Journal of the Korean Statistical Society 38 (2009) 367–375

Contents lists available at ScienceDirect

Journal of the Korean Statistical Society

journal homepage: www.elsevier.com/locate/jkss

A general adaptive allocation design for continuous responses in the presence of covariates

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ARTICLE INFO

Article history:
Received 28 October 2008
Accepted 7 February 2009
Available online 10 March 2009

AMS 2000 subject classification:
62L05

Keywords:
Adaptive design
Continuous response
Mixture distribution
Prognostic factor

ABSTRACT

Several adaptive allocation designs are available in the clinical trial literature for allocating the entering patients among two competing treatments, having binary responses and skewing the allocation in favor of the better treatment. No adaptive design is available for continuous responses in the presence of prognostic factors, which is not model based. In the present paper, a general allocation design is introduced which assumes no specific regression model or distribution of responses. Some performance characteristics of the design are studied. Some related inference, following the allocation, is also studied. The proposed procedure is compared with some possible competitors. A real data set is used to illustrate the applicability of the proposed design.

1. Introduction

A major objective of implementing response-adaptive allocation designs in sequential phase III clinical trials, involving two competing treatments, is to allocate a larger number of patients to the better treatment in course of the trial. Most of the available works in this direction are urn designs, for binary treatment responses (see Wei and Durham (1978), for the randomized play-the-winner rule; Ivanova, Rosenberger, Durham, and Flournoy (2000), for the birth and death urn design; Ivanova (2003), for the drop the loser rule). Some real life applications of such adaptive designs have been carried out for binary treatment responses (see Bartlett et al. (1985), Biswas and Dewanji (2004) and Tamura, Faries, Andersen, and Heiligenstein (1994)). Urn designs can be extended for ordinal categorical responses (see Bandyopadhyay and Biswas (2000)), but not for count or continuous responses.

Atkinson (1982, 1999a,b) provided some biased coin-type designs for continuous responses to allocate in a 50:50 fashion. Bandyopadhyay and Biswas (2001) provided some adaptive design for continuous responses to skew the allocation pattern in favor of the better treatment. But that approach is totally model-based, assuming simple linear regression for the covariates, and moreover it needs distributional assumption to implement and study the properties of the design. Atkinson and Biswas (2005a,b) discussed some optimality based adaptive designs for continuous responses, where a linear model assumption is needed for implementation. Biswas, H.H. Huang, and W.T. Huang (2006) discussed several logistics in the response-adaptive designs for continuous responses.

In the present paper, the objective is to provide a suitable simple-minded adaptive design for continuous responses, where no distributional assumption or regression assumption is needed to study or implement the design. The idea is to provide a model-free general adaptive allocation design with intuitive appeal, which is easy to implement, easy to interpret, and applicable for all types of responses—categorical, count, continuous. Moreover, the design should be flexible enough to incorporate other logistics like prognostic factors and delayed responses. The allocation design is introduced in Section 2,

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1226-3192/$ – see front matter
doi:10.1016/j.jkss.2009.02.003

and the design is interpreted as an optimal design and also an urn design. Some properties of the design are discussed and studied in Section 3. Choice of design parameters is discussed in Section 4. Section 5 describes results from some related inference. Presence of prognostic factors in the design is briefly discussed in Section 6. Section 7 provides a comparison of the proposed design with some possible competitors. Section 8 illustrates the applicability of the proposed design using some real data set. Section 9 ends with some concluding discussions.

2. The allocation design

Suppose we have two competing treatments A and B under study and patients are to be sequentially allocated by the adaptive allocation design. For the nth entering patient, we define an indicator variable of assignment, δ_n, which takes the value 1 or 0 according to whether the nth patient is treated by treatment A or B. Let us denote the response by treatment A by X, and the response of the treatment B by Y. Thus, the response of the nth patient, assumed to be instantaneous, possibly in continuous scale, denoted by U_n, is $U_n = \delta_n X_n + (1-\delta_n)Y_n$. Our objective is to use all the previous allocation and response history for any allocation.

Assume that $X \sim F_1(x)$ and $Y \sim F_2(x)$, independently of each other, where F_1 and F_2 are arbitrary distribution functions (d.f.'s). Let 'c' be a point which will be called the allocation reference point (ARP), to be chosen by the experimenter, with some prior idea about the response distribution. Let $c = 0$, without loss of generality.

The allocation design for the nth entering patient depends on a mixture random variable V_n having d.f. $G_n(x|\text{past data})$ based on the past data, and allocate the nth entering patient to treatment A or B with probability $\{1 - G_n(0|\text{past data})\}$ and $G_n(0|\text{past data})$. That means, we draw a random sample on $V_n \sim G_n$ and treat the nth patient by A or B according as $V_n > 0$ or $V_n \leq 0$. We start with an initial allocation distribution $F_0(x)$, possibly symmetric, such that $F_0(0) = 1/2$. Thus, $G_1(x) = F_0(x)$. If the first patient is treated by treatment A and results in a response x_1, we define G_2 as a mixture of F_0 and $J(x - x_1)$ with mixing coefficients $(1 - \phi_1)$ and ϕ_1, respectively, where $J(x)$ is a distribution, symmetric about '0'. On the other hand, if the first patient is treated by treatment B and results in a response y_1, G_2 will be the mixture distribution of $F_0(x)$ and $J(x + y_1)$ with mixing coefficients $(1 - \phi_1)$ and ϕ_1, respectively. Thus, if we define $W_n = \delta_n X_n - (1 - \delta_n)Y_n$, the mixture distribution G_2 is the mixture of $F_0(x)$ and $J(x - W_1)$ with mixing coefficients $(1 - \phi_1)$ and ϕ_1, respectively. For a large response of the first patient, the allocation probability of the second patient to treatment A increases (decreases) if the first patient is treated by treatment A (B). We then allocate the second entering patient to treatment A or B with probabilities $\{1 - G_2(0|\text{past data})\}$ and $G_2(0|\text{past data})$.

We define a sequence $\{\phi_n,\ n \geq 1\}$ such that $\phi_{n+1} \geq \phi_n$ for all n and $\phi_n \to 1$ as $n \to \infty$. Now, for the allocation of the $(n + 1)$st entering patient, using the past data of the first n patients, G_{n+1} is the mixture distribution of F_0 and the n distributions $J(x - W_1), \ldots, J(x - W_n)$, where the mixing coefficient of F_0 is $(1 - \phi_n)$ and the mixing coefficient of any $J(x - W_i)$, $1 \leq i \leq n$, is ϕ_n/n. Thus,

$$G_{n+1}(x|\text{past data}) = (1 - \phi_n)F_0(x) + \frac{\phi_n}{n}\sum_{j=1}^{n} J(x - W_j). \tag{2.1}$$

We allocate the $(n + 1)$st entering patient to treatment A or B with probabilities $\pi_{n+1} = \{1 - G_{n+1}(0|\text{past data})\}$ and $1 - \pi_{n+1} = G_{n+1}(0|\text{past data})$, respectively. We call this design a *general adaptive design* (GAD). Note that this design can be explained by an urn model to ease its interpretation. Also the design GAD can be interpreted as an optimal design which minimizes $\{\Psi_A n_A + \Psi_B n_B$ subject to a prefixed (asymptotic) variance of the treatment difference θ, assuming equal variances for F_1 and F_2, where n_A and n_B patients are treated by treatments A and B respectively, $n_A + n_B = n$, and

$$\sqrt{\Psi_A} = \frac{1 - \phi_n}{2} + \frac{1}{n}\sum_{j=1}^{n} \phi_n J(-W_j), \qquad \sqrt{\Psi_B} = -\frac{1 - \phi_n}{2} + \frac{1}{n}\sum_{j=1}^{n} \left(1 - \phi_n J(-W_j)\right).$$

3. Properties of the design

In this section, we mostly study the allocation probabilities and proportions of the proposed design GAD, both exact and limiting. Let us denote $p_n = P(\delta_n = 1)$, the unconditional probability of allocating the nth patient to treatment A. Suppose $H_n(x)$ is the marginal d.f. of W_n. Clearly,

$$H_n(x) = E\left[J(x - W_n)\right] = p_n \int J(x - y)\mathrm{d}F_1(y) + (1 - p_n)\int J(x + y)\mathrm{d}F_2(y).$$

Then the unconditional allocation distribution function for the $(n + 1)$st patient, denoted by $G^*_{n+1}(x)$, is given by

$$G^*_{n+1}(x) = (1 - \phi_n)F_0(x) + \frac{\phi_n}{n}\sum_{j=1}^{n} H_j(x).$$

Consequently, the unconditional allocation probability distribution for the $(n + 1)$st patient is $\{1 - G^*_{n+1}(0)\}$ and $G^*_{n+1}(0)$, for treatments A and B, respectively.