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Covariates Adaptive Randomization Designs in Clinical Trials: A Comparative Study

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Abstract: This paper investigated in covariate adaptive randomization designs, which are used to reduce covariate variables imbalance between treatments in clinical trials. Critical percentage and imbalance minimization methods are compared each one to another, and both are compared with pure randomization method in term of imbalance. The comparison is intended to show which method has minimum imbalance at three covariate variables with twelve single layers and three sample sizes 10, 20 and 100. The results which carried out from the simulation experiment clearly shown that the performance of critical percentage approach is closely similar to imbalance minimization method in full balance case as well as maximum imbalance at all sample sizes. And pure randomization method has the maximum imbalance compared to others at each sample size.

Keywords: Clinical Trials, Imbalance, Minimization, Randomization

1. Introduction

Adaptive design is a design which allows modifications to the trial or statistical procedures of the trial after its initiation without undermining the validity and integrity. The purpose is to make clinical trials more flexibility, effectively and fast. Due to the level of flexibility involved, these trial designs are termed as flexible design [1].

Liu and Pledger have addressed the following definition. The adaptive design methods are usually developed based on observed treatments effects to allow wider flexibility, and adaptations in clinical investigation of treatment. These may include changes of sample size, inclusion or exclusion criteria, study dose, study endpoints or methods of analysis [2].

According to Chow and Chang adaptive design is design which allows for changing or modifications the characteristics of a trial based on cumulating information to increase the probability of success, reduce the cost, reduce the time or preserve the and validity of the trial [3].

Food and Drug Administration (FDA) is an American organization interested on statistical procedures in biological industries. In 2010 FDA addressed guidance for that industry titled in "adaptive design clinical trials for drugs and biologics". That guidance has defined adaptive design as "a study that includes a prospectively planed opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study". Analysis of the accumulating study data are performed at pre-planned endpoints within the study, not important if with or without formal statistical hypotheses testing [4].

The covariate adaptive randomization (CAR) is usually used instead of pure randomization to reduce the covariate imbalance between treatment groups in clinical trials. Allocation probability for the covariate adaptive randomization is adapted over time during the trial based on the cumulative information about baseline covariates and treatment assignments. The following methods are addressed by biostatisticians to reduce the covariate imbalance in experiments. "Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial" [5] is one of the famous papers that discussed (CAR). The paper by Zelen "The randomization and stratification of patients to clinical trial" [6] is one of the most important designs in (CAR), too. Wei has mentioned two designs. The first one aimed to decrease the imbalance between treatments, by depending on marginal urn design. The second one used "Play the Winner Rule" for achieving the desired balance [7]. "Atkinson Optimal Model" is a model which considered a linear regression model to obtain the same

above advantage [8]. "Imbalance minimization method" has been addressed by Birkett [9]. The minimization method (MIN) has been widely used in clinical trials. The using of this method achieves minimum imbalance in the number of patients and their characteristics also, in each treatment. "Critical percentage method" (CPM) is the last method in CAR methods which suggested by Osman [10]. In critical percentage method, all previous data is used to assign a new patient to treatments. It is designed to bridge the gap between the goal of covariate adaptive randomization designs and the current methods which are used to achieve this purpose.

This paper aims to compare two of CAR methods with pure randomization method (RM). The comparison is between imbalance minimization (MIN), critical percentage methods (CPM) and RM. Which one of these methods has the minimum imbalance is our purpose.

2. Adaptive Randomization Methods

Covariate adaptive randomization methods which the comparison will be between are addressed in this paragraph.

2.1. Imbalance Minimization Method

The minimization method (MIN) has been widely used in clinical trials. The using of this method achieves minimum imbalance in the number of patients and their characteristics also, in each treatment [9].

If there are T treatments and C covariates. Let $l_1, l_2, l_3, \dots, l_c$ be the levels of covariates $1, 2, 3, \dots, c$ respectively. Then the number of strata here are $l_1 * l_2 * l_3 * \dots * l_c$.

Let n_{ijk} be the number of patients who were assigned with covariate i in level j to treatment k.

Where $i = 1, 2, 3, \dots, c$; $j = 1, 2, 3, \dots, l_i$ and $k = 1, 2, 3, \dots, T$, the next step is to assign $(n_{ijk})st$ patients. Let $r_1, r_2, r_3, \dots, r_c$be the levels of new a patient covariates.

The assigning of this patient is as follows:

$Step$ 1:

Add the new patient to the first treatment, treatment 1 say, temporarily.

Then compute the amount of imbalance:

$$d_i = n_{ir_{j1}} - n_{ir_{j2}}$$

where, $n_{ir_{j1}}$ is the number of patients with covariate i in level j that are assigned to treatment 1.

$n_{ir_{j2}}$is the number of patients with covariate i in level j who that are assigned to treatment 2.

$$G = (d_{i1}, d_{i2}, \dots, d_{iT}) = \sum_{i=1}^{c} |d_i|$$

$Step$ 2:

Add the new patient to treatment 2 temporarily.

Then compute the amount of imbalance:

$$d_i = n_{ir_{j1}} - n_{ir_{j2}}$$

where, $n_{ir_{j1}}$ be the number of patients with covariate i in level j who have been assigned to treatment T_1.

$n_{ir_{j2}}$ be the number of patients with covariate i in level j have been assigned to treatment T_2.

$$G = (d_{i1}, d_{i2}, \dots, d_{iT}) = \sum_{i=1}^{c} |d_i|$$

$Step$ 3:

Add a new patient to treatment T_1 or T_2 which one leads to minimum imbalance (G).

2.2. Critical Percentage Method

In critical percentage method, all previous data is used when assigning a new patient to treatments. It is designed to bridge the gap between the goal of covariate adaptive randomization designs and the current methods which are used to achieve this purpose[9].

As mentioned earlier, adaptive randomization designs are used in clinical trials to avoid the imbalance in the number of patients and their characteristics which could happen in pure randomization. The earliest method of adaptive randomization worked to reduce the imbalance by making more balance in each single layer in the experiment, but ignored the total of layers. This problem is solved in MIN method which focuses on total randomization imbalance. But the imbalance increases in single layers in this method. So, the purpose of CPM is to make more balance in the single layers and in the total randomization at the same time.

In the following paragraphs, assumptions and steps of CPM are explained for two treatments, and it is easy to generalize it for more than two treatments.

It is assumed in CPM that, patients are entered to the trial sequentially.

Suppose that there are two treatments T_1 and T_2, and C covariate variables. The i^{th} covariate has l_i levels,

Where $C \geq 1, l_i \geq 2, i = 1, 2, 3, \dots, C$

There are thus $l_1 * l_2 * l_3 * \dots * l_c = S$ single layers (strata) in the trial.

$Step$ 1:

In this step the desirable percentage (critical percentage) to divide each part of each covariate variable between treatments is determined. That means, if we choose critical percentage equal 50% for l_{i_j} (j^{th} level of i^{th} covariate) the number of patients who have the j^{th} level of the i^{th}covariate must be such that half of them in treatment T_1, and the other half in T_2. And if we choose 60% as a critical percentage for l_{i_j}, that means the number of patients who have l_{i_j} in T_1 or T_2 is≤ 60% from the total patients in this layer.

Let λ_{ij} be the critical percentage for level j of covariate i. Where $0 < \lambda_{ij} < 1$.

The value of λ_{ij} would increase or decrease according to the importance of the covariate or the covariate level. And this flexibility in λ_{ij} value is considered as an of advantage of CPM.

$Step$ 2:

1) The first patient in the trial would be assigned randomly to treatment T_1 or T_2 with probability equal $\frac{1}{2}$ for each.

2) To assign the $(k+1)st$ patient,

where$k = 1, 2, 3, \dots, n-1$ with n the number of patients in the experiment,

a. Determine the covariates levels of the patient, let this $(i = 1, \dots, c;\ j = 1, \dots, l_i)$. This specifies the stratum to be k_{ij} which the patient belongs.

b. Letting:

$n_{ki_{j^1}}$ ≡The number of patients in level *j* of covariate *i* who are assigned to treatment T_1 after k assignments.

$n_{ki_{j^2}}$ ≡The number of patients in level *j* of covariate *i* who are assigned to treatment T_2 after k assignments.

Compute:

$$p_{ij1} = \frac{n_{ki_{j^1}}}{n_{ki_{j^1}} + n_{ki_{j^2}}} \quad (1)$$

$$p_{ij2} = \frac{n_{ki_{j^2}}}{n_{ki_{j^1}} + n_{ki_{j^2}}} \quad (2)$$

c. Compute the r_i values defined as:

$$r_1 = \begin{cases} 1 \ if p_{ij1} \le \lambda_{ij}, \forall_{ij} \\ 0 \ otherwise \end{cases}$$

$$r_2 = \begin{cases} 1 \ if n_{ki_{j^1}} < n_{ki_{j^2}} \\ 0 \ otherwise \end{cases}$$

$$r_3 = \begin{cases} 1 \ if p_{ij2} > \lambda_{ij}, \exists_{ij} \\ 0 \ otherwise \end{cases}$$

$$r_4 = \begin{cases} 1 \ if p_{ij2} \ge \lambda_{ij}, \forall_{ij} \\ 0 \ otherwise \end{cases}$$

$$r_5 = \begin{cases} 1 \ if n_{ki_{j^1}} = n_{ki_{j^2}} \\ 0 \ otherwise \end{cases}$$

$$r_6 = \begin{cases} 1 \ if p_{ij1} = \lambda_{ij}, \forall_{ij} \\ 0 \ otherwise \end{cases}$$

$$r_7 = \begin{cases} 1 \ if p_{ij1} > \lambda_{ij}, \exists_{ij} \\ 0 \ otherwise \end{cases}$$

$$r_8 = \begin{cases} 1 \ if p_{ij2} > \lambda_{ij}, \exists_{ij} \\ 0 \ otherwise \end{cases}$$

Patient number $(k+1)$ will then be assigned to treatment T_1 with probability $p_{k+1,1}$ where:

$$p_{k+1,1} = \begin{cases} 1 \ if r_1 = 1 \ or \ (r_2 = 1 \ and \ (r_3 = 1 \ or r_4 = 1)) \\ \frac{1}{2} if r_5 = 1 \ and \ (r_6 = 1 \ or \ (r_7 = 1 \ and r_8 = 1)) \\ 0 \ otherwise \end{cases} \quad (3)$$

3. The Simulation Experiment

In this section a description is given to the simulation experiment conducted to examine the performance of the CPM relative to that of RM and the MIN. To conduct this simulation, we assumed that, there are two treatments T_1 and T_2, and three covariate variables c_1, c_2 and c_3. The first covariate c_1 has two levels l_{11} and l_{12}, c_2 has three levels l_{21}, l_{22} and l_{23} and c_3 has two levels l_{31} and l_{32}. This yields $2 * 3 * 2 = 12$ single layers in the trial. The data will be generated with above covariates then allocated to the treatments by MIN method and CPM with $\lambda = 50\%$ and by RM with equal probabilities. When the sample is allocated, the imbalance would be calculated as the absolute difference between numbers of units which are assigned to treatmentsT_1 and T_2 for each method.

Different sample sizes are chosen to make reliable simulation. The first sample size is 10. This helps to test the methods performance in case, when the sample size is less than the size of single layers in the trial. Other sample sizes are 20 and 100. The simulation would be repeated 1000 times for each sample size. Imbalance calculated as the absolute value between numbers of patients who are assigned to treatment T_1 and T_2 at each single layer and total assigning. The software STATA[12] is used to conduct this simulation.

4. Summary Results

The following table and figures show the frequencies and percentages of the imbalance for MIN, CPM and RM from the simulation study.

Table 1. *Imbalance and its percent for the three randomization methods when sample size 10, 20 and 100.*

Imbalance	Sample size 10			Sample size 20			Sample size 100		
	CPM%	MIN%	RM %	CPM %	MIN%	RM %	CPM%	MIN%	RM %
0	72.8	82.1	23.2	69.3	81.5	17.8	62.9	79.6	7.2
2	27.2	17.9	43.5	30.4	18.5	32.3	35.7	20.3	16.2
4	0.0	0.0	23.5	0.3	0.0	24.2	1.4	0.1	16.7
6	0.0	0.0	8.8	0.0	0.0	15.6	0.0	0.0	12.7
8	0.0	0.0	0.8	0.0	0.0	6.9	0.0	0.0	10.2
10	0.0	0.0	0.2	0.0	0.0	2.0	0.0	0.0	10.7
12	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0	7.5
14	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	6.6
16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.6
18	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.8
20	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.3
22	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.8
24	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.7

Table 1 above shows the imbalance values and its percent. The first column is the imbalance amount (the absolute difference between units which assigned to T_1 and T_2) according to randomization method and sample size.When the sample size 10, CPM has 72.8% full balance case (728 of 1000) compared to 82.1% in MIN and 23.2% in RM. And the maximum imbalance is 2 in both CPM and MIN, while is 10 in RM. In case of sample size 20 we find zero imbalance cases are 69.3% for CPM, 81.5% for MIN and 17.8% for RM. The maximum imbalance is large in RM (14), but is small for each of CPM (2) and MIN (4). Performances of CPM and MIN are similar where sample size 100. Maximum imbalance is 4 for both, compared to 24 for RM. And full balance is 62.9% in CPM and 79.6% in MIN compared to 7.2% in RM.

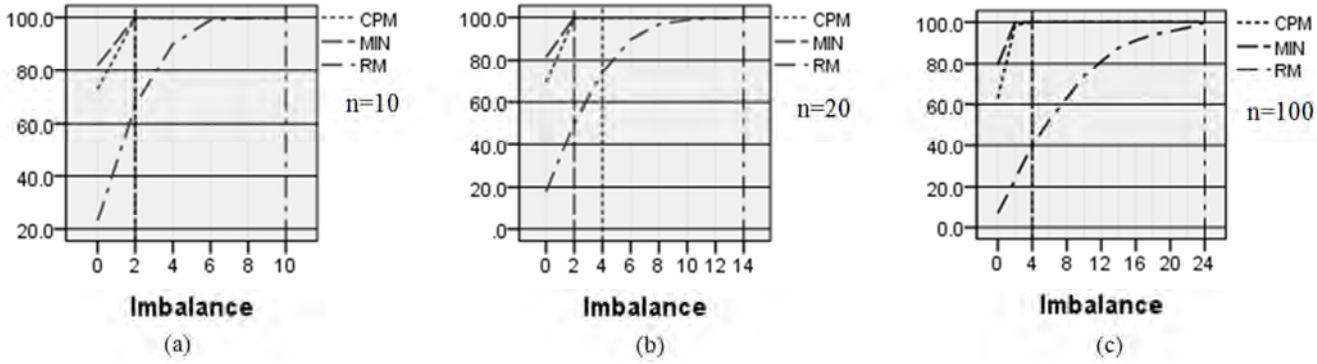

Figure 1. *Imbalance and its cumulative percent for the three randomization methods when sample size 10, 20 and 100.*

From Figure 1 (a), it is clear that the cumulative percent equal 100 when the imbalance is just 2 in each of CPM and MIN where is 10 in case of RM with sample size 10. Figure 1 (b) shows the cumulative percent is 100 where imbalances are 4, 2 and 14 for CPM, MIN and RM respectively when sample size 20. Cumulative percent is converged to a large extent in CPM and MIN and both are different from RM in Figure 1 (c).

5. Conclusion

From above results, we can conclude:

1) CPM has minimum imbalance compared with RM at all sample sizes.

2) The performance of CPM is similar to a large extend to MIN in terms of full balance and maximum imbalance.

3) The similarity between methods performance is unaffected by sample size.

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