COVARIATE-ADJUSTED ADAPTIVE DESIGNS FOR CONTINUOUS RESPONSES IN A PHASE III CLINICAL TRIAL: RECOMMENDATION FOR PRACTICE

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One adaptive design is proposed and studied by Bandyopadhyay and Biswas (2001) for comparing two treatments having continuous responses with covariates at hand in a phase III clinical trial. On the other hand, a drop-the-loser urn design is recently proposed by Ivanova (2003), which is known to have the least variability among urn-based adaptive designs for binary responses. The drop-the-loser rule for continuous data was recently introduced by Ivanova et al. (2005). But neither of the works considered covariates for the allocation design. The present paper provides a version of the newly proposed adaptive design, drop-the-loser rule, but for continuous responses and by incorporating the covariate information in the allocation procedure. Several exact and limiting properties of the design, and also of a simpler version of it, are studied. We compare the design of Bandyopadhyay and Biswas (2001) with the covariate-adjusted drop-the-loser-type rule for continuous responses and conclude that, although the drop-the-loser rule is better for binary responses, the design of Bandyopadhyay and Biswas (2001) performs better than the drop-the-loser-type rule for continuous responses with covariates. We recommend the existing design of Bandyopadhyay and Biswas (2001) for practical purposes.

Key Words: Immigration ball; Limiting proportion of allocation; Probit link; Proportion of allocation; Randomisation; Response-driven adaptive design; Treatment difference; Urn model.

1. INTRODUCTION

Response-driven adaptive designs are used in phase III clinical trials with an objective to treat a larger number of patients by the eventual better treatment. The objective of a phase III trial is to compare the performances of two or more competing treatments where the patients often arrive sequentially into the study. Quite often the patients are treated one after another, and thus the procedure allows the use of past allocation-and-response history up to any entering patient to determine his/her treatment. Thus, the adaptive designs have their role to play in

such a scenario to help us achieve some ethical gain by treating a larger number of patients with the preferred treatment. At the same time, we also need a significant amount of allocation to the worse treatment, to enable us to make meaningful inferences about the treatment difference in an efficient manner. Adaptive design is all about the trade-off between ethical gain (which is achieved if a larger number of patients are treated by the better treatment) and power/efficiency of the follow-up inference (which is maximized through optimal allocation).

Quite a few real applications of adaptive designs have been performed with increasing frequency in the recent days. Some real applications of adaptive clinical trials for dichotomous responses are due to Professor M. Zelen (in a breast cancer trial, reported by Iglewicz, 1983), Bartlett et al. (1985), Tamura et al. (1994), Ware (1989), Rout et al. (1993), Müller and Schäfer (2001), and Biswas and Dewanji (2004). Several adaptive designs are available in literature, although most of them are suitable for binary treatment responses. Some of the well-known designs are the play-the-winner rule (see Zelen, 1969), the randomized play-the-winner rule (see Wei and Durham, 1978), and the success-driven design (see Durham et al., 1998). For such designs, the expected proportion of allocation to the better treatment arm is more than 50%, and this proportion increases with the increase in treatment difference. However, most of these designs are birth processes, and accordingly, the variability is too high. In fact, the standard deviations of the proportion of allocation for these designs are so high that an allocation that is less than one or two standard deviation(s) from the expectation often leads less than 50% of patients to be treated by the better treatment, in the case of a two-treatment experiment. Recently, Ivanova (2003) introduced a new adaptive design for two-treatment allocation, called the drop-the-loser (DL) rule, which is a death process. Consequently, the variation is quite low, as it is known from the results of stochastic processes that death processes have less variability than the birth processes. Hu and Rosenberger (2003) observed that the drop-the-loser rule has the smallest variability among the available adaptive designs for binary responses.

All the above designs are for binary treatment responses. Certainly the amount of research on adaptive design is very low with more general treatment responses, e.g., continuous treatment responses. The reason for this is mostly the complexity that arises with such general responses. The question naturally arises: how to adapt? The few works available in this context are Rosenberger (1993) and Bandyopadhyay and Biswas (2004) where some nonparametric score functions are used. Bandyopadhyay and Biswas (2001) (henceforth referred as BB) considered continuous responses with covariates influencing the responses.

The important question that naturally comes to mind is whether one can adopt a version of the drop-the-loser rule, applicable for continuous responses in the presence of covariates, and provide a better adaptive design than the existing Bandyopadhyay and Biswas (2001) rule. Recently Ivanova et al. (2006) provided a version of the drop-the-loser rule, applicable for continuous responses, which is called the continuous drop-the-loser (CDL) rule. Here, in this present paper, we provide a version of the drop-the-loser rule applicable for continuous responses where some of the covariates can take an important role in the responses. Thus, a response with an unfavorable covariate should get much weight in favor of the treatment concerned than the same response with a favourable covariate. In any realistic design, these aspects are to be considered. So, for the purpose of

application, we need a version of the drop-the-loser rule, which is equipped with continuous responses and properly takes care of the covariates of the patients. The goal of the present paper is the development and comparison of this design with the existing Bandyopadhyay and Biswas (2001) design.

The rest of the paper is organized as follows. In Section 2, we provide a covariate-adjusted drop-the-loser rule for continuous treatment responses, which we abbreviate as CCDL. There we consider a linear model for the responses and for the sake of mathematical simplicity we assume normality. Section 3 deals with an approach to carry out the proposed CCDL without having a linear model of responses. Section 4 provides some properties, exact and limiting, of the design. The exact properties include the proportion of allocation to the better treatment, its standard deviation, and also some inferential issues that are evaluated by numerical simulations. We also introduce the expected number of responses less than a threshold as a performance characteristic. We provide a numerical comparison with the BB rule and the 50:50 randomized design. Section 5 discusses the issues concerned with the choice of design parameters in our proposed CCDL. An illustration with real data is given in Section 5. Section 6 ends with some conclusions.

2. COVARIATE-ADJUSTED ADAPTIVE DESIGNS FOR CONTINUOUS RESPONSES

2.1. The Setup

Suppose we have two competing treatments, say A and B, in a phase III clinical trial. We have a setup where the patients enter sequentially and each entering patient is treated either by A or B using some randomization where the probability of allocating any treatment is adaptively determined according to the state of art based on the data up to that stage. Here we have a setup where the responses are continuous and a covariate vector x affects the responses. For illustration, at this stage, we assume simple linear model of responses where the covariate vector influences the responses in the same way for both treatments. For many types of treatment responses, a simple transformation of the response variable, e.g., the logarithm of survival time, leads to normality. Thus, for simplicity, we assume a normally distributed response structure, although this assumption is not needed for the development and implementation of our technique. Normality, of course, brings some elegance in the mathematics. Suppose we have n patients in the trial. Let T_i be an indicator that takes the value 1 or 0, accordingly, as the ith patient is treated by A or B. Consequently, Y_i is the response. Thus, we assume that $Y_i \sim N(\mu_A + x_i^T\beta, \sigma^2)$ or $Y_i \sim N(\mu_B + x_i^T\beta, \sigma^2)$ depending on the ith patient is treated by A or B, where x_i is the covariate vector of the ith patient. Such a linear model holds in many real situations, either directly or after taking a transformation of the data. Note that different σ^2 could be one real possibility. But we decide to describe our design in a simple setup. Such types of extra modifications can be done in our approach with little difficulty.

Note that, in our model above, the treatment difference (see Ware, 1989; Wei et al., 1990) is $\mu_A - \mu_B$. Our allocation design should be such that it will allocate a larger number of patients to treatment A if $\mu_A - \mu_B > 0$, and the allocation proportion to treatment A should increase with the increase in the

difference $\mu_A - \mu_B$. But we should note the covariate values of each patient and give appropriate weights to them in the allocation design.

2.2. The BB Design

In the BB design, the $(i+1)$st patient is treated by treatment A with probability

$$\Phi\left(\frac{\hat{\mu}_{Ai} - \hat{\mu}_{Bi}}{\sigma_\Phi}\right)$$

where $\hat{\mu}_{Ai} - \hat{\mu}_{Bi}$ is the covariate-adjusted estimate of $\mu_A - \mu_B$ based on the data up to the first i patients and σ_Φ is a scaling constant. It is observed in Bandyopadhyay and Biswas (2001) that the design works well in terms of allocating a larger proportion of patients to the better treatment. The design is intuitive in nature. The limiting proportion of allocation to treatment A is given by

$$\pi^*_{BB,A} = \Phi\left(\frac{\mu_A - \mu_B}{\sigma_\Phi}\right)$$

See Bandyopadhyay and Biswas (2001) for details.

2.3. Continuous Drop-the-Loser Rule of Ivanova et al. (2005)

The rule can be illustrated by an urn model as follows. An urn contains one ball of each of the three types, types 1 and 2, which represent the two treatments, and also type 1, representing an immigration ball. Every entering patient is treated by drawing a ball from the urn. If an immigration ball is drawn, we add one ball each of kind, 1 and 2. If the drawn ball is of kind i, $i = 1, 2$, we treat the patient by the corresponding treatment. We replace the ball with probability $\Phi\left(\frac{Y_{i+1}-c}{\sigma_\Phi}\right)$ for some scalars c and σ_Φ. This procedure is continued.

2.4. Covariate-Adjusted Drop-the-Loser Design for Continuous Responses

It is observed that the DL rule for binary responses or continuous responses allocates with quite low variability. In the light of the comments of Hu and Rosenberger (2003) in the context of binary responses, we want to see whether we should use the BB design in practice or some possible version of the DL/CDL rule, applicable for continuous responses, in the presence of covariates. Here we propose the covariate-adjusted continuous drop-the-loser rule (CCDL). Our proposed allocation design is as follows.

We start with an urn having one ball each of type A, B, and 1, where 1 is the immigration ball. For the $(i+1)$st entering patient, $i \geq 0$, we draw a ball from the urn, and treat the patient by treatment A or B if the drawn ball is of type A or B. On the other hand, if the drawn ball is of type 1, we add one ball each of the types A and B to the urn, replace the 1 ball, and draw one ball from the urn afresh. We continue this procedure until we get a ball of A or B to treat the patient

accordingly. Let the response of the patient be Y_{i+1}, the covariate vector is x_{i+1}, and the indicator of allocation is T_{i+1}. We then replace the drawn ball with a probability $p_{i+1} = p_{i+1}(Y_{i+1}, T_{i+1}, x_{i+1})$, which is also a function of all the accumulated data up to the first $(i+1)$ patients. We then carry out the same procedure for the next entering patient.

The all important problem lies in determining p_{i+1}. For this we proceed as follows. Let $\hat{\beta}_i$ be the estimate of β up to the data of the first i patients. Then we suggest to set p_{i+1} as

$$p_{i+1} = G(Y_{i+1} - \hat{\beta}_i^T x_{i+1} - c) \tag{2.1}$$

where G is the cumulative distribution function (cdf) of a symmetric random variable. Specifically, we can use the cdf of a normal distribution with variance σ_Φ^2. Thus, (2.1) reduces to

$$p_{i+1} = \Phi\left(\frac{Y_{i+1} - \hat{\beta}_i^T x_{i+1} - c}{\sigma_\Phi}\right) \tag{2.2}$$

Here c is a constant, which is set to make most of the p_i-values not too close to 0 or 1. Thus, a meaningful idea can be to choose c as the prior idea of $(\mu_A + \mu_B)/2$. One can sequentially update c by replacing it by $(\hat{\mu}_{Ai} + \hat{\mu}_{Bi})/2$. The choice of σ_Φ should also be driven by the fact that all the p_i-values should not be too close to 0 or 1. Note that a small value of σ_Φ will make the p_i-values too sensitive to the Y_i-values, p_i will be close to 0 or 1 accordingly, as $Y_i - \hat{\beta}_{i-1}^T x_i - c < 0$ or >0. But, on the other hand, a very large value of σ_Φ will make the p_i's close to 0.5, irrespective of the corresponding responses, thus making the adaptive mechanism very weak. This is also not desirable. It is the experimenter's task to choose σ_Φ moderately by balancing this trade-off.

In the present setup, our data up to the ith patients comprises the allocation indicators $\{T_1, \Lambda, T_i\}$, the responses $\{Y_1, \Lambda, Y_i\}$, and the covariate vectors $\{x_1, \Lambda, x_i\}$. We denote the following;

$$\bar{Y}_{Ai} = \frac{\sum_{j=1}^i T_j Y_j}{\sum_{j=1}^i T_j}, \quad \bar{Y}_{Bi} = \frac{\sum_{j=1}^i (1-T_j) Y_j}{\sum_{j=1}^i (1-T_j)},$$

$$\bar{x}_{Ai} = \frac{\sum_{j=1}^i T_j x_j}{\sum_{j=1}^i T_j}, \quad \bar{x}_{Bi} = \frac{\sum_{j=1}^i (1-T_j) x_j}{\sum_{j=1}^i (1-T_j)},$$

$$n_{Ai} = \sum_{j=1}^i T_j, \quad n_{Bi} = \sum_{j=1}^i (1-T_j),$$

$$S_{xx,i} = \sum_{j=1}^i T_j (x_j - \bar{x}_{Ai})(x_j - \bar{x}_{Ai})^T + \sum_{j=1}^i (1-T_j)(x_j - \bar{x}_{Bi})(x_j - \bar{x}_{Bi})^T,$$

$$S_{xy,i} = \sum_{j=1}^i Y_j x_j - n_{Ai} \bar{Y}_{Ai} \bar{x}_{Ai} - n_{Bi} \bar{Y}_{Bi} \bar{x}_{Bi}$$

The normal equations are

$$\sum_{j=1}^{i}\begin{pmatrix} T_j \\ 1-T_j \\ x_j \end{pmatrix}(T_j \quad 1-T_j \quad x_j)\begin{pmatrix} \mu_A \\ \mu_B \\ \beta \end{pmatrix} = \sum_{j=1}^{i} Y_j \begin{pmatrix} T_j \\ 1-T_j \\ x_j \end{pmatrix}$$

implying

$$\begin{pmatrix} n_{Ai} & 0 & \sum_{j=1}^{i} T_j x_j^T \\ 0 & n_{Bi} & \sum_{j=1}^{i}(1-T_j)x_j^T \\ \sum_{j=1}^{i} T_j x_j & \sum_{j=1}^{i}(1-T_j)x_j & \sum_{j=1}^{i} x_j x_j^T \end{pmatrix}\begin{pmatrix} \mu_A \\ \mu_B \\ \beta \end{pmatrix} = \begin{pmatrix} n_{Ai}\overline{Y}_{Ai} \\ n_{Bi}\overline{Y}_{Bi} \\ \sum_{j=1}^{i} Y_j x_j \end{pmatrix}$$

and hence

$$\hat{\beta}_i = S_{xx,i}^{-1} S_{xy,i} \tag{2.3}$$

We use (2.3) and the current patient's response and covariate vector values to obtain the ball replacement probability (2.1) or (2.2). Note that in such a situation, the estimate of the treatment difference, $\mu_A - \mu_B$, is

$$\hat{\mu}_{Ai} - \hat{\mu}_{Bi} = \overline{Y}_{Ai} - \overline{Y}_{Bi} - (\bar{x}_{Ai} - \bar{x}_{Bi})^T \hat{\beta}_i \tag{2.4}$$

Clearly, the above covariate-adjusted rule is the usual drop-the-loser rule (Durham and Ivanova, 2001, Ivanova, 2003) with the unconditional probability of replacing the ball as

$$p_{i+1}^{*} = E\left[\Phi\left(\frac{Y_{i+1} - \hat{\beta}_i^T x_{i+1} - c}{\sigma_\Phi}\right)\right] \tag{2.5}$$

which depends on x_{i+1} if that is assumed to be non-stochastic. If, on the other hand, we assume a stochastic covariate vector X with a distribution function H, then the expectation in p_{i+1}^{*} in (2.5) is also taken over the distribution of X. We denote it by $p_{A,i+1}^{*}$ or $p_{B,i+1}^{*}$ accordingly, as the patient is treated by A or B. Quite naturally, the exact expression becomes complicated.

2.5. Simulation

We provide a detailed simulation study to examine the nature of ethical gain obtained through this allocation design. In fact, we study the proportion of allocation to the two treatments for different parametric values and for different distributions of the responses and covariates. Some of the simulation results are presented in Table 1. It is observed that we have a larger allocation to the better treatment, but never too large. We compare our results with the standard allocation

Table 1 Comparison of Prop(A) and SD (within parentheses) of the CCDL rule with the 50:50 randomized rule and the BB design. Here only one covariate is considered and $\sigma = 1, 2$, $\beta = 2$, $x \sim N(1, 1)$, $n = 40, 100$, $\mu_B = 0$ always

	μ_A				
Design	0.0	0.6	1.2	1.8	2.4
			$n = 40,\ \sigma = 1$		
(a)	0.500 (0.082)	0.520 (0.082)	0.538 (0.081)	0.550 (0.081)	0.558 (0.080)
(b)	0.500 (0.082)	0.522 (0.082)	0.543 (0.081)	0.562 (0.080)	0.582 (0.080)
(c)	0.500 (0.073)	0.507 (0.073)	0.517 (0.074)	0.523 (0.075)	0.529 (0.074)
(d)	0.500 (0.073)	0.500 (0.070)	0.500 (0.076)	0.500 (0.078)	0.500 (0.079)
(e)	0.500 (0.183)	0.700 (0.150)	0.829 (0.100)	0.891 (0.081)	0.922 (0.076)
(f)	0.500 (0.096)	0.572 (0.095)	0.636 (0.097)	0.699 (0.088)	0.758 (0.082)
(g)	0.500 (0.078)	0.520 (0.075)	0.545 (0.077)	0.564 (0.078)	0.588 (0.077)
			$n = 40,\ \sigma = 2$		
(a)	0.500 (0.093)	0.516 (0.093)	0.532 (0.092)	0.540 (0.093)	0.551 (0.093)
(b)	0.500 (0.093)	0.517 (0.092)	0.531 (0.092)	0.551 (0.093)	0.571 (0.092)
(c)	0.500 (0.087)	0.504 (0.086)	0.513 (0.087)	0.516 (0.086)	0.516 (0.087)
(d)	0.500 (0.076)	0.500 (0.072)	0.500 (0.072)	0.500 (0.077)	0.500 (0.077)
(e)	0.500 (0.298)	0.648 (0.275)	0.766 (0.231)	0.843 (0.170)	0.893 (0.120)
(f)	0.500 (0.151)	0.567 (0.143)	0.640 (0.141)	0.698 (0.128)	0.751 (0.118)
(g)	0.500 (0.090)	0.521 (0.087)	0.544 (0.086)	0.563 (0.085)	0.589 (0.089)
			$n = 100,\ \sigma = 1$		
(a)	0.500 (0.053)	0.523 (0.053)	0.539 (0.054)	0.554 (0.053)	0.560 (0.052)
(b)	0.500 (0.053)	0.524 (0.053)	0.546 (0.054)	0.566 (0.055)	0.585 (0.052)
(c)	0.500 (0.048)	0.509 (0.049)	0.519 (0.049)	0.526 (0.050)	0.532 (0.050)
(d)	0.500 (0.050)	0.500 (0.049)	0.500 (0.048)	0.500 (0.049)	0.500 (0.049)
(e)	0.500 (0.142)	0.721 (0.126)	0.862 (0.093)	0.933 (0.057)	0.963 (0.028)
(f)	0.500 (0.067)	0.578 (0.065)	0.651 (0.066)	0.717 (0.063)	0.775 (0.060)
(g)	0.500 (0.051)	0.523 (0.053)	0.546 (0.049)	0.569 (0.050)	0.592 (0.049)
			$n = 100,\ \sigma = 2$		
(a)	0.500 (0.060)	0.517 (0.059)	0.533 (0.060)	0.545 (0.060)	0.553 (0.060)
(b)	0.500 (0.060)	0.518 (0.060)	0.540 (0.059)	0.560 (0.060)	0.581 (0.061)
(c)	0.500 (0.050)	0.503 (0.050)	0.513 (0.050)	0.520 (0.050)	0.525 (0.051)
(d)	0.500 (0.049)	0.500 (0.049)	0.500 (0.050)	0.500 (0.048)	0.500 (0.049)
(e)	0.500 (0.275)	0.684 (0.249)	0.825 (0.185)	0.905 (0.122)	0.939 (0.085)
(f)	0.500 (0.104)	0.577 (0.107)	0.647 (0.099)	0.717 (0.087)	0.776 (0.088)
(g)	0.500 (0.056)	0.521 (0.056)	0.547 (0.059)	0.569 (0.055)	0.589 (0.053)

Designs in the above tables:
(a) CCDL ($\sigma_\Phi = 1, c = 0$), (b) CCDL ($\sigma_\Phi = 1, c = (\mu_A + \mu_B)/2$),
(c) CCDL ($\sigma_\Phi = 10, c = 0$), (d) Randomized 50:50,
(e) BB ($\sigma_\Phi = 1$), (f) BB ($\sigma_\Phi = 3$), (g) BB ($\sigma_\Phi = 10$).

design provided by Bandyopadhyay and Biswas (2001) for continuous responses with covariates, as that seems to be the only comparable adaptive design in this case. We observe that the BB design is ethically more sound in the sense that on an average a much larger proportion of patients are treated by the better treatment. Even though the standard deviation (SD) of the proportion of allocation for the BB design is slightly higher in some cases, the larger allocation proportion compensates for that.

3. PERFORMANCE OF THE DESIGN: COMPARISON WITH COMPETITORS

As the most obvious performance measure, we study the expected proportion of allocations to the better treatment by our design CCDL. This proportion is denoted by Prop(A). We also study the standard deviation (SD) of the proportion, as the initial goal of the DL rule is to reduce the variability. These are presented in Table 1 for different parametric values. We also present the same for the 50:50

Table 2 Comparison of power for the one-sided test based on CCDL rules with the 50:50 randomized rule and the BB design. Here only one covariate is considered and $\sigma = 1$, $\beta = 2$, $x \sim N(1, 1)$, $\sigma_\Phi = 1, 2$, $n = 40, 100$, $\mu_B = 0$ always

	μ_A				
Design	0.0	0.6	1.2	1.8	2.4
			$n = 40,\ \sigma = 1$		
(a)	0.050	0.158	0.329	0.564	0.768
(b)	0.050	0.159	0.335	0.559	0.758
(c)	0.050	0.135	0.325	0.548	0.758
(d)	0.050	0.495	0.970	1.000	1.000
(e)	0.050	0.389	0.885	0.989	0.999
(f)	0.050	0.495	0.968	1.000	1.000
(g)	0.050	0.537	0.978	1.000	1.000
			$n = 40,\ \sigma = 2$		
(a)	0.050	0.072	0.156	0.334	0.528
(b)	0.050	0.071	0.157	0.339	0.528
(c)	0.050	0.067	0.136	0.328	0.528
(d)	0.050	0.183	0.453	0.818	0.970
(e)	0.050	0.100	0.195	0.322	0.517
(f)	0.050	0.106	0.378	0.665	0.901
(g)	0.050	0.185	0.500	0.824	0.969
			$n = 100,\ \sigma = 1$		
(a)	0.050	0.258	0.531	0.764	0.866
(b)	0.050	0.259	0.535	0.758	0.858
(c)	0.050	0.237	0.524	0.758	0.858
(d)	0.050	0.842	1.000	1.000	1.000
(e)	0.050	0.777	0.999	1.000	1.000
(f)	0.050	0.892	1.000	1.000	1.000
(g)	0.050	0.877	1.000	1.000	1.000
			$n = 100,\ \sigma = 2$		
(a)	0.050	0.083	0.219	0.361	0.413
(b)	0.050	0.084	0.215	0.359	0.412
(c)	0.050	0.073	0.204	0.342	0.398
(d)	0.050	0.317	0.842	0.997	1.000
(e)	0.050	0.103	0.259	0.507	0.725
(f)	0.050	0.327	0.841	0.993	0.999
(g)	0.050	0.323	0.873	0.997	1.000

Designs in the above tables:
(a) CCDL ($\sigma_\Phi = 1, c = 0$), (b) CCDL ($\sigma_\Phi = 1, c = (\mu_A + \mu_B)/2$),
(c) CCDL ($\sigma_\Phi = 10, c = 0$), (d) Randomized 50:50,
(e) BB ($\sigma_\Phi = 1$), (f) BB ($\sigma_\Phi = 3$), (g) BB ($\sigma_\Phi = 10$).

randomized rule and also for the BB design for the sake of comparison. We observe that Prop(A) is never too large for the better treatment in CCDL, and hence the ethical gain is less than that of the BB design. But the SD values are less for the CCDL rule.

The natural question following the allocation is to carry out the inference. Here we want to carry out a test for the null hypothesis $H_0 : \mu_A = \mu_B$ against the one-sided alternative $H_1 : \mu_A > \mu_B$. For simplicity, we carry out the test for a fixed-sample size n. Quite naturally, a right-tailed test based on the test statistic $S_n = \hat{\mu}_{An} - \hat{\mu}_{Bn}$ is recommended. The test is to reject H_0 if $S_n > u_{0.05}$, where $u_{0.05}$ is chosen appropriately (by extensive simulation study) to have a 5% level of the test. Thus, $u_{0.05}$ is the upper 5% cut-off point of the null distribution of S_n. In practice, we simulate S_n for 10,000 times and find $u_{0.05}$ as the 95th quantile of the null distribution of S_n. We present the power of the test in Table 2 for both designs.

A good design is that which induces good ethical allocation (by treating a larger proportion of patients to the better treatment) as well as the design having large power to detect treatment difference. Although some other criteria, such as expected number of failures or variability of allocation, can be used as indicator of a good design, we recommend concentration on the two basic criteria, namely a) ethical allocation and b) large power. All other criteria are, in some sense, dependent on these two. It is interesting to note that ethical allocation does not necessarily give high power. This is a trade-off. So the experimenter needs to find the appropriate

Table 3 Comparison of ERLT_d's of the CCDL rule with the 50:50 randomized rule and the BB design. Here only one covariate is considered and $\sigma = 1$, $\beta = 2$, $x \sim N(1, 1)$, $n = 100$, $d = 1, 2$, and $\mu_B = 0$ always

	μ_A				
Design	0.0	0.6	1.2	1.8	2.4
			$d = 1$		
(a)	32.736	28.017	23.855	20.431	17.998
(b)	32.736	28.008	23.740	20.165	17.341
(c)	32.736	28.144	24.184	21.053	18.735
(d)	32.736	28.225	24.498	21.630	19.577
(e)	32.736	26.231	18.533	12.013	7.393
(f)	32.736	27.521	22.009	16.811	12.340
(g)	32.736	28.017	23.740	20.098	17.156
			$d = 2$		
(a)	50.000	44.468	38.991	33.957	29.928
(b)	50.000	44.457	38.848	33.609	29.032
(c)	50.000	44.616	39.400	34.768	30.931
(d)	50.000	44.711	39.788	35.521	32.078
(e)	50.000	42.374	32.394	22.982	15.483
(f)	50.000	43.886	36.703	29.237	22.221
(g)	50.000	44.469	38.848	33.523	28.781

Designs in the above tables:
(a) CCDL ($\sigma_\Phi = 1, c = 0$), (b) CCDL ($\sigma_\Phi = 1, c = (\mu_A + \mu_B)/2$),
(c) CCDL ($\sigma_\Phi = 10, c = 0$), (d) Randomized 50:50,
(e) BB ($\sigma_\Phi = 1$), (f) BB ($\sigma_\Phi = 3$), (g) BB ($\sigma_\Phi = 10$).

design after judicious judgment. For binary response design, another criterion makes sense. That is the expected number of failures. In contrast, here responses are continuous, and hence there is no meaning of failures/successes. Here we can think of an alternative idea, namely, the expected number of responses less than a threshold d. We denote it by ERLT_d. We carried out a detailed computation of ERLT_d. Only a part of that is presented Table 3, for the sake of brevity.

As a natural comparison, we compare the performance of the CCDL design and the follow-up test with a test procedure that randomizes the patients among the two treatments in a 50:50 way and also with a test following an allocation by BB design. The power values for the BB rule are much more than that of the CCDL rule. In fact, the powers for CCDL are often nearly 30% of that of the BB rule. For the 50:50 randomized design, the power is sometimes larger, but it is not an ethical (skewed) allocation. In a nutshell, the powers of CCDL are very small and there is not much gain in allocation proportion (and hence not much gain in ERLT_d) than the 50:50 randomized design. Hence, we do not recommend CCDL. Note that BB ($\sigma_\Phi = 3$) have almost the same power as the 50:50 design, but with a higher proportion of allocation to the better treatment (and hence have smaller ERLT_d) than the 50:50 design. Thus, for a clinical trial with continuous responses and covariates, we strongly recommend the existing BB rule with appropriate Φ over the drop-the-loser-type rule or 50:50 design.

4. CHOICE OF DESIGN PARAMETERS IN CCDL

Choice of design parameters, c and σ_Φ in (2.2) is a very important for implementation of such designs. Clearly, there seems no optimal choice of these unless one uses some standard optimality criterion like the D-optimality or the D_A-optimality (see Atkinson, 1982). That is also quite difficult in this scenario, mainly because the algebra becomes much too cumbersome. However, in principle, that is doable. We, instead, concentrate on a sensible choice of these parameters depending on our requirement.

We clearly want to distinguish between the ball replacement probabilities for the two treatments when there is treatment difference. One way to achieve this is to set c to be equal to $(\mu_A + \mu_B)/2$ and σ_Φ to be equal to σ. In the presence of prior idea, that can be used to set these design parameters. Another way might be to allocate the first m patients randomly in a 50:50 way among the two competing treatments and use that data to estimate μ_A, μ_B, σ, and β, and set the design parameters accordingly. Then, from the $(m+1)$st patient onwards, we carry out our adaptive design CCDL. A more complicated but more efficient way may be to estimate μ_A, μ_B, σ, and β adaptively, and use the current estimate to determine the design parameters adaptively. It will certainly impose a more complicated dependence in the process and the mathematics will become more cumbersome. However, there seems no problem in interpretation and implementation of this adaptive estimation technique.

In fact, the role of c, σ_Φ, and G is to fix the ball replacement probability function. Theoretically, one would like to determine these design issues optimally by optimizing some criterion of interest. For example, one can think of minimizing the expected number of failures. But, as this is a very complicated expression, the easier,

practical way out is to study different possible choices of c, σ_Φ, and G numerically and find that combination for which the expected number of failures is minimum.

5. AN EXAMPLE: FLUOXETINE HYDROCHLORIDE

As an example of the construction of designs, we use part of the data from Tamura et al. (1994) on the treatment of patients of depressive disorder. In order to correspond to our formalization of the present models, we denote treatment A control and B fluoxetine. We have a categorical covariate with values 0 and 1 dividing the patients by sleep dysfunction before the trial. The response is the negative of the change in $HAMD_{17}$, a measure of depression. Since $HAMD_{17}$ is measured on a 53-point scale, we treat it as a continuous variable. Large values are desired. There are 88 observations, since one observation in the data set does not have a response.

From the data we observe that the covariate follows a Bernoulli (0.5) distribution, $\hat{\beta} = 0.7862$, $\hat{\mu}_A = -11.0288$, $\hat{\mu}_B = -7.4255$, and $\hat{\sigma}^2 = 51.0808$. Using the BB rule, we find the allocation probabilities to treatment A for different σ_Φ for the 89th patient. Also, using these estimates as true values, we simulate the allocation probabilities for the 89th patient by the CCDL rule for the same σ_Φ values. The computations are given below.

σ_Φ	1	3	5	10	15	20	30
BB	0.0002	0.1149	0.2356	0.3593	0.4051	0.4285	0.4522
CCDL ($c = 0$)	0.4468	0.4502	0.4550	0.4583	0.4686	0.4754	0.4758
CCDL ($c = (\hat{\mu}_A + \hat{\mu}_B)/2$)	0.4074	0.4156	0.4204	0.4372	0.4496	0.4662	0.4748

From the allocation probabilities we observe that the BB rule is more ethical than the CCDL in the sense that a smaller proportion of patients are treated by the worse treatment by the BB rule (than the CCDL). Although the variability of the CCDL rule is slightly less, one or two SD less than the expected allocation for the better treatment for the BB design are often higher than CCDL. Again, if σ_Φ is poorly set (without having much idea about the variability of the response distributions), the allocation proportion in the BB rule can become negligibly small (e.g., for $\sigma_\Phi = 1$ in the above computation). This is undesirable, as one of the major goals of any clinical trial is to make inferences about the treatment difference, which can be done by having reasonable allocation to both the treatment arms. Thus, one needs to be cautious about setting σ_Φ in the BB design. On the other hand, the allocation in CCDL is quite robust with respect to the choice of σ_Φ. But we observed from Table 2 that the BB procedure is more powerful than the CCDL rule.

6. CONCLUSIONS

The present work assumes a very simple structure having continuous responses and covariates. In this paper we introduced drop-the-loser type designs for

continuous responses with covariates. These designs are then compared with the existing adaptive design of Bandyopadhyay and Biswas (2001). Although the designs are for phase III clinical trials, they may be applied in suitable form for phase II or phase IIB clinical trial designs as well. In the present context, so far as the comparison of the adaptive designs for continuous responses is concerned, we observe that:

- The BB design is more ethical in terms of allocating a larger proportion of patients to the better treatment.
- Variability for the drop-the-loser-type rule is less, but a much higher proportion of allocation by the BB rule indicates that even an allocation of one/two SD less than the expectation for the BB rule is more ethical than the DL rule for many cases.
- The test following BB design-based allocation has much higher power than the test following CCDL allocation.

We recommend the Bandyopadhyay and Biswas (2001) design for practice.

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