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Comparison of statistical and operational properties of subject randomization procedures for large multicenter clinical trial treating medical emergencies

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Abstract

Large multicenter acute stroke trials demand a randomization procedure with a high level of treatment allocation randomness, an effective control on overall and within-site imbalances, and a minimized time delay of study treatment caused by the randomization procedure. Driven by the randomization algorithm design of *A Study of the Efficacy and Safety of Activase (Alteplase) in Patients With Mild Stroke (PRISMS)* (NCT02072226), this paper compares operational and statistical properties of different randomization algorithms in local, central, and step-forward randomization settings. Results show that the step-forward randomization with block urn design provides better performances over others. If the concern on the potential time delay is not serious and a central randomization system is available, the minimization method with an imbalance control threshold and a biased coin probability could be a better choice.

Keywords

step-forward randomization; acute stroke trial; treatment time delay; baseline balance; allocation randomness

1. Introduction

In randomized controlled clinical trials, the subject randomization procedure involves two components: the treatment allocation algorithm and the implementation method. Currently available treatment allocation algorithms for clinical trials with sequential treatment allocation over extended periods of time include the permuted block design initially proposed by Hill [1], Soares and Wu's big stick design [2], Efron's biased coin design [3], Chen's biased coin design with imbalance tolerance method [4], and the block urn design

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recently proposed by Zhao and Weng [5]. These aforementioned randomization designs are classified as restricted randomization methods aimed to control the imbalance between treatment group sizes [6]. Covariate-adaptive randomizations are used to balance the distribution of baseline covariate between treatment arms, including the stratified randomization [7], the hierarchical balancing method [8–9], and the minimization method [10–11]. In a stratified randomization, a restricted randomization method is applied independently within each stratum constructed by the combination of cross-classified baseline covariate categories. The hierarchical balancing method controls imbalances in multiple baseline covariates sequentially according to the priority order. The minimization method proposed by Taves [10] uses deterministic assignment to control the imbalances in each covariate category (also called margins). The minimization method proposed by Pocock and Simon [11] allows the deterministic assignment be replaced by a biased coin assignment in order to reduce the allocation predictability. Statistical properties of these algorithms can be quantitatively evaluated based on the treatment allocation randomness and the treatment group size imbalances [12].

The implementation of the randomization algorithm can be classified into two types: local randomization and central randomization. Their major differences are reflected in the timing of the randomization procedure and the capacity for covariate balancing. Local randomization uses only information collected at the local site for subject treatment allocation. The stratified permuted block design is commonly implemented via local randomization. Local randomization allows the treatment allocation sequence, i.e. the randomization code list, to be pre-generated and distributed to each site before enrolling patients. When an eligible subject is enrolled at the site, the treatment assignment is immediately available. However, this approach is vulnerable to treatment allocation concealment failures and is incapable of adapting to previous randomization errors and study drug damages. Local randomization can practically only control imbalances within strata composed by intersections of baseline covariate categories. This often prohibits stratification beyond site for multicenter trials involving a large number of sites, because the average stratum size could be too small for meaningful treatment group size imbalance control.

In central randomization, site investigators access the central randomization database via an interactive voice response system (IVRS) or an interactive web response system (IWRS) to get treatment assignment for eligible subjects. The minimization method is often implemented via central randomization. Central randomization uses information collected across all sites and allows imbalance control within baseline covariate margins and/or within strata composed by the intersection of baseline covariate categories. In addition, central randomization allows an automated study drug/device management function to be integrated into the IVRS/IWRS. However, in a central randomization, there are potential delays and interruptions due to glitches in user authentication, user privilege verification, subject eligibility checking, baseline covariate information collection, and randomization result confirmation. As a result, compared to local randomization, central randomization is more vulnerable to technical malfunctions and user errors.

While the potential time delay associated with the central randomization procedure is not a serious concern for many clinical trials, it can be a problem for trials treating medical emergencies, such as acute stroke. A sub-study from the Interventional Management of Stroke III (IMS III) trial [13] shows that every 30-minute delay in breaking up a blood clot from a stroke was associated with a 10% decrease in the probability of a good outcome (defined as a modified Rankin Scale score of 0–2 at 3 months), regardless of stroke severity [14]. A recent publication in the Journal of the American Medical Association demonstrated that every 15 minutes saved to initiate IV tPA led to a 3–4% increase in good outcomes (discharge to home, ambulation at discharge) and a 3–4% decrease in undesired outcomes (hospital mortality, sICHsymptomatic intracranial hemorrhage (sICH) [15]. Because of the implication that “time is brain” [16], local randomization, such as the stratified permuted block design, has been favored by many investigators of acute stroke trials, in spite of its vulnerabilities to large overall imbalance and treatment allocation concealment failures.

As a practical compromise between local and central randomization methods, Zhao et al. proposed the step-forward randomization [17], in which a study drug kit is identified using a central randomization for each site and is labeled as [Use Next] prior to the enrollment of the first subject and after the enrollment of each subject at a site. Eligible subject can be treated with the local [Use Next] drug kit with no time delay. If the randomization needs to be stratified by baseline covariate categories, one [Use Next] assignment could be created for each stratum at each site. The central randomization algorithm used for the assignment of the [Use Next] drug kit provides the potential of controlling imbalances within each clinical site, within each baseline covariate margin, as well as across the entire study.

The step-forward randomization strategy has been implemented in the Albumin in Acute Ischemic Stroke (ALIAS) Part 1 and Part 2 trials [18] and the IMS III trial [9]. In the ALIAS trials, the randomization was stratified by IV tPA use status (Yes vs. No) prior to study enrollment in order to control the imbalance in tPA use between the two treatment arms. Similarly, in the IMS III trial, the randomization was stratified by the stroke severity, defined according to the National Institutes of Health Stroke Scale score at baseline (NIHSS score 19 vs. 20) in order to control the imbalance in baseline severity between the two arms. The time saving benefit of the step-forward randomization has been observed in both trials [14]. However, two “Use Next” assignments maintained at each site due to stratification of the randomization resulted in increases in randomization procedure complexity and site operation error rate. In both ALIAS and IMS III trials, glitches during the subject randomization and study treatment delivery processes were recorded due to various site operation mistakes [14]. The procedure can be simplified by eliminating stratification, which requires only one [Use Next] treatment assignment at each site. However this simplified step-forward procedure controls only the overall imbalance, leaving the covariate imbalance uncontrolled.

The above discussion on the advantages and limitations of local randomization, central randomization, and step-forward randomization are generally descriptive and conceptual. The statistical properties of the step-forward randomization procedure are affected by the selections of the treatment allocation algorithm (such as the permuted block design, the big stick design, the block urn design), parameters (such as the block size) used in the

randomization algorithm, stratification options (with or without stratification within site), and the trial setting (such as the sample size and the number of sites). If randomization is stratified by sites (with or without other stratification factors such as baseline covariates), and a restricted randomization algorithm is applied independently within each stratum, there will be no difference in the statistical performance of the randomization method with or without the step-forward randomization. In fact in this case, the randomization method itself can be implemented locally. However, if the randomization algorithm balances treatment distribution across site and therefore is a central randomization, the statistical performance of the randomization method with or without step-forward implementation remains unclear to many investigators. In this paper, quantitative evaluation of the statistical properties of different randomization procedures under specific trial settings, determined via simulation, will provide important information for investigators to select the design of the subject randomization procedure.

2. Background

A Study of the Efficacy and Safety of Activase (Alteplase) in Patients With Mild Stroke (PRISMS) (NCT02072226) is a double-blind, multicenter, randomized, Phase IIIb study to evaluate the efficacy and safety of intravenous (IV) Activase in patients with mild acute ischemic strokes that do not appear to be clearly disabling. Patients will be randomized in a 1:1 ratio to receive either 1) one dose of IV Activase and one dose of oral aspirin placebo or 2) one dose of IV Activase placebo and one dose of oral aspirin 325 mg [19] within 3 hours of last known well time. The trial is planned to enroll 948 subjects from 75 sites in North America. Due to the potential variation in trial operations across sites, it is desirable to control the potential imbalance between the sizes of the two treatment groups within each site. It is also desirable to control imbalances in important prognostic factors including the baseline NIHSS and age between the two treatment groups. For this reason, baseline NIHSS is dichotomized into two categories: (≤ 3 vs. $4-5$), and baseline age is divided into two categories: (≤ 60 vs. > 60). Compared to other acute stroke trials, this PRISMS trial requires a unique procedure for study drug delivery. The IV tPA lyophilized vial needs to be prepared and reconstituted prior to drug delivery. This could cause additional delay for subject treatment. The design of the corresponding subject randomization procedure has three primary goals: 1) to protect treatment allocation randomness; 2) to control imbalances in treatment group sizes and baseline covariate distributions; and 3) to minimize time delay caused by the subject randomization procedure. However, there is no randomization procedure currently available able to simultaneously achieve these three goals. Trial investigators of the PRISMS have to select one randomization procedure and optimize the parameter settings based on the combined consideration of trial operation characteristics and statistical properties.

3. Method

3.1. Computer simulation plan

A computer simulation program was developed to evaluate the statistical properties of different randomization designs in the context of the PRISMS trial. The simulation includes nine local randomization scenarios, four central randomization scenarios, and three step-

forward randomization scenarios. The nine local randomization scenarios consist of the combination of three options for treatment allocation algorithms (permuted block design, big stick design, and block urn design) and three options for stratification (by site; by site and NIHSS category; and by site, NIHSS and age categories). The four central randomization scenarios include two minimization methods (one with deterministic assignments and the other with biased coin assignments) and two hierarchical biased coin designs (with different biased coin probabilities) in which imbalance items are controlled in a pre-specified priority order: within-site imbalance first, followed by the imbalance in the NIHSS category, and then the imbalance in the age category. If the within-site imbalance exceeds a pre-specified limit, a biased coin assignment is used favoring reduction of the within-site imbalance. Otherwise, the algorithm moves to the next imbalance item on the hierarchy. If all imbalances are within their pre-specified thresholds, a simple random assignment is used. The three step-forward randomization scenarios are based on three options for within-site balancing (permuted block design, big stick design, and block urn design). In all these three scenarios, the overall imbalances are controlled with a biased coin approach. When the conditional allocation probability obtained from the within-site balancing algorithm equals to 0.5, a biased coin assignment is applied to reduce the treatment imbalance in the overall study [20]. As a reference point, the complete randomization (also called simple randomization) is included in the simulation.

To facilitate the computer simulation of the PRISMS study, it is assumed that each subject has an equal probability (i.e. 1/75) belong to each site, a 40% chance in the lower NIHSS category, and a 30% chance in the lower age category. These three covariates are assumed to be independent from each other.

3.2. Conditional allocation probability

To ensure the validity of the computer simulation results, it is necessary to accurately define the conditional allocation probability used by each randomization algorithm. Let $P_{i,A} = \Pr\{T_i = A | \mathbf{T}_{i-1}, \mathbf{X}_i\}$ be the probability for subject i being assigned to treatment arm A , where $\mathbf{T}_{i-1}$ is the treatment assignment vector for the first $(i-1)$ subjects, and $\mathbf{X}_i$ is the baseline data (site, NIHSS, age) matrix for the first i subjects. Subject i will be assigned to treatment A if the value of a random number with a uniform distribution on $(0, 1)$ obtained by the simulation program is less than $p_{i,A}$; otherwise, the subject is assigned to treatment arm B . For complete randomization, the conditional allocation probability is a constant, i.e.

$$p_{i,A} |_{\text{complete randomization}} \equiv 0.5 (i=1, 2, \dots) \quad (1)$$

For all restricted randomization algorithms, let λ be the maximal tolerated imbalance, $n_{i-1,A}$ and $n_{i-1,B}$ be the number of subjects among the first $i-1$ subjects assigned to arms A and B respectively within the domain of the algorithm, i.e. a site, a category of a baseline covariate, or the entire study. For permuted block design, the conditional allocation probability can be obtained by using the urn model [6]:

$$p_{i,A} |_{\text{permuted block}} = \frac{\lambda + \lambda u - n_{i-1,A}}{2\lambda + 2\lambda u - (i-1)} \quad (2)$$

Here λ is the maximal tolerated imbalance, or half of the block size; u is the number of previously completed blocks. The conditional allocation probability for the big stick design is given by Soares and Wu [2]:

$$p_{i,A} |_{\text{big stick}} = \begin{cases} 0 & \text{if } (n_{i-1,A} - n_{i-1,B}) \geq \lambda \\ 1 & \text{if } (n_{i-1,B} - n_{i-1,A}) \geq \lambda \\ 0.5 & \text{otherwise} \end{cases} \quad (3)$$

The conditional allocation probability for the block urn design is given by Zhao and Weng [5]

$$p_{i,A} |_{\text{block urn}} = \frac{\lambda + u^* - n_{i-1,A}}{2\lambda + 2u^* - (i-1)} \quad (4)$$

Here $u^* = \min(n_{i-1,A}, n_{i-1,B})$ is the number of previously balanced pairs of assignments. The conditional allocation probability for the biased coin design with imbalance tolerance (BCDWIT) is defined by Chen [4]:

$$p_{i,A} |_{\text{BCDWIT}} = \begin{cases} p_{bc} & \text{if } (n_{i-1,B} - n_{i-1,A}) \geq \lambda \\ 1 - p_{bc} & \text{if } (n_{i-1,A} - n_{i-1,B}) \geq \lambda \\ 0.5 & \text{otherwise} \end{cases} \quad (5)$$

The minimization method was independently proposed by Taves [10] and Pocock and Simon [11]. The Taves version of the minimization method compares the sums of subject counts in all covariate margins associated with the current subject, and assigns the current subject to the arm with the smaller sum. The Pocock and Simon version of the minimization method compares the sums of imbalances in all covariate margins associated with the current subject under the assumptions of the two possible treatment assignments for the current subject, and takes the one with the smaller sum of marginal imbalances. When the minimization target is a weighted sum of the absolute values of each imbalance items, the two versions of minimization method point to the same treatment arm. Let $n_{i-1,h,A}$ and $n_{i-1,h,B}$ be the number of subjects previously assigned into the two arms in the margin of covariate h ($h = \text{site, NIHSS, age}$) associated with the current subject, the conditional allocation probability for the minimization method can be written as:

$$G_{i-1} = \sum_{h=\text{site, NIHSS, age}} w_h (n_{i-1,h,A} - n_{i-1,h,B}) \quad (6)$$

$$p_{i,A} |_{\text{minimization}} = \begin{cases} p_{bc} & \text{if } G_{i-1} < 0 \\ 1 - p_{bc} & \text{if } G_{i-1} > 0 \\ 0.5 & \text{otherwise} \end{cases} \quad (7)$$

Here w_h is a non-negative weight representing the importance of the balance in covariate h , and p_{bc} is a pre-specified biased coin probability. In the deterministic version of the minimization method, $p_{bc} = 1.0$.

3.3. Statistical property measures

The statistical properties of randomization designs are evaluated based on treatment allocation randomness and treatment group size imbalances. Clinical trials can be subverted simply by selection bias [21]. With real-time randomization, selection bias can be eliminated if all treatment assignments are pure random, even when allocation concealment is not perfect or not available. On the other hand, risk of selection bias emerges when an assignment can be predicted with certainty, no matter how well the allocation concealment is [22]. Measures for treatment allocation randomness include the proportion of deterministic assignments (DA) and the proportion of complete random assignment (CR); both are defined based on the conditional allocation probability $p_{i,A}$. Treatment assignment T_i is considered deterministic if $p_{i,A} = 1$ or 0 , and complete random if $p_{i,A} = 0.5$. The correct guess probability is another measure for treatment allocation randomness. It is not included in this simulation study because it carries information less definitive compared with DA and CR . Four imbalance items are estimated in the simulation. They are overall imbalance $IB_{overall}$, within-site imbalance IB_{site} , NIHSS imbalance IB_{NIHSS} , and age imbalance IB_{age} . Let $n_{k,T}$ ($T = A, B$) be the total number of subjects assigned to treatment arm T at the end of the simulation k , $n_{j,k,T}$ ($j = 1, 2, \dots, g; T = A, B$) be the number of subjects at site j assigned to treatment arm T , $n_{h,l,k,T}$ ($h = NIHSS, age; l = low, high; T = A, B$) be the number of subjects in the l category of the h covariate assigned to treatment arm T . At the end of simulation run k , the overall imbalance $d_k = n_{k,A} - n_{k,B}$ for simulation run k ($k = 1, 2, \dots, m$), the within-site imbalance $d_{j,k} = n_{j,k,A} - n_{j,k,B}$ for site j ($j = 1, 2, \dots, g$), the within-NIHSS group imbalance $d_{NIHSS,l,k} = n_{NIHSS,l,k,A} - n_{NIHSS,l,k,B}$ for NIHSS group l ($l = low, high$) and the within-age group imbalance $d_{Age,l,k} = n_{Age,l,k,A} - n_{Age,l,k,B}$ for Age group l ($l = low, high$) are calculated. At the end of the simulation, the standard deviations $s_{overall}$, $s_{NIHSS,low,k}$, $s_{NIHSS,high,k}$, $s_{Age,low,k}$, and $s_{Age,high,k}$ are calculated for d_k , $d_{NIHSS,low,k}$, $d_{NIHSS,high,k}$, $d_{Age,low,k}$, and $d_{Age,high,k}$ respectively across the m simulation runs. Imbalances $IB_{overall}$, IB_{NIHSS} , and IB_{Age} are evaluated by $s_{overall}$, $(s_{NIHSS,low} + s_{NIHSS,high})/2$, and $(s_{Age,low} + s_{Age,high})/2$ respectively. Both NIHSS and Age have two categories. Under a fixed sample size, the two category sizes are complementary to each other. The average of the standard deviations in the two categories is used for imbalances in baseline NIHSS and Age. The number of clinical sites could be much large than the number of covariate categories. There are about seventy five sites in this PRISMS trial. We use the standard deviation of within-site imbalances $d_{site,k}$ as a measure for the within-site imbalance in the simulation run k . Notice that $\sum_{j=1}^g d_{jk} = d_k$, and $d_{site,k} = d_k / g$. When g is large, there is $s_{site,k} \approx \sqrt{\sum_{j=1}^g (d_{jk})^2 / g}$. It is not hard to see that the value of $s_{site,k}$ is larger than the average absolute value of $d_{site,k}$ and less than the maximal absolute value of $d_{site,k}$. At the end of the simulation, the within-site imbalance IB_{site} is evaluated by the mean of $s_{site,k}$ across the m simulation runs.

4. Results

4.1. Treatment allocation randomness

The treatment allocation randomness is mainly determined by the randomization algorithm and its parameters. Impact of other factors, such as sample size, number of baseline covariates, number of categories for each covariate, number of sites, and the randomization stratification method, are trivial. In theory, the randomization implementation type (local, central, or step-forward) has no impact on the treatment allocation randomness. When a restricted randomization algorithm with a fixed imbalance control limit is applied, deterministic assignments are unavoidable. The proportion of deterministic assignments for the permuted block design, the big stick design, and the block urn design can be found in references [1], [2], and [5] respectively; whereas the proportion of complete random assignments for the permuted block design and the block urn design were given by Zhao et al. [5, 7]. For the big stick design, the deterministic assignments and complete random assignments are complementary to each other. For permuted block design and block urn design, there are biased coin assignments, in addition to deterministic assignments and complete random assignments. Table 1 lists the theoretical results of the randomness measures for the three restricted randomization algorithms. In computer simulations under the specific settings of real trials, the proportion of deterministic assignments may be lower than the theoretical value, due to the small stratum size.

In randomized controlled clinical trials, deterministic assignment is the primary source for selection bias [21]. The high proportion of deterministic assignments associated with the permuted block randomization has been criticized [23]. Quite a few trials with suspicious selection biases were traced back to the use of permuted block designs [24, 21]. Table 1 shows that, under the same level of the maximal tolerated imbalance λ , the permuted block design has the highest proportion of deterministic assignments among the three randomization algorithms, and the proportion decreases slowly as λ increases. The block urn design has the lowest proportion of deterministic assignments, which drops quickly as λ increases. When $\lambda = 3$, only 5.9% assignments are expected to be deterministic under the block urn design, which can be considered as safe enough in practice. For this reason, when a restricted randomization algorithm with a maximal tolerated imbalance is specified, the block urn design should be considered with priority if deterministic assignment is a main concern, and otherwise the big stick design is recommended.

The proportion of complete random assignment is important if the restricted randomization algorithm is the first step of the randomization procedure, and additional imbalance controls steps could be considered when the conditional allocation probability obtained from the first step is 0.5. For example, if the randomization procedure is designed to contain the within-site imbalance with a fixed limit, and followed by a biased coin design to control the overall imbalance, the big stick design if adopted in the first step provides the highest effectiveness for the second step, due to the highest possible proportion of complete random assignments in the first step. Should the big stick design be considered, a maximal tolerated imbalance $\lambda = 3$ is suggested, in order to avoid the higher proportion of deterministic assignments.

A total of 17 randomization procedures are studied with computer simulations. Results of treatment allocation randomness and imbalances are listed in Table 2. Corresponding to the setting of the PRISMS trial, the simulation assumes a sample size of 948 subjects enrolled at 75 sites. The four measures of imbalance are defined by formulas (12), (13), (15), and (16) respectively. As expected, the complete randomization offers the highest level of treatment allocation randomness and the largest imbalances.

4.2. Local randomization

In stratified local randomization, effectiveness of imbalance control diminishes as the number of covariate strata increases. For example, with stratified permuted block randomization, as the number of strata increases 75 (site) to 150 (site-NIHSS) to 300 (site-NIHSS-Age), the within-site imbalance increases from 1.08 to 1.53 to 2.20; and the overall imbalance increases from 9.36 to 13.23 to 18.94. Another concern for local randomization is the treatment allocation predictability. With the knowledge of the maximal tolerated imbalance λ , which is usually set to 2 or 3 and is easy for a correct guess, and the imbalance information within the site, investigators could potentially have the capacity to predict all upcoming deterministic assignments. This especially becomes a practical concern when perfect treatment assignment blinding is not available.

4.3. Central randomization

Central randomization procedures provide the best control on overall imbalance and baseline covariate imbalances. The simulation shows that the minimization method works better than the hierarchical biased coin design. Minimization method has been proven as the most effective treatment allocation algorithm for simultaneously balancing multiple baseline covariates in multicenter clinical trials [25, 26]. However, the high proportion of deterministic assignments remains a serious concern as it may lead to treatment allocation concealment failure and potential selection bias [21, 25]. Furthermore, the necessity of strict imbalance control in randomized controlled large multicenter clinical trials is highly questionable [26]. To alleviate these two problems, we can consider a modified version of the minimization method with an imbalance control threshold δ and a biased coin probability p_{bc} . With the same definition of imbalance sum as

$G_{i-1} = \sum_{h=site, NIHSS, age} w_h (n_{i-1,h,A} - n_{i-1,h,B})$ (6), the conditional allocation probability (7) can be modified as:

$$p_{i,A}|_{minimization} = \begin{cases} p_{bc} & \text{if } G_{i-1} < -\delta \\ 1 - p_{bc} & \text{if } G_{i-1} > \delta \\ 0.5 & \text{otherwise} \end{cases} \quad (17)$$

Figure 1 shows the computer simulation of the four imbalances under different values of δ and p_{bc} . In this simulation, $w_{site} = 2$ is used because the number of sites is much larger than the number of categories for NIHSS and age. It is clear that with the same level of imbalance control threshold, a biased coin probability of 0.75 or 0.8 will not lead to imbalances much larger than those under the deterministic version of the minimization method.

The impact of the control threshold on imbalances is relatively small. Consider the sample size of 958 and the sizes of all NIHSS and age categories greater than 280, an imbalance with the standard deviation of 3 or less is small enough. Computer simulation reveals that if $\delta = 4$ and $p_{bc} = 0.8$ is used in this modified minimization method, an average of 62% treatment assignments are complete random. This will greatly ease the concern of selection bias caused by the high proportion of deterministic assignments in the minimization method.

The main concern for central randomization is the potential time delay caused by the randomization procedure.

4.4. Step-forward randomization

In step-forward randomization, with one “Use Next” assignment for each site, there is no direct control on imbalances in baseline NIHSS and age categories. However, due to the control on the overall imbalance, the actual imbalances in NIHSS and age are similar to those under the local randomization stratified by site, NIHSS and age. Computer simulation results show that there are no big differences in any of the four imbalances among the three step-forward randomization procedures. However, the proportion of deterministic assignments is much lower under the block-urn design than that of the other two randomization algorithms.

Among the 17 randomization procedures, if potential time delay is a serious concern, the step-forward randomization with block urn design and a within site imbalance limit of 3 is the best choice. Otherwise, the minimization method with a biased coin probability of 0.75 or 0.8 should be considered.

5. Discussion

Step-forward as a randomization implementation method, it shares some pros and cons from both local and central randomization. Because the [Use Next] assignments contain no information on any baseline covariate other than the clinical site, it is not applicable to minimization and hierarchical balancing randomization designs where information on baseline covariates other than clinical site is involved.

In step-forward randomization with one “Use Next” assignment at each site, information used for the randomization of a new “Use Next” assignment includes the current distribution of enrolled subjects between the two groups, the current distribution of assigned “Use Next” assignments, and the fact that the assignment will be used by the next subject in this site. However, when this assignment will be used remains unknown. Before this assignment is used, the distributions of enrolled subjects and “Use Next” assignments could change. While this fact does not affect the within-site imbalance control, it does affect the overall imbalance control. Computer simulation results demonstrate that the overall imbalance increases when the number of sites increases, as shown in Figure 2. Simulation results also showed that the number of sites has little impact on imbalances in NIHSS and age categories.

Ideally in a large multicenter trial, sites are randomly divided into two groups, one using central randomization, while the other using step-forward randomization, and the time between hospital arrival and treatment delivery is collected and analyzed. Until then, the time-saving benefit for step-forward randomization remains a conceptual expectation, rather than a quantitatively verified feature. Nevertheless, the potential time-saving benefit is attractive to investigators treating medical emergencies like stroke, where time is brain.

6. Conclusions

For large multicenter trials like PRISMS, the step-forward randomization with block urn design is a better option than the commonly used local randomization procedure with permuted block stratified by site. The step-forward method offers a much lower overall imbalance, much lower proportion of deterministic assignments, similar imbalances in baseline covariates other than site, and the same time saving benefit over central randomization procedures.

For trials with less serious concerns on the potential time delay caused by the randomization procedures, a modified minimization method with an imbalance control threshold and a biased coin probability is suggested. It provides effective controls on imbalances in multiple baseline covariates while maintaining a high level of treatment allocation randomness.

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Figure 1.
Imbalances under Modified Minimization Method Sample size=958, Sites=75, NIHSS
low=40%, Age low=30%, Simulation run=1000.

Figure 2.
Impact of number of sites on overall Imbalance

Treatment allocation randomness (theoretical results) of restricted andomization algorithms

Table 1

Maximal Tolerated Imbalance λ	Proportion of deterministic assignments (D/A)			Proportion of complete random assignments (CR)		
	Permuted Block Design	Big Stick Design	Block Urn Design	Permuted Block Design	Big Stick Design	Block Urn Design
1	0.500	0.500	0.500	0.500	0.500	0.500
2	0.333	0.250	0.167	0.416	0.750	0.333
3	0.250	0.167	0.059	0.365	0.833	0.265
4	0.200	0.125	0.021	0.329	0.875	0.225
5	0.167	0.100	0.008	0.307	0.900	0.199
6	0.143	0.083	0.003	0.285	0.917	0.180

Table 2

Randomness and Imbalance Comparison for Different Randomization Procedures

No.	Randomization Procedure			Parameter	Randomness		Imbalance				
	Randomization Type	Randomization Algorithm	Imbalance Control		λ	$p_{ba}^{\dagger}$	DA	CR	$IB_{overall}$	IB_{site}	IB_{NIHSS}
1	Complete randomization	Permutated Block	Site	3		0%	100%	30.77	3.56	21.68	21.21
2											
3			Site, NIHSS	3	16.6%	41.6%	13.23	1.53	9.35	15.84	
4			Site, NIHSS, Age	3	9.5%	47.3%	18.94	2.20	13.43	13.39	
5		Site	3	12.5%	87.5%	15.30	1.78	17.18	16.51		
6											
7		Big Stick	Site, NIHSS	3	8.9%	90.1%	21.00	2.44	14.87	17.97	
8											
9	Block Urn	Site, NIHSS, Age	3	5.3%	94.7%	25.39	2.96	18.08	17.97		
10											
11	Central Randomization	Minimization	Site	3	3.3%	37.1%	16.68	1.93	11.78	16.79	
12											
13			Site, NIHSS, Age	3	2.0%	45.3%	21.30	2.45	15.04	14.85	
14			Site, NIHSS, Age	0	1.0	83.9%	16.1%	1.26	0.89	1.10	
15		Hierarchy Biased Coin	Site, NIHSS, Age	3	0.75	0%	9.6%	2.48	1.74	2.17	2.15
16											
17			Site, NIHSS, Age	3	0.7	0%	32.6%	3.71	2.38	3.08	3.58
18			Site, NIHSS, Age	3	0.85	51.1%	2.39	1.98	2.11	2.19	
19	Step-forward Randomization	Permutated block	Site, Overall	3	0.85	22.8%	7.4%	5.94	1.08	15.63	14.34
20											
21		Big Stick	Site, Overall	3	0.85	13.1%	33.5%	6.09	1.78	15.48	14.62
22		Block Urn	Site, Overall	3	0.85	5.0%	4.7%	6.21	1.39	15.64	14.42

Sample size = 958, Number of sites = 75, NIHSS low category = 40%, Age low category = 30%, Simulation run = 5000.

[†] Biased coin probability used in the randomization algorithm.