Contemporary Clinical Trials Communications 2 (2016) 75–79

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

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

Generalization of Wei's urn design to unequal allocations in sequential clinical trials

Wenle Zhao*, Viswanathan Ramakrishnan

Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC 29425, USA

ARTICLE INFO

Article history:
Received 29 October 2015
Received in revised form
14 December 2015
Accepted 22 December 2015
Available online 14 January 2016

Keywords:
urn design
Unequal allocation
Randomization

ABSTRACT

Wei's urn design was proposed in 1987 for subject randomization in trials comparing $m \geq 2$ treatments with equal allocation. In this manuscript, two modified versions of Wei's urn design are presented to accommodate unequal allocations. First one uses a provisional allocation of $r_1^2 : r_2^2$ to achieve the target allocationr_1:r_2, and the second one uses equal allocation for $r_1 + r_2$ arms to achieve an unequal allocationr_1:r_2 based on the concept Kaiser presented in his recent paper. The properties of these two designs are evaluated based on treatment imbalance and allocation predictability under different sample sizes and unequal allocation ratios. Simulations are performed to compare the two designs to other designs used for unequal allocations, include the complete randomization, permuted block randomization, block urn design, maximal procedure, and the mass weighted urn design.

1. Introduction

Based on the generalized Friedman's urn model [1], Wei proposed an urn design for sequential trials comparing $m \geq 2$ treatments with equal allocations in 1978, as a compromise between the complete randomization (CR), which may result in large treatment imbalances, and the permuted block randomization (PBR), which has high allocation predictability [2]. Wei's urn design, denoted byUD(w,α,β), starts from an urn with$w$ balls color coded for each of the$m \geq 2$ treatments. When a subject is ready for randomization, a ball is drawn and replaced. The subject is assigned to the treatment represented by the ball. Then α more balls for the treatment and β more balls for each of the other treatments are added to the urn. Wei proved that the unconditional allocation probability for each treatment assignment in the UD converges to the equal allocation. Wei also indicated that the treatment allocation predictability of the UD was lower than that of the PBR, and the treatment imbalance was comparable to that of Pocock and Simon's Minimization method [2,3]. The UD is easy to implement and is considered as one of the commonly used restricted randomization method in clinical trials [4].

In recent years, the use of unequal allocation in clinical trials is growing, partially due to the emergence of Bayesian adaptive designs [5] and response adaptive randomization [6] motivated by ethical, trial efficiency, economical, and patient recruitment feasibility considerations [4]. However, randomization designs for unequal allocations are largely limited to CR and PBR. The generalizing of the UD to unequal allocations has received some attentions. For example, in their book published in 2002, Rosenberger and Lachin briefly described a procedure to generalize Wei's UD from equal allocation to two-arm unequal allocations [4]. Recently in 2012, Kaiser pointed out that this generalization is incorrect and provided a fix for a specific scenario of unequal allocation 2:1 [7]. In the same article, Kaiser described another randomization strategy for unequal allocationr_1:r_2 between the experimental and the control arms as to perform randomization for equal allocation to$r_1 + r_2$ treatment arms, and then combiner_1 of these arms for the experimental arm assignment andr_2 of these arms for control [7]. Kaiser did not provide details on the statistical properties of these two unequal allocation randomization procedures. In this manuscript, these two procedures described by Kaiser for unequal allocations are rigorously defined, evaluated, and compared to other commonly used unequal allocation randomization methods. Evaluation criteria include the unconditional allocation probability, the allocation predictability, the treatment imbalance, and their advantages and limitations under different trial scenarios. In Section 2, notations and measures used in this article are defined. In Section 3, a modified version of Wei's UD is proposed by using a provisional allocation. In Section 4, an alternate approach using Kaiser's equal

* Corresponding author. Department of Public Health Sciences, Medical University of South Carolina, 135 Cannon Street, Suite 305H, Charleston, SC, 29425, USA.
E-mail address: zhaow@musc.edu (W. Zhao).

http://dx.doi.org/10.1016/j.conctc.2015.12.007

allocation randomization is introduced. In Section 5, the performances of these two designs are compared with other randomization methods, and in Section 6 a discussion is provided.

2. Notations and measures

Let n be the sample size, m be the number of treatment arms, n_{ij} denote the number of subjects assigned to treatment j after i subjects have been randomized in to the study, and b_{ij} represent the number of balls in the urn for treatment j after i subjects randomized. Let p_{ij} be the conditional allocation probability of assigning subject i to treatment j. In an urn model, there is $p_{ij} = b_{i-1,j}/\sum_{k=1}^{m} b_{i-1,k}$. Let u_{ij} be the unconditional allocation probability of assigning the ith subject to treatment j prior to the start of the trial. To prevent selection bias, it is desired that the unconditional allocation probability equals the target allocation probability for each treatment assignment [7,10].

Let $r_1^*:r_2^*:\cdots:r_m^*$ represent the allocation ratio desired by the study design. For example, when two treatments are compared to one single control, 1:1:2 is the optimal allocation defined by Dunnett [9]. By default, an allocation ratio is expressed in terms of allocation probabilities with the sum of allocation elements equals to 1. For example, 1:1:2 = 0.2929:0.2929:0.4142. Let r_1:r_2:⋯:r_m be the allocation ratio targeted by the randomization algorithm. For example, using PBR for the Dunnett allocation, one may choose 2:2:3 = 0.2857:0.2857:0.4286 or 5:5:7 = 0.2941:0.2941:0.4118 as the target allocation. Recognizing the difference between the desired allocation and the target allocation is important because not all randomization designs are able to target any desired allocation. A randomization design is valid only if it has an asymptotic allocation equal to the target allocation. Based on the notations described above, the following measures are defined for the evaluation of randomization designs:

Allocation precision is measured by the Euclidian distance between the achieved allocation and the target allocation after i subjects randomized, $d_i = \sqrt{\sum_{j=1}^{m}(n_{ij} - ir_j)^2}$.

Allocation accuracy is measured by the Euclidian distance between the target allocation and the desired allocation multiplied by the sample size [8], $\eta = \sqrt{\sum_{j=1}^{m}(r_j - r_j^*)^2}$.

Allocation error d_i^* is measured by the Euclidian distance between the achieved allocation and the desired allocation after i subjects. It increases as i increases when η is not negligible.

$$d_i^* = \sqrt{\sum_{j=1}^{m}\left(n_{ij} - ir_j^*\right)^2} = \sqrt{d_i^2 + 2i\sum_{j=1}^{m}(n_{ij} - ir_j)\left(r_j - r_j^*\right) + i^2\eta^2}$$

Allocation predictability is defined by the Euclidian distance between the conditional allocation probability and the target allocation probability for each treatment assignment [8], $\varphi_i = \sqrt{\sum_{j=1}^{m}(p_{ij} - r_j)^2}$.

φ_i equals zero when the CR is applied. Unlike to the correct guess probability defined based on the Blackwell and Hodges' convergence strategy [11], which applies to equal allocations only, measure (4) generally applies to both equal and unequal allocations.

Desired features for a good randomization design for unequal allocations include:

a) High allocation accuracy, represented by a small value of η, ideally η=0.
b) High allocation precision, represented by a small value in $\overline{d} = \sum_{i=1}^{n} d_i/n$.
c) Low allocation predictability, represented by a small value in $\overline{\varphi} = \sum_{i=1}^{n}\varphi_i/n$.
d) Unconditional allocation probability equals to, or at least converges to, the target allocation probability, i.e. $p_{ij} = r_j$ for $i = 1,2,\cdots$; and $j = 1,2,\cdots,m$.

3. A modified urn design with provisional allocation

3.1. An unequal allocation urn procedure needs to be modified

Wei's UD(w,α,β) for $m \geq 2$ equal allocations can be defined by the conditional allocation probability $p_{ij}(UD) = \frac{w+\alpha n_{i-1,j}+\beta(i-1-n_{i-1,j})}{wm+\alpha(i-1)+\beta(i-1)(m-1)}$ for $i = 1,2,\cdots; j = 1,2,\cdots,m$ [12]. Historically, only integers are used for the constants w,α, and β in the UD for easy illustration purpose. Theoretically, w and β can be any positive number, α can be any real number. The ratios α/w and β/w determine the UD. Let $w = 1$, Wei's UD procedure can be specified by $p_{ij}(UD) = \frac{1+\alpha n_{i-1,j}+\beta(i-1-n_{i-1,j})}{m+\alpha(i-1)+\beta(i-1)(m-1)}$. Rosenberger and Lachin described a modified urn design (mUD) for two-arm trials targeting an unequal allocation of v_1:v_2 [4]. Their urn starts from Refs. wv_1 and wv_2 color coded balls for the two treatment arms, respectively. To perform a subject randomization, a ball is randomly drawn from the urn and replaced. The subject is assigned to the treatment, e.g. 1, based on the color of the ball selected. After that, βv_2 balls are added to the urn for treatment 2. Otherwise, βv_1 balls are added to the urn for treatment 1 [4]. The conditional allocation probability of the mUD in this case is $p_{i,1}(mUD) = \frac{wv_1+n_{i-1,2}\beta v_1}{wv_1+wv_2+n_{i-1,1}\beta v_2+n_{i-1,2}\beta v_1}$. Since v_1+v_2 = 1 and both w and β are positive real numbers, this formula can be simplify to $p_{i,1}(mUD) = \frac{v_1+n_{i-1,2}\beta v_1}{1+n_{i-1,1}\beta v_2+n_{i-1,2}\beta v_1}$. When β=0, the mUD is reduced to the CR. When $\beta > 0$, and w.l.o.g., assuming $0 < v_2 < v_1 < 1$, the unconditional allocation probability for the second subject is:

$$u_{2,1} = v_1\frac{v_1}{1+\beta v_2} + v_2\frac{v_1+\beta v_1}{1+\beta v_1} < v_1\frac{v_1}{1+\beta v_2} + v_2\frac{v_1+\beta v_1}{1+\beta v_2} = v_1. \quad (1)$$

This inequality suggests that the unconditional allocation for the second assignment is affected by the value of parameter β. For example, with v_1:v_2 = 2/3:1/3 and β=1, $u_{2,1}$ = 3/5 = 0.6. Similar calculation leads to $u_{3,1}$ = 558/845 = 0.5905. These results are consistent with Kaiser's findings [7]. When β=10, $u_{2,1}$ = 0.4214. As β approaches infinity, $u_{2,1}$ approaches $v_2 = 1 - v_1$.

Although it is desirable for a randomization design to have an unconditional allocation probability that equals the target allocation probability at each treatment assignment, not all randomization designs have this property [8,10]. However, it is necessary for all randomization designs to have an unconditional allocation probability that converges to the target allocation asymptotically. Let $r_j = \lim_{i\to\infty}(n_{ij}/i)$ be the asymptotic allocation ratio for the mUD. When $i \to \infty$, the conditional allocation probability is

$$p_{i1}(i\to\infty) = \lim_{i\to\infty}\frac{v_1+n_{i-1,2}\beta v_1}{1+n_{i-1,1}\beta v_2+n_{i-1,2}\beta v_1} = \frac{(1-r_1)v_1}{r_1 v_2+(1-r_1)v_1} = r_1. \quad (2)$$

This leads to a quadratic equation $(v_1 - v_2)r_1^2 - 2v_1 r_1 + v_1 = 0$ with its positive root representing the asymptotic allocation of the mUD as a function of the target allocation.