a \in [A,B]$ there exists N_ε such that whenever $n > N_\varepsilon$ we have*

$$|I_n(a) - I_{n+1}(a)| < \varepsilon.$$

Proof. Fix some $M > 0$, then for each $n > M$ we can write

$$I_n(a) = \frac{1}{n} I_M(a) + \frac{1}{n} \sum_{i=1}^{n-M} \rho_{M+i},$$

where $\rho_j = \psi'\{x_j,a\}/\psi\{x_j,a\}$, if subject j experienced a toxicity at dose x_j and $\rho_j = -\psi'\{x_j,a\}/[1-\psi\{x_j,a\}]$, otherwise. Now let D_1 and D_2 be bounds such that $|I_M(a)| < D_1$ and $\rho_j < D_2$ over $[A,B]$. Next, if $N_\varepsilon = \max(\sqrt{2D_1/\varepsilon}, 2D_2/\varepsilon)$ and $n > N_\varepsilon$ then we have

$$\begin{aligned}
&|I_{n+1}(a) - I_n(a)| \\
&= \left| \frac{1}{n} I_M(a) + \frac{1}{n} \sum_{i=1}^{n-M} \rho_{M+i} - \frac{1}{n+1} I_M(a) - \frac{1}{n+1} \sum_{i=1}^{n-M+1} \rho_{M+i} \right| \\
&= \left| \frac{1}{n(n+1)} I_M(a) + \frac{1}{n(n+1)} \sum_{i=1}^{n-M} \rho_{M+i} - \frac{1}{n+1} \rho_{n+1} \right| \\
&< \frac{1}{n(n+1)} D_1 + \frac{n-M+1}{n(n+1)} D_2 \leqslant \frac{1}{n(n+1)} D_1 + \frac{1}{n} D_2 < \varepsilon/2 + \varepsilon/2,
\end{aligned}$$

where the last equation follows from our choice of N_ε. □

For each n let $a(n)$ be the unique vanishing point of $I_n(a)$.

Corollary 2. *For each $\varepsilon > 0$ there exists N_ε such that $|a(n) - a(n+1)| < \varepsilon$, whenever $n > N_\varepsilon$.*

Proof. Let $J_n(a) = I_n(a) - I_{n+1}(a)$. The continuity of $J_n(a)$ follows from that for I_n and I_{n+1}. Also, in view of Condition 6, $J_n(a)$ is strictly monotonic in a, hence the result.

Lemma 1. *If $y_n = 1$ then $a(n) < a(n-1)$, otherwise $a(n) > a(n-1)$.*

3.1. Implications of lemmas and corollaries on operating characteristics

The lemmas and corollaries follow from the conditions on $\psi(x,a)$ so we assume that these are respected. They tell us something about the operating characteristics in individual studies. Theorem 1 and its corollary show that the parameter space breaks down in a logical way into a partition, the members of which indicate which level is to be used. This result hints that we do not expect to wildly jump around the dose levels and that we can anticipate "nice" behavior, as long as we choose a sensible partition. The illustration indicates how the lemma and corollary could be used in practice in constructing a model. Theorem 2 and its corollary provide the statements indicating this hoped for stability. Changes in our current estimates of the probability of toxicity

become smaller and smaller with n. This corresponds to the eventual settling at some level, in practice, following a reasonable division of $\mathscr{A}$, a settling which typically takes place after relatively few subjects have been included. Corollary 2 states that behavior is logical in that observed toxicities lead to a steeper estimated dose-toxicity curve and the tendency to recommend lower levels, observed non-toxicities tending to push toward the recommendation of higher levels. This is important in that some authors have speculated the contrary whereby experimentation could be somewhat erratic until we have good estimates. The underparameterization greatly contributes toward creating stability.

3.2. Consistency

It can be shown (Shen and O'Quigley, 1996), under the assumptions on $R(d_i)$ and $\psi(x_i, a)$, that $S(a_0)$ is an open and convex set. This result is the key to rewriting $\tilde{I}_n(a)$ below in a way that is convenient. Then,

$$\sup_{a\in[A,B]} |I_n(a) - \tilde{I}_n(a)| \to 0, \quad \text{almost surely.} \tag{8}$$

This convergence result follows intuitively and can be demonstrated rigorously in a number of ways. For instance, observe that for each dose level d_i, $(\psi'/\psi)(d_i, \cdot)$ and $\{\psi'/(1-\psi)\}(d_i, \cdot)$ are uniformly continuous in a over the finite interval $[A, B]$. Shen and O'Quigley (1996) applied this result to a sufficiently fine partition of the interval $[A, B]$ in order to bound by arbitrarily small quantities the above differences. The result then follows.

The next important step is to consider the finite interval $S_1(a_0) = [a_{(1)}, a_{(k)}]$ in which $a_{(1)} = \min\{a_1, \ldots, a_k\}$ and $a_{(k)} = \max\{a_1, \ldots, a_k\}$. Condition 2 on $R(x)$ and the convexity of the set $S(a_0)$ imply that $S_1(a_0) \subset S(a_0)$. Define $\pi_n(d_i) \in [0, 1]$ to be the frequency that the level d_i has been used by the first n experiments. Then we can rewrite $\tilde{I}_n(a)$ as

$$\tilde{I}_n(a) = \sum_{i=1}^{k} \pi_n(d_i) \left\{ R(d_i) \frac{\psi'}{\psi}(d_i, a) + (1 - R(d_i)) \frac{-\psi'}{1-\psi}(d_i, a) \right\}. \tag{9}$$

Now, let $\tilde{a}_n$ be the solution to the equation $\tilde{I}_n(a) = 0$, i.e., $\tilde{a}_n$ solves

$$\sum_{i=1}^{k} \pi_n(d_i) \left\{ R(d_i) \frac{\psi'}{\psi}(d_i, a) + (1 - R(d_i)) \frac{-\psi'}{1-\psi}(d_i, a) \right\} = 0. \tag{10}$$

For each $1 \leqslant i \leqslant k$, the definition of a_i and Condition 1 on the dose toxicity function indicate that a_i is the unique solution to the equation

$$\left\{ R(d_i) \frac{\psi'}{\psi}(d_i, a) + (1 - R(d_i)) \frac{-\psi'}{1-\psi}(d_i, a) \right\} = 0.$$

It follows that $\tilde{a}_n$ will fall into the interval $S_1(a_0)$. Since $\hat{a}_n$ solves $I_n(a) = 0$, (8) and uniform continuity ensure that, almost surely, $\hat{a}_n \in S(a_0)$ for n sufficiently large. Hence, for large n, $\hat{a}_n$ satisfies

$$|\psi(d_0, \hat{a}_n) - \theta| < |\psi(d_i, \hat{a}_n) - \theta|, \quad \text{for } i = 1, \ldots, k, \ d_i \neq d_0.$$

Thus for n large enough $x_{n+1} \equiv d_0$ so that at this dose level x_{n+1} satisfies $|x_{n+1} - d_0| < |x_n - d_0|$ if $x_n \neq d_0$. In other words, x_n converges to d_0 almost surely. Since there are only a finite number

of dose levels, x_n will stay at d_0 ultimately. To establish the consistency of $\hat{a}_n$, observe that, as n tends to infinity, $\pi_n(d_i)$, $(i = 1, \ldots, k)$ in (9) become negligible, except $\pi_n(d_0)$, which tends to 1. Thus $\tilde{a}_n$, being the solution for (10), will tend to the solution to

$$R(d_0)\,\frac{\psi'}{\psi}\,(d_0, a) + \{1 - R(d_0)\}\,\frac{-\psi'}{1-\psi}\,(d_0, a) = 0.$$

The solution to the above equation is a_0. Applying (8) again, we obtain the consistency of $\hat{a}_n$ and, further, that the asymptotic distribution of $\sqrt{n}(\hat{a}_n - a_0)$ is $N(0, \sigma^2)$, with $\sigma^2 = \{\psi'(d_0, a_0)\}^{-2}\theta_0(1-\theta_0)$.

3.3. Efficiency

O'Quigley (1992) proposes using $\hat{\theta}_n = \psi(x_{n+1}, \hat{a}_n)$ to estimate the probability of toxicity at the recommended level x_{n+1}, where $\hat{a}_n$ is the maximum likelihood estimate. An application of the δ-method (Shen and O'Quigley, 1996), shows that the asymptotic distribution of $\sqrt{n}\{\hat{\theta}_n - R(d_0)\}$ is $N\{0, \theta_0(1-\theta_0)\}$. The estimate then provided by CRM is fully efficient for large samples. This is what our intuition would suggest given the convergence properties of CRM. What actually takes place in finite samples needs to be investigated on a case by case basis. The relatively broad range of cases studied by O'Quigley (1992) show a mean squared error for the estimated probability of toxicity at the recommended level under CRM to correspond well with the theoretical variance for samples of size n, were all subjects to be experimented at the correct level. Some of the cases studied showed evidence of super-efficiency, translating non negligible bias that happens to be in the right direction while a few others indicated efficiency losses large enough to suggest the potential for improvement.

A useful tool in studies of finite sample efficiency is the idea of an optimal design. We can derive a non-parametric optimal design (O'Quigley et al., 2002) based upon a monotonicity toxicity assumption. Such an optimal design is not generally available in practice but can serve as a gold standard in theoretical studies. The monotonicity assumption implies that if a subject has a toxic reaction at level d_k $(k \leqslant 6)$ then they would necessarily have a toxic reaction at d_ℓ $(k \leqslant \ell \leqslant 6)$. As for their reaction at levels below d_k we have no information on this. On the other hand, should the subject tolerate the treatment at level d_k $(1 \leqslant k \leqslant 6)$ then they would necessarily tolerate the treatment at all levels d_ℓ $(1 \leqslant \ell \leqslant k)$. Thus, in practice, we only ever have partial (in some sense censored) information on actual subjects included in the study. However, for theoretical purposes, we can construct virtual subjects for whom the responses at all levels is known. As an illustration let's suppose that subject h experiences a toxicity at d_5 and subject j a non-toxicity at level d_3. This is summarized in the table in which missing or incomplete information is indicated by the * symbol.

Doses	d_1	d_2	d_3	d_4	d_5	d_6
Observed incomplete vector Y_{hk}	*	*	*	*	1	1
Unknown complete vector Y_{hk}	0	0	1	1	1	1
Observed incomplete vector Y_{jk}	0	0	0	*	*	*
Unknown complete vector Y_{jk}	0	0	0	0	0	1

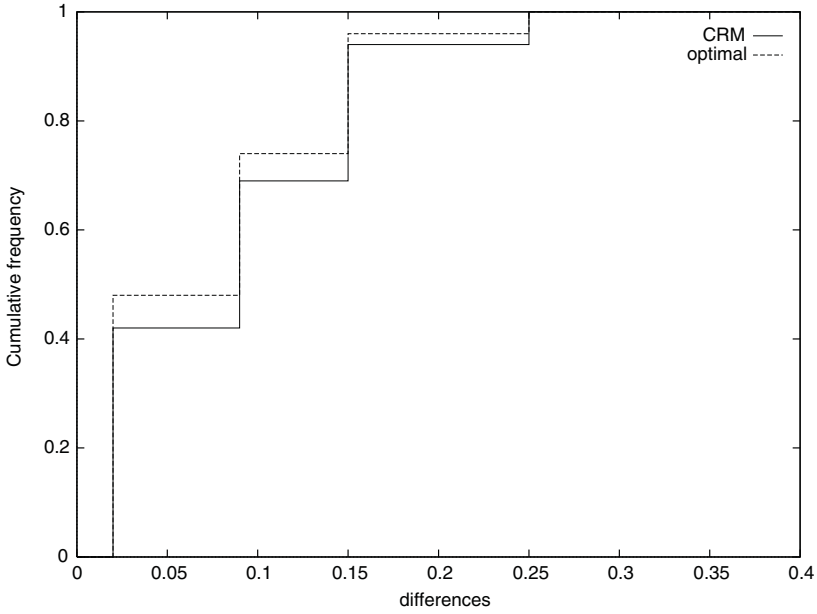

Fig. 2. Cumulative probability of error differences for the optimal and CRM design.

An illustration is given in O'Quigley et al. (2002) in which a two stage CRM design is compared with the optimal method. The initial stage of the two stage CRM design used 3 by 3 escalation, that is we start off at the lowest level and escalate one level after having seen 3 successive non-toxicities. The probability of recommending any level was estimated on the basis of 5000 simulations. The discrepancy between the true probability of toxicity at the recommended level and the probability of toxicity at the target level is called the error. The cumulative distributions of these errors for the two algorithms are shown in Fig. 2. For the particular situation studied we might conclude here that the potential for improvement is limited, the two stage CRM design being only slightly inferior to the optimal design.

It is possible to summarize the information in the graph into a single summary measure of finite sample efficiency using; $e(n) = \{\sum_k p_k(n)q_k(n)\}/\{\max(\sum_k p_k(n)^2, \sum_k q_k(n)^2)\}$ where, on the basis of n observations, $p_k(n)$ is the percentage recommendation for level k provided by the optimal design and $q_k(n)$ is that for the reference method. This is a measure of distance between the two cumulative distributions but, naturally, there are other candidate measures potentially worthy of investigation. For the above two stage CRM design, based on a total sample size of 16 patients, it was calculated that $e(16) = 0.93$.

3.4. Non-identifiability of fully parameterized models

Under the conditions outlined above we will ultimately only include patients at dose level d_0. Under very much broader conditions (Shen and O'Quigley, 1996) we can guarantee convergence to some level, not necessarily d_0 but one where the probability of toxicity will not be far removed from that at d_0. The consequence of this is that, for the most common case of a single homogeneous group of patients, we are obliged to work with an underparameterized model, notably a one

parameter model in the case of a single group. Although a two parameter model may appear more flexible, the convergence property of CRM means that ultimately we will not obtain information needed to fit two parameters. Having settled at dose level d_i the only quantity we can estimate is $R(d_i)$ which can be done consistently in light of the Glivenko–Cantelli lemma. Under our model conditions we have that $R(d_i) = \psi(d_i, a_i)$ and that $\hat{a}_j$ will converge almost surely to a_i. Adding a second parameter can only overparameterize the situation and, for example, the commonly used logistic model has an infinite number of combinations of the two parameters which lead to the same value of $R(d_i)$. A likelihood procedure can then be unstable and may even break down whereas a two parameter fully Bayesian approach (Gatsonis and Greenhouse, 1992; Whitehead and Williamson, 1998) may work initially, although somewhat artificially, but behave erratically as sample size increases and the structural rigidity provided by the prior gradually wanes. This is true even when starting out at a low or the lowest level, initially working with an up and down design for early escalation, before a CRM model is applied. Indeed, any design that ultimately concentrates all patients from a single group on some given level can fit no more than a single parameter without running into problems of identifiability.

4. Randomization and two parameter models

Suppose that j subjects are already entered in the trial. Instead of systematically selecting the level estimated as being closest to the target, a different approach would be to use the available knowledge to randomly select a level from $d_1, \ldots, d_k$ according to some given discrete distribution Δ. This distribution does not have to be fixed in advance but can depend on the available levels and the current estimate of the MTD. Let x_{j+1} be defined as before. However, we will no longer allocate systematically subject $j+1$ to dose level x_{j+1} as before. Instead we allocate to w_{j+1} where we define

$$w_{j+1} = \left\{ \begin{array}{ll} x_{j+1}^{\Delta_j} + \{(x_{j+1}+1)I(x_{j+1} < k)\}^{1-\Delta_j}; & \hat{R}(x_{j+1}) < \theta \\ x_{j+1}^{\Delta_j} + \{(x_{j+1}-1)I(x_{j+1} > 1)\}^{1-\Delta_j}; & \hat{R}(x_{j+1}) > \theta \end{array} \right\} \tag{11}$$

and where Δ_j, for each j, is a Bernoulli (0,1) random variable with parameter δ_j. In words, instead of allocating to the level closest to $\hat{R}(x_{j+1})$ we allocate, on the basis of a random mechanism, to the level just above $\hat{R}(x_{j+1})$ or the level just below $\hat{R}(x_{j+1})$. In the cases where $\hat{R}(x_{j+1})$ is lower than the lowest available level, or higher than the highest available level then the allocation becomes, again, systematic. The purpose of the design is then to be able to sample on either side of the target. Aside from those cases in which the lowest level appears to be more toxic than the target or the highest level less toxic than the target, observations will tend to be concentrated on two levels. One of these levels will have an associated estimated probability below the target while the other level will have an estimated probability above the target. Fig. 3, showing typical behavior, ought be contrasted with Fig. 1.

An immediate consequence of forcing experimentation to take place at more than a single level is that the non-identifiability described above changes. It is now possible to estimate more than a single parameter, for example the rate of toxicity at, say, the lower of the two levels as well as the rate of toxicity at the next level up. Working with a one parameter model and randomizing to two levels, say d_ℓ and $d_{\ell+1}$, the estimate $\hat{a}$ will converge to the value which solves the

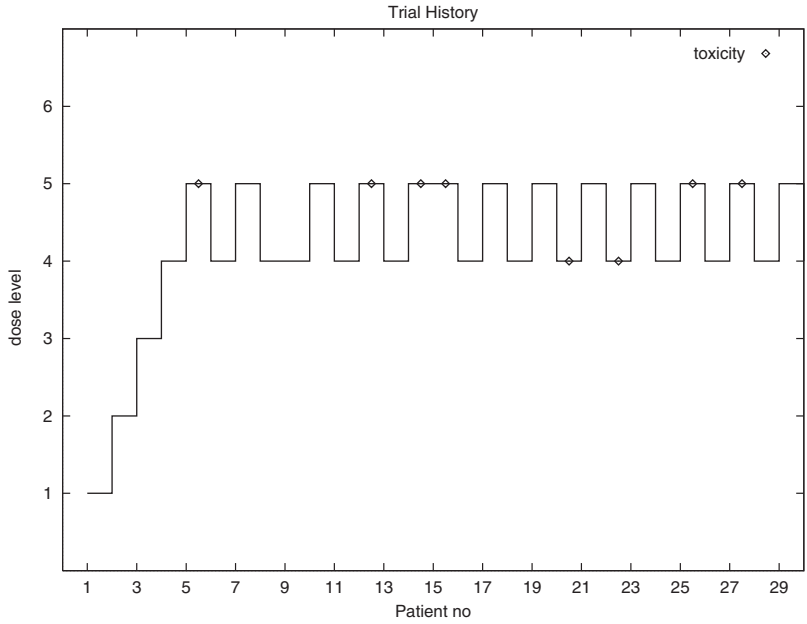

Fig. 3. Simulated of the CRM trial using randomization.

estimating equation

$$\pi(d_\ell)\left\{R_\ell\,\frac{\psi'}{\psi}\,(d_\ell,a)+(1-R_\ell)\,\frac{-\psi'}{1-\psi}\,(d_\ell,a)\right\}$$

$$\{1-\pi(d_\ell)\}\left\{R_{\ell+1}\,\frac{\psi'}{\psi}\,(d_{\ell+1},a)+(1-R_{\ell+1})\,\frac{-\psi'}{1-\psi}\,(d_{\ell+1},a)\right\}=0,$$

where $\pi(d_\ell)$ is the stable distribution (long term proportion) of patients included at level d_ℓ. Comparing this equation with Eq. (10) we can see that we will not, unless the working model generates the observations, obtain consistent estimates of the probabilities of toxicities at the two doses of the stable distribution. However, introducing a second parameter into the model, one which describes the differences between the probabilities of toxicity at the two dose levels, we obtain consistent estimates at these two doses of the stable distribution. To see this it is enough to parameterize the probability of toxicity at the current level d_ℓ as $\psi(d_\ell, a)$ and that at level $d_{\ell+1}$ by $\psi(d_\ell, a+b)$. The estimates will converge to the solution of

$$\pi(d_\ell)\left\{R_\ell\,\frac{\psi'}{\psi}\,(d_\ell,a)+(1-R_\ell)\,\frac{-\psi'}{1-\psi}\,(d_\ell,a)\right\}$$

$$\{1-\pi(d_\ell)\}\left\{R_{\ell+1}\,\frac{\psi'}{\psi}\,(d_{\ell+1},a+b)+(1-R_{\ell+1})\,\frac{-\psi'}{1-\psi}\,(d_{\ell+1},a+b)\right\}=0$$

for which, each term separately, can be then accommodated within the framework describing consistency given above.

In practice we would use a model such as the logistic where

$$\psi(d_k, a, b) = \frac{\exp(a\alpha_k + b)}{1 + \exp(a\alpha_k + b)}$$

which, once settling takes place, is then a saturated model.

5. Subject heterogeneity

As in other types of clinical trials we are essentially looking for an average effect. Patients naturally differ in the way they may react to a treatment and, although hampered by small samples, we may sometimes be in a position to specifically address the issue of patient heterogeneity. One example occurs in patients with acute leukemia where it has been observed that children will better tolerate more aggressive doses (standardized by their weight) than adults. Likewise, heavily pre-treated patients are more likely to suffer from toxic side effects than lightly pre-treated patients. In such situations we may wish to carry out separate trials for the different groups in order to identify the appropriate MTD for each group. Otherwise we run the risk of recommending an "average" compromise dose level, too toxic for a part of the population and suboptimal for the other. Usually, clinicians carry out two separate trials or split a trial into two arms after encountering the first DLTs when it is believed that there are two distinct prognostic groups. This has the disadvantage of failing to utilize information common to both groups. The most common situation is that of two samples where we aim to carry out a single trial keeping in mind potential differences between the two groups. A multi-sample CRM is a direct generalization although we must remain realistic in terms of what is achievable in the light of the available sample sizes.

O'Quigley et al. (1999) and O'Quigley and Paoletti (2003) focus mostly on models for the two group case, since this case is the most common and there are not usually enough resources, in terms of patient numbers, to deal with more complex structures. Elaborating higher dimensional models, at least conceptually, is straightforward. The dose toxicity model is written

$$Pr(Y = 1 \mid d_i, z) = \psi(d_i, a, b), \tag{12}$$

where the parameter b measures to some extent the difference between the groups. An obvious example which has been used successfully is

$$\psi(d_i, a, b) = \alpha_i^{\exp(a+bz)}, \quad (i = 1, \ldots, k), \tag{13}$$

where again, $0 < \alpha_1 < \cdots < \alpha_k < 1$; $-\infty < a < \infty$, $-\infty < b < \infty$ and z is a binary group indicator. Asymptotic theory is cumbersome for these models but consistency can be shown under restrictive assumptions (O'Quigley et al., 1999).

An alternative approach, in harmony with the underlying CRM idea of exploiting underparameterized models, is to be even more restrictive than allowed by the above regression models. Rather than allow for a large, possibly infinite, range of potential values for the second parameter b, measuring differences between the groups, the differences themselves are taken from a very small finite set. Since, in any event, if the first group finishes with a recommendation for some level, d_0 say, then the other group will be recommended either the same level or some level, one, two or more, steps away from it. The idea is to parameterize these steps directly. The indices themselves are modeled and the model is less cluttered if we work with $\log \psi(d_i, a)$ rather than $\psi(d_i, a)$ writing

$$\log \psi(d_i, a) = \exp(a) \log \alpha_{\phi(i)}, \quad \phi(i) = i + zh(i), \tag{14}$$

where

$$h(i) = mI(1 \leqslant i + m \leqslant k) + kI(i + m > k) + I(i + m < 1),$$
$$m = 0, 1, 2, \ldots, \tag{15}$$

the second two terms in the above expression taking care of edge effects. It is easy to put a discrete prior on m, possibly giving the most weight to $m = 0$ and only allowing one or two dose level shifts if the evidence of the accumulating data points strongly in that direction. No extra work is required in order to generalize to several groups. Under a condition, analogous to Condition 7, applied to both groups separately, consistency of the model in terms of identifying the correct level, can be demonstrated. This is of interest but it is more relevant to study small sample properties, often via the use of simulations, since, for dose finding studies, samples are invariably rather small.

Acknowledgements

The author would like to thank the reviewers and editors for having provided an extensive list of suggested improvements on an earlier version of this work. Thanks are also due to Ethan Reiner for discussion on the conditions leading to covergence and to Xavier Paoletti for help with the figures.

References

Babb, J., Rogatko, A., Zacks, S., 1998. Cancer Phase I clinical trials: efficient dose escalation with overdose control. Statist. Med. 17, 1103–1120.

Braun, T., 2002. The bivariate-continual reassessment method. Extending the CRM to phase I trials of two competing outcomes. Controlled Clin. Trials 23, 240–256.

Chevret, S., 1993. The continual reassessment method in cancer phase I clinical trials: a simulation study. Statist. Med. 12, 1093–1108.

Faries, D., 1994. Practical modifications of the continual reassessment method for phase I cancer clinical trials. J. Biopharm. Statist. 4, 147–164.

Gatsonis, C., Greenhouse, J.B., 1992. Bayesian methods for phase I clinical trials. Statist. Med. 11, 1377–1389.

Goodman, S., Zahurak, M.L., Piantadosi, S., 1995. Some practical improvements in the continual reassessment method for phase I studies. Statist. Med. 14, 1149–1161.

Ishizuka, N., Ohashi, Y., 2001. The continual reassessment method and its applications: a Bayesian methodology for phase I cancer clinical trials. Statist. Med. 20, 2661–2681.

Legedeza, A., Ibrahim, J., 2002. Longitudinal design for phase I trials using the continual reassessment method. Controlled Clin. Trials 21, 578–588.

Mahmood, I., 2001. Application of preclinical data to initiate the modified continual reassessment method for maximum tolerated dose-finding trial. J. Clin. Pharmacol. 41, 19–24.

Moller, S., 1995. An extension of the continual reassessment method using a preliminary up and down design in a dose finding study in cancer patients in order to investigate a greater number of dose levels. Statist. Med. 14, 911–922.

O'Quigley, J., 1992. Estimating the probability of toxicity at the recommended dose following a Phase I clinical trial in cancer. Biometrics 48, 853–862.

O'Quigley, J., Paoletti, X., 2003. Continual reassessment method for ordered groups. Biometrics 59, 429–439.

O'Quigley, J., Shen, L.Z., 1996. Continual reassessment method: a likelihood approach. Biometrics 52, 163–174.

O'Quigley, J., Pepe, M., Fisher, L., 1990. Continual reassessment method: a practical design for Phase I clinical trials in cancer. Biometrics 46, 33–48.

O'Quigley, J., Shen, L., Gamst, A., 1999. Two sample continual reassessment method. J. Biopharm. Statist. 9, 17–44.

O'Quigley, J., Paoletti, X., Maccario, J., 2002. Non-parametric optimal design in dose finding studies. Biostatistics 3, 51–56.

Piantodosi, S., Fisher, J., Grossman, S., 1998. Practical implementation of a modified continual reassessment method for dose-finding trials. Cancer Chemother. Pharmacol. 41, 429–436.

Shen, L.Z., O'Quigley, J., 1996. Consistency of continual reassessment method in dose finding studies. Biometrika 83, 395–406.

Silvapulle, M.J., 1981. On the existence of maximum likelihood estimators for the binomial response models. J.R. Statist. Soc. B 43 (3), 310–313.
Storer, B.E., 1989. Design and analysis of Phase I clinical trials. Biometrics 45, 925–937.
Whitehead, J., Williamson, D., 1998. Bayesian decision procedures based on logistic regression models for dose-finding studies. J. Biopharm. Statist. 8, 445–467.

Further reading

Ivanova, A., Montazer-Haghighi, A., Mohanty, S., Durham, S.D., 2003. Improved up-and-down designs for Phase I trials. Statist. Med. 22, 69–82.
O'Quigley, J., 2002. Curve free and model based CRM designs. Biometrics 58, 77–81.