Balancing Treatment Allocation and Randomization with Combinatorics

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Abstract

For a randomized clinical trial, it is a basic requirement that the actual allocation among treatment groups is similar to that which is specified in the original trial design. This maximizes the power and efficacy of the trial and helps to prevent statistical biases. For example, in a multi-site clinical trial (when randomized by site), each site will assign blocks of treatment codes. Since the total number of enrolled subjects is ultimately random, each site may not be balanced over all treatments and such imbalances can be accumulated over the entire trial. One of the post popular approaches to this challenge is known as centralized randomization; this approach is most effective when the number of sites is large and each site typically has a small number of subjects (relative to the number of treatment groups). However, when randomization by site is also necessary (e.g. in an allergy study), finite size imbalances can become a serious limiting factor. Here, we present a modified treatment allocation method based upon a combinatoric approach.

Key Words: Combinatorics, randomization by site, treatment balance, Latin-squares, centralized randomization, clinical trial design, allergy studies

1. Introduction

When designing a clinical trial, it is important to know how many enrolled subjects are required to achieve maximum efficacy [1-3]. This number is typically based on a sample size calculation and depends on factors ranging from the expected treatment difference to the power of the hypothesis testing. Each such factor is itself dependent on the overall proportion of treatment allocation and the expected sample size for each treatment group. Therefore, in a clinical trial, it is crucial that the actual experimental allocation is as close as possible to that specified by the trial design [4].

While centralized randomization can achieve an overall balanced treatment allocation, certain clinical trials are required to use randomization by center. This is especially true when the conditions across test centers can represent an important confounding factor (e.g. the pollen count at a center in an allergy study). In a multi-center clinical trial, (when randomized by center) each center will typically assign blocks of treatment code designed to achieve internal balance. Owing to finite size effects, in real-world clinical trials, one often finds unbalanced treatment allocations, which in certain instances, can substantially weaken the power of the trial [5-6].

2. Origin of Treatment Imbalance

To illustrate the origin of such finite size imbalances, let us consider a trial with 4 treatment groups that are randomized in a 1:1:1:1 ratio (with block size 4). Suppose that the situation before data-base lock is as follows:

Center	1st block				2nd block			
1	x	x	x	x				
2	x	x	x	x	x			
3	x	x	x					
4	x	x	x	x	x	x	x	

Being balanced, center 1 has no impact on the treatment imbalance; however, centers 2, 3 and 4, will each contribute to the overall study imbalance with different relative importance. For example, center 3 has the most serious imbalance issue since all of its subjects contribute; meanwhile for center 4, more than 50% of the enrolled subjects have already achieved treatment balance. As expected, this shows that a large center usually has a relatively small imbalance issue and that our approach is most applicable when a trial consists of many small centers [7].

To be specific, consider a phase 2 dose finding trial with 6 dosing levels. Based on a power calculation, let us assume that the trial requires 45 subjects per treatment group for the first interim analysis. To achieve the total of 270 randomized subjects, the clinical data management team decides to open 90 study centers with an enrolment cap of 5 for each center. To explore the possible issues associated with treatment imbalance, we perform numerics to simulate the clinical trial. We randomly assign 1 to 5 subjects for each site and consider a total of 200 simulation runs. For each run, a relevant measure of the imbalance is captured by the largest enrolment difference between any two treatment groups. We summarize the results below:

Maximum difference among 6 arms for each simulation run:

runs	min	mean	std	max
200	4	11.5	3.8	26

The Worst Run with maximum difference (desired average: 45/arm)

treatment	A	B	C	D	E	F
N	32	37	39	47	55	58

As one can see, the worst run resulted in maximum difference of 26 and in that case, there exists two groups with a relatively small number of subjects (32 and 37). It would be particularly prohibitive if these groups represented the placebo and the highest-dosage as this would significantly weaken the statistical power of the trial. Thus, a natural and simple question is whether there exists a combinatorial method to improve the balance of treatment allocation in such situations?

3. Latin Squares Based Method

A basic motivation is to try to balance the overall treatment allocation while still maintaining the required randomization by center. Let us provide an example of Latin-

squares-based method. In particular, if a trial has 4 treatment groups, labelled as 1, 2, 3 and 4, then we can construct a 4 x 4 matrix (so-called Latin-Square), as shown below:

Sequence(center)	Treatment			
1	1	2	3	4
2	2	3	4	1
3	3	4	1	2
4	4	1	2	3

Suppose that we see an allocation before data-base lock as shown in table below:

Sequence(center)	Treatment			
1	X	x		
2	x	x	x	x
3	x	x	x	
4	x	x		

Using the previous centralized method, only the 4 subjects in center 2 are balanced and all other subjects can potentially contribute to a large overall imbalance. On the other hand, if we had utilized the Latin-square allocation we know that the 8 subjects in the first 2 columns are completely balanced. The power of this method is that a latin-square has each symbol appear only once in both rows and columns.

While there are many ways to implement a randomization by center with this new method, the key step is to construct a Latin-square of treatment codes. We use the following example to illustrate how to operate a trial. As before, consider a trial with 4 treatment groups and an allocation ratio of 1:1:1:1. When the first center requests a new treatment code block and the system generates a random set (3, 2 , 4, 1), then a new Latin-Squares matrix can generated by a simple permutative mapping:

Center	Treatment					New latin-square			
1	1,(3)	2,(2)	3,(4)	4,(1)		3	2	4	1
2	2	3	4	1	➔	2	4	1	3
3	3	4	1	2		4	1	3	2
4	4	1	2	3		1	3	2	4

4. Applying the Method

Let us now consider implementing the method in our previous numerics. Below is the summary of simulation results based the Latin-squares allocation approach utilizing the same previous conditions (e.g. those of the phase 2 dose finding trial).

Maximum difference among 6 arms for each simulation run:

Method	runs	min	mean	std	max
Old	200	4	11.5	3.8	26
Latin-squares	200	2	7.2	2.6	14

The Worst Run with max difference (average 45/arm)

Method	treatment	A	B	C	D	E	F

Old	N	32	37	39	47	55	58
Latin-squares	N	38	40	44	47	47	52

As is evident, the maximum difference has been reduced from 26 to 14 and even for that worst simulation run, the two smallest group sizes are now significantly closer to the desired value of 45.

To further improve our method, we can employ an effective smoothing algorithm. In particular, we note that for any trial, if we sort all centers by the number of enrolled subjects, we will obtain a monotonic list. In cases where the clinical data management team has an accurate prediction of center enrolment, we can utilize such a sorted list to reduce the overall noise. By grouping centers with a similar predicted enrolment, we can optimize the allocation method to take maximum advantage of the Latin-squares. More specifically, after sorting, we group the centers into blocks of size k where k is the rank of the Latin-squares matrix. Each block of centers is then assigned a random instance of a k x k Latin-squares based treatment code. Of course, such a method is only beneficial when the true enrolment closely matches that predicted by the data management team.

Assuming such an optimal scenario, we perform the numerics with the smoothed Latin-squares approach. The results are summarized below:

Summary of maximum difference among 6 arms for each run:

Method	runs	min	mean	std	max
Old	200	4	11.5	3.8	26
Latin-squares	200	2	7.2	2.6	14
Optimal LS	200	1	1.8	0.7	3

The Worst Run with max difference (average 45/arm)

Method	treatment	A	B	C	D	E	F
old	N	32	37	39	47	55	58
Latin-squares	N	38	40	44	47	47	52
Optimal LS	N	43	44	45	45	45	46

The maximum difference is further reduced from 14 to 3 and even the worst simulation run reveals an overall allocation nearly identical to the desired value of 45 subjects.

5. Examples from an actual Clinical Trial

Let us finally apply our method to data from an actual clinical trial. In this trial, there were 4 treatment arms (block size of 4) and 50 centers with a total enrollment of 566 subjects. The enrollment varied between centers and ranged from 1 to 30.

Actual Trial Results : max difference = 10=147-137

treatment	A	B	C	D
N	137	140	142	147

Utilizing these parameters, let us again perform numerics with the three methods previously described.

Summary of maximum difference among 4 arms :

Method	runs	min	mean	std	max
Old	200	1	6.6	3.0	16
Latin-squares	200	1	6.6	2.8	14
Optimal LS	200	1	1.7	0.8	3

The Worst Run with maximum diff =16 , 14 and 3

Method	treatment	A	B	C	D
old	N	134	140	142	150
Latin-squares	N	135	139	143	149
Optimal LS	N	140	141	142	143

As expected, both the Latin-squares and optimal LS method outperform the generic centralized randomization approach. In conclusion, we have proposed and analyzed a combinatorics based approach to reducing finite-size imbalances in clinical trials which require randomization by center.

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