Contemporary Clinical Trials 45 (2015) 21–25

Contents lists available at ScienceDirect

Contemporary Clinical Trials

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

The pursuit of balance: An overview of covariate-adaptive randomization techniques in clinical trials

Yunzhi Lin [a,*], Ming Zhu [b], Zheng Su [c]

[a] Takeda Development Center Americas, Inc., Deerfield, IL 60015, USA
[b] AbbVie Inc., North Chicago, IL 60064, USA
[c] Deerfield Institute, New York, NY 10017, USA

ARTICLE INFO

Article history:
Received 7 May 2015
Received in revised form 25 June 2015
Accepted 8 July 2015
Available online 2 August 2015

Keywords:
Clinical trials
Randomization
Block randomization
Stratified randomization
Minimization
Dynamic hierarchical randomization

ABSTRACT

Randomization is fundamental to the design and conduct of clinical trials. Simple randomization ensures independence among subject treatment assignments and prevents potential selection biases, yet it does not guarantee balance in covariate distributions across treatment groups. Ensuring balance in important prognostic covariates across treatment groups is desirable for many reasons. A broad class of randomization methods for achieving balance are reviewed in this paper; these include block randomization, stratified randomization, minimization, and dynamic hierarchical randomization. Practical considerations arising from experience with using the techniques are described. A review of randomization methods used in practice in recent randomized clinical trials is also provided.

1. Introduction

Over the seventy years since the first randomized, controlled trial (RCT) in clinical medicine, RCTs have become firmly established as the gold standard of clinical research [1]. Randomization, in conjunction with blinding where possible, provides a fundamental tool for eliminating bias in treatment assignment and achieving precise and valid estimates of the treatment effect. The International Conference on Harmonization (ICH) guideline on statistical principles for clinical trials summarizes the key benefits of randomization as follows [2]:

> *Randomisation introduces a deliberate element of chance into the assignment of treatments to subjects in a clinical trial. During subsequent analysis of the trial data, it provides a sound statistical basis for the quantitative evaluation of the evidence relating to treatment effects. It also tends to produce treatment groups in which the distributions of prognostic factors, known and unknown, are similar. In combination with blinding, randomisation helps to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments.*

Although the method of randomization can be as simple as flipping a coin, such simple randomization may result in imbalanced sample size and baseline characteristics (i.e. covariates) among various treatment groups [3,4]. These chance imbalances in group size and baseline covariates, which have long been realized and discussed, can influence the comparison between treatment groups and introduce potential bias or confounding. Various techniques have been developed to address these issues, including block randomization, stratified randomization, and covariate-adaptive techniques, which have become more and more frequently adopted by today's clinical trialists. Each technique has its advantages and disadvantages, which must be carefully considered before a method is selected.

The objective of this review is to assess the state of the art in randomization techniques and evaluate the utilization of these techniques in RCTs. A brief overview of simple randomization and block (unstratified) randomization is provided; but the focus of this review is on randomization methods for achieving the balance of important baseline covariates. The pros and cons of each method are evaluated and practical considerations arising from experience with using these methods are discussed. Finally, we performed a review of randomization methods used in practice in recent randomized clinical trials.

2. Conventional randomization methods

In this section we describe the "conventional" randomization methods – methods that do not control for the balance of covariates – and why these methods may be limited in the design of clinical trials.

* Corresponding author.
E-mail address: yzlinn@gmail.com (Y. Lin).

http://dx.doi.org/10.1016/j.cct.2015.07.011
1551-7144/

2.1. Simple randomization

Randomization based on a single sequence of random assignments is known as simple randomization [5]. Also known as "complete" randomization, it prevents any conscious or unconscious selection bias by allocating subjects to treatment groups completely at random. The most common and basic method of simple randomization is flipping a fair coin.

Despite simple randomization's usefulness in mitigating selection bias and forming the basis for statistical analysis, it may lead to chance imbalances in group sizes and in the distribution of key baseline covariates, which may in turn cause "accidental" bias [6]. Clinical trials with substantial imbalances often come under criticism, even when these imbalances are due to chance alone [7,8] or to randomization methods that do not control for balance [9,10]. Imbalances in baseline subject characteristics are often blamed when trials fail to show the expected treatment effects [11]. For these reasons, more and more trialists today have being turning to methods that, in contrast to simple randomization, ensure balance (to some extent) with respect to group sizes and pre-specified baseline characteristics.

2.2. Block randomization

The method most commonly used to balance the group size (i.e. overall balance) is the unstratified permuted-block randomization (PBR) or block randomization which randomizes participants within blocks. Blocks are small and balanced with predetermined group assignments, which ensure that the treatment groups are balanced for the overall trial, both as the trial progresses and at the trial's end. Although balance in sample size may be achieved with this method, groups may be generated that are incomparable in terms of certain covariates.

3. Randomization methods for achieving covariate balance

Ensuring balance in important prognostic covariates across treatment groups is desirable for a number of reasons. When interim analyses are planned, ensuring covariate balance throughout the trial increases precision at the time of the interim where the number of subjects is small. Similarly, it increases the precision of subgroup analyses or tests for interaction between treatment and potential prognostic factors. It also decreases excess noise in clinical trial data to allow for maximal power of detecting the treatment effect in primary and secondary outcome analyses. Last but not least, with the advancement of modern technologies such as Interactive voice response (IVR) and interactive Web response (IWR) systems, the organizational effort and costs involved in ensuring balance in randomization have become relatively small. Hence the pursuit of balance can be viewed as a low-cost insurance policy against the likelihood of extreme imbalances, albeit the chance of such imbalances occurring might be low.

The techniques for achieving covariate balance (i.e. covariate-adaptive randomization methods) can be generally divided into three categories: (1) stratified (block) randomization, (2) minimization, and (3) dynamic hierarchical randomization. We review and evaluate each technique in detail in this section.

3.1. Stratified (block) randomization

The most common way to achieve balance in given baseline covariates (i.e. factors) is stratified randomization. It creates a separate randomization schedule, most commonly a permuted block schedule, for each unique stratification cell (i.e. stratum) formed by the combination of the levels of covariates [2,4]. Some commonly controlled stratification factors include center, disease stage, baseline medication, etc. In our experience, the stratified permuted block randomization (stratified PBR) is the most used randomization method in both academic and industry sponsored clinical trials.

3.1.1. Choice of block size and predictability

Care should be taken to choose block sizes for stratified PBR. They should be sufficiently short to limit possible imbalance, but long enough to avoid predictability towards the end of the sequence in a block. Having many stratification factors may lead to many incomplete blocks and thereby imbalance. Therefore choice of block size(s) should as well take into account the number of stratification factors [4]. A variant of stratified PBR that uses varied block sizes (e.g. a mixture of blocks of size 2, 4 or 6 at random) may be employed with the intention of making it harder for the investigator to guess the next treatment assignment and hence reducing the potential selection bias [2].

A common criticism of stratified PBR, and block randomization as a whole, is that it is overly restricted and provides substantial potential for selection bias as the treatment allocation is predictable towards the end of a block [12]. Berger suggested that block randomization should not be used at all for this reason [13]. To overcome the deterministic features of block randomization, Berger et al. proposed the maximal procedure [14], which generates the least restrictive allocation procedure subject to a constraint on the maximum tolerated imbalance. Soares and Wu proposed the big stick design, which has high allocation randomness but is limited to two-treatment balanced allocation scenarios only [15]. Zhao and Weng proposed the blocked urn design that is applicable to trials with more treatments and balanced or unbalanced allocations [16].

3.1.2. Limitations

The popularity of the stratified PBR among clinical trialists is greatly attributed to its ability to achieve balance within strata and its ease of use. However, as pointed out by several authors [12,17], with the stratified PBR severe imbalance can still occur for the overall treatment assignments, especially if there is a large number of incomplete blocks at the end of the trial. It may also results in imbalance at the individual prognostic factor level, i.e. marginal imbalance, which would affect the inference if an additive model is adopted for the analysis. To avoid severe imbalances at the trial level, Lin and Su's modified PBR is an option where the balance for the overall treatment assignment is maintained by checking the overall imbalance whenever a new block is opened during the PBR procedure [18].

A more important limitation of stratified PBR is that it can only balance a small number of factors. When there are too many strata relative to the number of subjects, some strata will have few or no subjects resulting in an inadequate balance at the individual strata level, at the covariate level, or for the study as a whole [19]. Therneau reported that the balance in covariates begins to fail when the total number of distinct combinations of factor levels approaches half the sample size [20]; while Kernan suggest that the number of strata be limited to N/4B, where N is the total sample size and B is the block size, with 4 being a safety factor [4]. The number of covariates that can be balanced is hence largely limited in smaller studies. Similarly in multicenter trials with a large number of sites, stratification beyond site is often prohibited if stratified PBR is used.

3.2. Minimization

When there are many important prognostic factors to handle, the so-called covariate-adaptive allocation procedures can be used to provide a balance in selected covariates [2]. Minimization, first described by Taves [21] and expanded by Pocock and Simon [22], is the most commonly used covariate-adaptive randomization method. It achieves the balance in treatment assignments across factor levels by choosing the allocation for the new subject that would lead to the smallest degree of imbalance possible across the set of his/her baseline characteristics.

Specifically, suppose the trial has already entered some subjects and the next subject is to be randomized. The minimization method

calculates for each treatment group the degree of imbalance that would occur if the subject were assigned to that group. The allocation that produces the least total imbalance is then chosen or assigned with a higher probability (e.g. p = 0.8) for this subject. In the case of ties, treatment assignment is determined at random. The imbalance measure for each covariate is calculated according to some measure of distance (for example range, standard deviation, variance, and others), and then the degree of imbalance for each hypothetical treatment assignment is calculated for the new subject by summing over the covariates either as an un-weighted sum or as a weighted sum if some covariates are considered more important than others [22].

Minimization considers the balance at the individual covariate levels (i.e., marginal balance) separately from each other but unlike stratification, it does not produce balance at the levels formed by the cross-classification of factors. For a given sample size, minimization can therefore handle more factors compared to stratified PBR, making it a more effective method of achieving balance across a large number of factors. It has been shown to provide a good marginal balance in a large number of covariates simultaneously [20–25] and is becoming more and more widely used in both academic and industry sponsored clinical trials [26].

3.2.1. Choice of imbalance measures

Minimization as a framework can be used with different kinds of imbalance measures. The most commonly used imbalanced measures, as described before, are range (absolute difference in group size), standard deviation, and variance. The variance measure tends to be adopted most frequently in randomized clinical trials due to its ease of calculation; it is equivalent to summing the numbers of existing subjects at all the (marginal) factor levels of the new subject and assigning him/her to the treatment with the lowest total [27]. These measures perform similarly in terms of achieving balance and statistical efficiency, yet all suffer from the limitation of handling only categorical covariates.

Colino et al. studied the impact of imbalances in continuous covariates in randomized clinical trials and found that power loss could be nontrivial when the balance of important continuous covariates were ignored even if adjustment is made in the analysis for these covariates [28]. A common practice is to simply dichotomize or categorize the important continuous covariates for them to be included in the minimization procedure; however, loss of information and chance imbalance still occur with this approach.

There are several approaches available in the literature for balancing both continuous and categorical covariates under a minimization framework. Frane proposed a p-value based approach where imbalances in the covariates are measured by the p-values that correspond to testing whether the median values of the covariates in the two treatment groups are identical [29]. Su used the largest difference in the three pairs of quartiles of the two distributions of the observed covariate values to quantify the imbalance level of a continuous covariate [30]. Endo et al. proposed to use the Kullback–Leibler divergence (KLD) of the two probability density functions (PDFs) of the observed covariate values in the two treatment groups as the imbalance metric [31]. Ma and Hu suggested balancing continuous covariates based on kernel densities [32]. Lin and Su used the area between the empirical cumulative distribution functions of the observed covariate values as the imbalance metric, which balance the entire distributions for key baseline covariates without making assumptions on the distributions [33]. Berger proposed a unifying framework for standard and covariate-adaptive randomization based on minimizing suitable imbalance functions [34].

3.2.2. Practical considerations

The use of minimization has been encouraged by methodological literature and practical guidelines alike. Most notably, Treasure, in his article published in the British Medical Journal, referred to minimization as the platinum standard for clinical trials [35]. The Consolidated Standards of Reporting Trials (CONSORT) statement, which is recognized and endorsed by leading medical journals, also states that "Minimization is an acceptable alternative to random assignment" without any reservations [36].

Some authors caution the use of minimization, warning that these minimization methods would preclude allocation concealment and invite selection bias [37]. This argument works off the premise that the investigator knows all the treatment allocations and values of all the stratification factors to date and the exact parameters of the minimization algorithm used, which may not be realistic in double-blind multicenter trials. In addition, a random element (biased coin with p between 0.5 and 1.0) may be added at every step of the minimization process, which makes it more difficult for a clinician to anticipate the next assignment and place the subject in a particular treatment group [38]. The ICH guidelines for the pharmaceutical industry also recommend that such random element should be incorporated into deterministic dynamic allocation procedures like minimization [2].

Another concern with minimization relates to the appropriate analysis following the use of minimization. The direct theoretical link between simple randomization and methods of statistical analysis has provided a solid foundation for reliable conclusions from clinical trials. However, the theoretical bases of minimization methods remain largely elusive. This concern over the validity of the analysis surrounds not just minimization but all adaptive allocation methods, as Rosenberger and Lachin [6] cautioned that "very little is known about the theoretical properties of covariate-adaptive designs."

In his original paper Taves recognized the implications minimization has for the analysis of the trial and recommended that adjustments should be made for the covariates used in the minimization using analysis of covariates [19]. It is also recommended that permutation tests can be conducted when analyzing clinical trials where minimization or other covariate-adaptive randomization methods are used [38–40]. In its 2013 draft guidelines, the European Medicines Agency (EMA) specifically suggested that covariate-adaptive randomization methods might impact the validity of conventional statistical methods and recommended the use of re-randomization methods to properly account for such problems in the analysis. In practice, however, a permutation test or re-randomization test is seldom used as it is usually not straightforward to perform. This practice is supported by the general agreement that the conventional test accounting for the covariates used in the randomization is sufficient and has satisfactory properties [39,41,42]. Further, in our experience, regulators in general do not question the use of conventional tests or request permutation tests for trials using minimization methods.

3.3. Dynamic hierarchical randomization

Another widely accepted covariate-adaptive randomization approach is the dynamic hierarchical randomization. First proposed by Signorini et al. in 1993, the dynamic hierarchical randomization (DHR) is an alternative to minimization to tackle the challenges of balancing a large number of stratification variables [43].

Dynamic hierarchical randomization is a tree-based method allowing different levels of imbalance in different covariates (hierarchy) which ensures a balance for each level of prognostic risk factors while at the same time preserving randomness. For a new patient, a hierarchical decision rule is applied, and a biased coin allocation is used if certain predefined limits are exceeded. Consider a clinical trial of a treatment T versus a control therapy C. Suppose there are two baseline factors under consideration: gender and site, where gender is a more important clinical factor. Then, three hierarchical levels of stratification will be examined successively: (1) gender within site, (2) site, and (3) overall trial. At each level i, the imbalance is define by $D_i = |T_i - C_i|$, where Ti and Ci are the respective numbers of patients allocated to treatment T

and C at level i, and the threshold of imbalance is pre-specified as δi. The algorithm can be concisely expressed as:

- If level i is the first level such that Di > δi, then the present patient is allocated using a biased coin in order to minimize Di; and
- If Di < δi for all levels then allocate the next patient by simple randomization.

Arguing that Signorini's DHR gives no guarantee that balance will be achieved for each individual prognostic factor, Heritier et al. [44] proposed a modification of the DHR, which ensures balance for each prognostic factor (marginal balance), named Marginal DHR. Under this modification, the successive checks are now performed on marginal imbalances hierarchically (e.g., firstly check on overall trial assignment, secondly on gender, and lastly on site).

One major limitation with balancing on the margins of the stratification variables is that there is an efficiency loss when the primary analysis for a trial is a stratified one [45]. Intuitively, the efficiency of a stratified analysis depends on the balance in the cells resulted from the crossing of the levels of the stratification variables (conditional balance), and good marginal balances do not necessary lead to good balances within the cells. Motivated by this limitation, Kaiser proposed a sequential randomization method named Stratified Biased Coin Randomization (sBCR), where the first level balances on the crossing of the stratification variables used in the analysis, and further stratification variables fall lower in the sequential hierarchy [45]. Similarly, Lin and Su proposed a hybrid DHR approach to achieving both marginal and conditional balances in sequential clinical trials, which is applicable to both continuous and categorical stratification variables [46].

4. Utilization of randomization techniques in contemporary clinical trials

4.1. Search and data extraction strategy

A PubMed search was carried out to identify RCTs published between January and December 2014 in three leading medical journals: The New England Medical Journal (NEMJ), The Lancet, and The Journal of the American Medical Association (JAMA). These journals were selected for their high quality and influence. A keyword search was conducted and all papers that contain the words “trial” and “randomiz(s)ed” in their abstracts were included for this review. Cluster-randomized trials were excluded, as were crossover trials as these methods do not involve the randomization of individual participants into separate treatment and control arms.

For each included trial, the following information was extracted by two reviewers using a form designed and agreed upon in advance.

- General trial information: sample size; number of centers; number and nature of interventions; nature of control.
- Detailed information on the randomization method used; number and nature of covariates / factors controlled; and whether center was as a stratification factor.

Discrepancies were resolved by discussion to reach a consensus. If detailed trial design and/or randomization information was not available in the paper, where possible, the design article and/or study protocol (usually published previously or available as Supplementary Appendix) were searched to gain further information.

4.2. Results

The literature search produced 224 articles that form the basis of this review. Table 1 summarizes the trial characteristics. Of the 224 included trials, over one-third were published in The Lancet (n = 92, 41%) with 57 (25%) published in NEJM and 75 (34%) in JAMA. The majority were two-armed, multi-center, active controlled trials. Over half of the trials assessed drug or device interventions.

Table 1
Characteristics of the 224 included RCT reports.

Trial characteristic		Number of included RCT reports (%)
Journal	The Lancet	92 (41)
	NEJM	57 (25)
	JAMA	75 (34)
Sample size	<200	39 (17)
	200–499	67 (30)
	500–999	49 (22)
	1000–9999	55 (25)
	10,000+	14 (6)
Centers	Multiple	206 (92)
	Single	18 (8)
Number of arms	Two	184 (82)
	Three	20 (9)
	Four	16 (7)
	>4	4 (2)
Interventions	Drug/device	146 (65)
	Surgery/screening	21 (10)
	Educational/behavioral	14 (6)
	Practice/care management	43 (19)
Nature of control	Active	137 (61)
	Placebo	87 (39)

Table 2 summarizes the randomization methods used. Of the 224 included trials, only 14 (6%) used simple randomization, based on information reported in the paper or in the published protocol. When there was no mention of restriction or stratification and simple randomization was not specifically reported, it is assumed that these trials used simple randomization. Twenty-seven (12%) trials used block randomization without controlling for any baseline covariates or stratification factors. The majority of the trials used stratified block randomization (n = 156, 70%). Minimization was used in 24 (11%) of the trials, while the dynamic hierarchical randomization (DHR) was used in only 3 (1%) of the trials reported.

Table 2 also summarizes the number of stratification factors / baseline covariates controlled in the trials using covariate-adaptive randomization methods. A mean of 2.52 (SD = 0.90) stratification variables were used in trials with stratified block randomization, 4.21 (SD = 2.57) were used in trials with minimization, and 2.67 (SD = 0.58) were used in trials that used DHR.

5. Discussion and conclusions

Although the method of randomization can be as simple as flipping a coin, such method does not guarantee that at the end of the trial, equal numbers of subjects will have received the various treatments — they only guarantee an equal chance of receiving each treatment. A related problem is the possibility that, even if the same numbers of subjects were exposed to the various treatments, there would be imbalance with respect to some important known confounders.

Table 2
Randomization methods used.

Randomization methods	Number (%)	Mean sample size (SD)	Mean number of factors (SD)
Conventional randomization methods			
Simple randomization	14 (6)	8781 (26,144)	
Block randomization	27 (12)	6820 (12,503)	
Covariate-adaptive randomization methods			
Stratified (block) randomization	156 (70)	1362 (2886)	2.52 (0.90)
Minimization	24 (11)	1960 (3108)	4.21 (2.57)
Dynamic hierarchical randomization	3 (1)	544 (261)	2.67 (0.58)

In this paper we summarized the randomization procedures used by researchers in both academia and the pharmaceutical industry. We devote most attention to covariate-adaptive randomization methods that control the balance of important prognostic covariates and the pros and cons of each method. The usage of these randomization methods in recent clinical trials is also summarized. With modern technologies such as IVR and IWR, generation of a randomization sequence takes little time and effort but affords big rewards in scientific accuracy and credibility. Investigators should devote appropriate resources to the assessment and selection of randomization methods during the trial design stage, and the methodologies adopted should be driven by scientific validity instead of convenience or precedence.

As discussed throughout the paper, there are many factors in a clinical trial that influence the choice of randomization methods, including the nature of the trial, number of prognostic covariates to balanced, nature of these prognostic covariates, allocation concealment methods, analyses methods, medication supply considerations, regulatory considerations, the sponsor's preference, etc. There is, therefore, no set rule for choosing a randomization method. When achieving balance for important prognostic variables is a priority, investigators should take into consideration the number of strata relative to the sample size and select a randomization method accordingly. As a rule of thumb, it is suggested that when using stratified blocks randomization the number of strata be limited to N/4B, where N is the total sample size and B is the block size [4]. Minimization and DHR are recommended when a relatively large number of covariates are to be balanced; they typically handle 5 to 6 factors, and have been shown to be able to cope with 10 to 20 factors (each with two or three levels) in trials as small as 50 subjects per group [20,43,44].

Seventy years have passed since the conduct of the first randomized trials, and randomization methodology remains an active research topic among trial practitioners. There has been and will continue to be constant debate on the validity of various randomization methods, which benefits the global clinical trials community as it attracts more attention to the importance of randomization and motivates continued pursuit of optimal balance in clinical trials.

References

[1] S.J. Pocock, Clinical Trials: A Practical Approach, Wiley, New York, 1983.
[2] International Conference on Harmonisation E9 Expert Working Group, ICH harmonised tripartite guideline. Statistical principles for clinical trials, Stat. Med. 18 (15) (1999) 1905–1942.
[3] K.F. Schulz, D.A. Grimes, Generation of allocation sequences in randomised trials: chance, not choice, Lancet 359 (9305) (2002) 515–519.
[4] W.N. Kernan, C.M. Viscoli, R.W. Makuch, L.M. Brass, R.I. Horwitz, Stratified randomization for clinical trials, J. Clin. Epidemiol. 52 (1) (1999) 19–26.
[5] D.G. Altman, J.M. Bland, How to randomise, BMJ 319 (7211) (1999) 703–704.
[6] W.F. Rosenberger, J.M. Lachin, Randomisation in Clinical trials: Theory and Practice, Wiley, New York, 2002.
[7] D.G. Altman, Randomisation in the SYMPHONY trial, Lancet 356 (2000) 1521–1522.
[8] The SYMPHONY investigators, Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomized trial, Lancet 355 (2000) 337–345.
[9] K. Wheatley, R. Gray, ICON4/AGO-OVAR-2.2: questions about trial design, cost-effectiveness, and clinical benefit, Lancet 362 (2003) 1333.
[10] N. Colombo, et al., On behalf of ICON4 collaborators. ICON4/AGO-OVAR-2.2: questions about trial design, cost-effectiveness, and clinical benefit, Lancet 362 (2003) 1334.
[11] Leyland-Jones B on behalf of the BEST Investigators Study Group, Breast cancer trial with erythropoietin terminated unexpectedly, Lancet Oncol. 4 (8) (2003) 459–460.
[12] J.P. Matts, J.M. Lachin, Properties of permuted-block randomization in clinical trials, Control. Clin. Trials 9 (1988) 327–344.
[13] V.W. Berger, Do not use blocked randomization, Headache 46 (2) (2006) 343-343.
[14] V.W. Berger, A. Ivanova, M.D. Knoll, Minimizing predictability while retaining balance through the use of less restrictive randomization procedures, Stat. Med. 22 (2003) 3017–3028.
[15] J.F. Soares, C.F. Wu, Some restricted randomization rules in sequential designs, Commun. Stat. Theory Methods 12 (1983) 2017–2034.
[16] W. Zhao, Y. Weng, Block urn design — a new randomization algorithm for sequential trials with two or more treatments and balanced or unbalanced allocation, Contemp. Clin. Trials 32 (2011) 953–961.
[17] S.J. Pocock, Statistical aspects of clinical trial design, Statistician 31 (1982) 1–18.
[18] Y. Lin, Z. Su, Quantifying the exact allocation ratios in randomized clinical trials with biased coin randomization, Comput. Methods Prog. Biomed. 108 (1) (2012) 197–202.
[19] R. Simon, Patient subsets and variation in therapeutic efficacy, Br. J. Clin. Pharmacol. 14 (1982) 473–482.
[20] T.M. Therneau, How many stratification factors are 'too many' to use in a randomization plan, Control. Clin. Trials 14 (1993) 98–108.
[21] D.R. Taves, Minimization: a new method of assigning patients to treatment and control groups, Clin. Pharmacol. Ther. 15 (5) (1974) 443–453.
[22] S.J. Pocock, R. Simon, Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial, Biometrics 31 (1) (1975) 103–115.
[23] C.B. Begg, B. Iglewicz, A treatment allocation procedure for sequential clinical trials, Biometrics 36 (1980) 81–90.
[24] C.J. Weir, K.R. Lees, Comparison of stratification and adaptive methods for treatment allocation in an acute stroke clinical trial, Stat. Med. 22 (2003) 705–726.
[25] G.A. Zielhuis, H. Straatman, A.E. van't Hof-Grootenboer, H.J. van Lier, G.H. Rach, P. van den Broek, The choice of a balanced allocation method for a clinical trial in otitis media with effusion, Stat. Med. 9 (1990) 237–246.
[26] D.J. McEntegart, The pursuit of balance using stratified and dynamic randomization techniques: an overview, Drug Inf. J. 37 (3) (2003) 293–308.
[27] L.S. Freedman, S.J. White, On the use of Pocock and Simon's method for balancing treatment numbers over prognostic factors in the controlled clinical trial, Biometrics 32 (1976) 691–694.
[28] J. Ciolino, W. Zhao, R. Martin, Y. Palesch, Quantifying the cost in power of ignoring continuous covariate imbalances in clinical trial randomization, Contemp. Clin. Trials 32 (2011) 250–259.
[29] J.W. Frane, A method of biased coin randomization, its implementation, and its validation, Drug Inf. J. 32 (1998) 423–432.
[30] Z. Su, Balancing multiple baseline characteristics in randomized clinical trials, Contemp. Clin. Trials 32 (2011) 547–550.
[31] A. Endo, F. Nagatani, C. Hanada, A. Yoshimura, Minimization method for balancing continuous prognostic variables between treatment and control groups using Kullback–Leibler divergence, Contemp. Clin. Trials 27 (2006) 420–431.
[32] Z. Ma, F. Hu, Balancing continuous covariates based on Kernel densities, Contemp. Clin. Trials 34 (2013) 262–269.
[33] Y. Lin, Z. Su, Balancing continuous and categorical baseline covariates in sequential clinical trials using the area between empirical cumulative distribution functions, Stat. Med. 31 (18) (2012) 1961–1971.
[34] V.W. Berger, A unifying framework for standard and covariate-adaptive randomization procedures based on minimizing suitable imbalance functions, Contemp. Clin. Trials 36 (2013) 527–530.
[35] T. Treasure, K. MacRae, Minimisation: the platinum standard for trials? Br. Med. J. 317 (1998) 362–363.
[36] D.G. Altman, et al., CONSORT group (consolidated standards of reporting trials). The revised CONSORT statement for reporting randomised trials: explanation and elaboration, Ann. Intern. Med. 134 (2001) 663–694.
[37] V.W. Berger, Minimization, by its nature, precludes allocation concealment, and invites selection bias, Contemp. Clin. Trials 31 (5) (2010) 406.
[38] R. Simon, Restricted randomization designs in clinical trials, Biometrics 35 (1979) 503–512.
[39] L.A. Kalish, C.B. Begg, Treatment allocation methods in clinical trials: a review, Stat. Med. 4 (1985) 129–144.
[40] H. Green, D.J. McEntegart, B. Byrom, S. Ghani, S. Shepherd, Minimization in crossover trials with non-prognostic strata: theory and practical application, J. Clin. Pharm. Ther. 26 (2001) 121–128.
[41] M. Buyse, Centralized treatment allocation in comparative clinical trials, Appl. Clin. Trials 9 (2000) 32–37.
[42] Y. Ohashi, Randomization in cancer clinical trials: permutation test and development of a computer program, Environ. Health Perspect. 87 (1990) 13–17.
[43] D.F. Signorini, O. Leung, R.J. Simes, E. Beller, V.J. Gebski, Dynamic balanced randomisation for clinical trials, Stat. Med. 12 (1993) 2343–2350.
[44] S. Heritier, V. Gebski, A. Pillai, Dynamic balancing randomization in controlled clinical trials, Stat. Med. 24 (2005) 3729–3741.
[45] L.D. Kaiser, Inefficiency of randomization methods that balance on stratum margins and improvements with permuted blocks and a sequential method, Stat. Med. 31 (2012) 1699–1706.
[46] Y. Lin, Z. Su, A hybrid approach to achieving both marginal and conditional balances for stratification variables in sequential clinical trials, Pharm. Stat. 12 (2013) 275–281.