SUST Journal of Natural and Medical Sciences (JNMS)vol. **16** (1) 2015
ISSN (Print): 1858-6805 e-ISSN (Online): 1858-6813

SUST
Journal of Natural and Medical Sciences

Journal homepage: http://journals.sustech.edu/

factors fordepression. *Journal of Abnormal Psychology.* 103. No. 2, 302 – 315.

A contribution to Covariate Adaptive Randomization

Montasir Ahmed Osman Mohamed*

*Mathematics Department, Kassala University- Sudan, Mobile: +249123989798, E-mail: a.montasir@yahoo.com

Article history: Received:21.07.2014
Accepted:02.11.2014

ABSTRACT

Adaptive randomization designs are statistical designs that are used as alternative to pure randomization designs in clinical trials, with the object of reducing imbalance in trials.A new method,to be called critical percentage method (CPM) is introduced and compared with the pure randomization method through a simulation experiment. The simulation showed that, the CPM has minimum imbalance, for all sample sizes (10, 100 and 1000).

المستخلص

التصاميم العشوائية التكيفية هي تصاميم إحصائية تستخدم كبديل للتصاميم العشوائية الكاملة في التجارب الطبية بهدف تقليل عدم التوازن في التجربة . و تعرّف الورقة بطريقة جديدة سُميت طريقة النسب المئوية الحرجة و التي تمت مقارنتها بالطريقة العشوائية الكاملة. و قد بينت تجربة المحاكاة التي استخدمت للمقارنة بين الطريقتين أن الطريقة المقترحة تؤدي إلى تقليل عدم التوازن بدرجة كبيرة جداً، وهو الغرض منالتصاميم العشوائية التكيفية. و أجريت التجربة عند ثلاثة أحجام عينات هي 10، 100 و 1000.

KEYWORDS:covariate variable, imbalance,adaptive design, clinical trial

INTRODUCTION

Adaptive randomization is an allocation that uses all previous assignments in the trial to influence the allocation of the current experimental unit[1,2]. The adaptive allocation (adaptive randomization) of experimental units upon treatments in clinical experiment has become an alternative to pure random allocation (pure randomization (RM)) for several decades. Covariate adaptive randomization is a type of adaptive randomization which uses only the covariate variables to make units allocations, and it is a flexible design aims to reduce imbalance between treatments[3-5].

Each design has its advantages and disadvantages, so, a researcher must choose the appropriate design after evaluating the available designs from different angles.

In this paper, a new method in covariate adaptive randomization will be suggested (this method would be called critical percentage method (CPM)). The new method will be compared with pure

randomization allocation under different sample sizes.

Covariate Adaptive Randomization Methods

Several methods are addressed by researchers in biostatistics in adaptive covariate randomization. All those methods aim to reduce imbalance between treatments[6,7]. In this section, three of those methods would be mention as well as the new method (CPM) which suggested by the researcher.

Zelen's method:

This method has been proposed by Zelen to reduce imbalance between treatments across the number of patients[8].

Atkinson Optimal Method:

Atkinson has mentioned what be called an optimal method in adaptive randomization. The implementation of this method achieves more balance of numbers of patients and their characteristics with treatment[9].

The method uses a general linear regression model to achieve the desired balance.

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[10].

Critical percentage method:

In the 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.

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 the 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 $\leq 60\%$ 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.

$Step\ 2$:

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.

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

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

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.

Letting:

$n_{ki_j1} \equiv$ The number of patients in level j of covariate i who are assigned to treatment T_1 after k assignments.

$n_{ki_j2} \equiv$ The number of patients in level j of covariate i who are assigned to treatment T_2 after k assignments.

Compute:

$$p_{ij1} = \frac{n_{ki_j1}}{n_{ki_j1} + n_{ki_j2}} \quad (1)$$

$$p_{ij2} = \frac{n_{ki_j2}}{n_{ki_j1} + n_{ki_j2}} \quad (2)$$

Compute the r_i values defined as:

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

$$r_2 = \begin{cases} 1 & if n_{ki_j1} < n_{ki_j2} \\ 0 & otherwise \end{cases}$$

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

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

$$r_5 = \begin{cases} 1 & if n_{ki_j1} = n_{ki_j2} \\ 0 & otherwise \end{cases}$$

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

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

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

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

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

THE SIMULATION WORK

A simulation experiment was conducted to examine the performance of CPM relative to that ofRM. The simulation assumed that, there are two treatments$(T_1 \& T_2)$and three covariate variables, the first one has two levels, the second has three levels and the third has two levels. The simulation was performed by $STATA_{12}$ software, and at three sample sizes, 10, 100 and 1000. The simulation was repeated 1000 times for each sample size.

Patients are assigned to $(T_1 \& T_2)$with critical percentage 50% for CPM, and randomly for RM. For each Method, imbalance between treatments is computed as absolute difference in number of patients between two treatments, in each case.

RESULTS

From Table (1) and Figures (1, 2 and(3) it is clear that:

CPM has minimum imbalance compared with RM when sample size is 10.

CPM has minimum imbalance compared with RM and the gap between the two figures is huge when sample size is 100.

CPM has minimum imbalance compared with RM and the gap between the two figures is very huge when sample size is 1000.

Table 1: the percentage of imbalance for CPM and RM.

Imbalance	Sample Size 10		Sample Size 100		Sample Size 1000	
	CPM	RM	CPM	RM	CPM	RM
0	72.8	23.2	62.9	7.2	61.2	2.2
2	27.2	43.5	35.7	16.2	36.7	6.1
4	0.0	23.5	1.4	16.7	2.1	4.4
6	0.0	8.8	0.0	12.7	61.2	5.8
8	0.0	0.8	0.0	10.2	0	5.1
10	0.0	0.2	0.0	10.7	0	4.0
12	0.0	0.0	0.0	7.5	0	5.2
14	0.0	0.0	0.0	6.6	0	4.1
16	0.0	0.0	0.0	3.6	0	4.6
18	0.0	0.0	0.0	2.8	0	4.1
20	0.0	0.0	0.0	1.3	0	3.3
22	0.0	0.0	0.0	1.8	0	4.5
24	0.0	0.0	0.0	2.7	0	4.0
26 to 60	0.0	0.0	0.0	0.0	0	42.6

who are assigned to $(T_1 \& T_2)$). The other columns display the percent of imbalance for each method.

In Table (1), the first column display the amount of imbalance (the absolute difference between number of patients

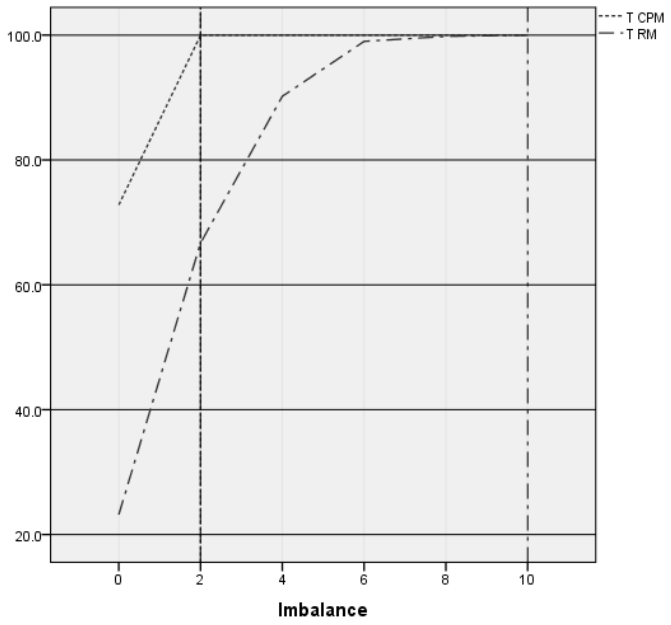

Figure 1 : cumulative percent of imbalance when sample size is 10

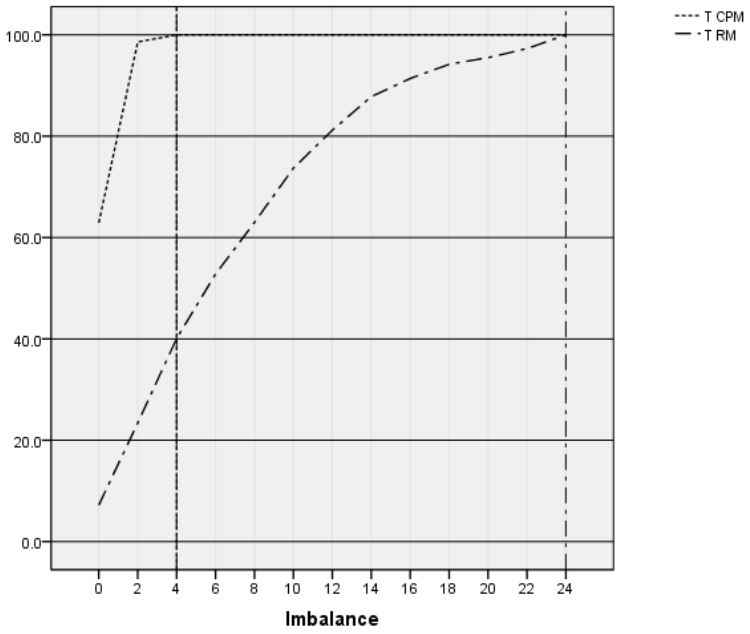

Figure 2: Cumulative percent of imbalance when sample size is 100

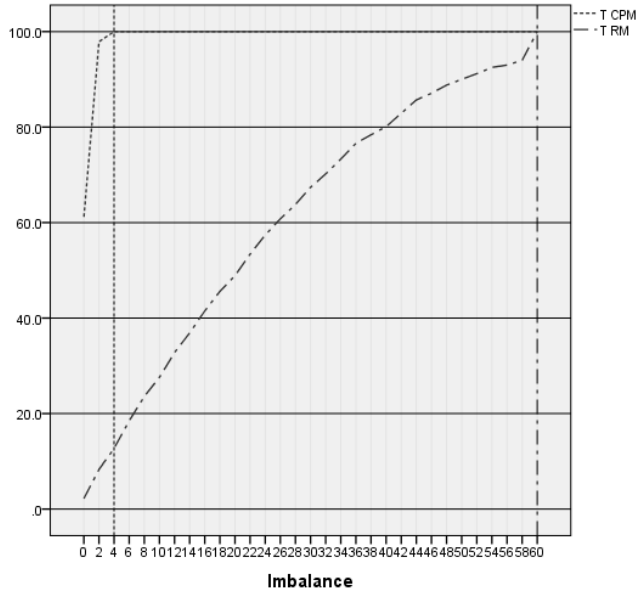

Figure 3: Cumulative percent of imbalance when sample size is 1000

CONCLUSION

From above results, we can conclude that, CPM has minimum imbalance compared with RM at all sample sizes. The difference in imbalance between CPM and RMexpandsby sample size increase.

RECOMMENDATION

Researchers in clinical trials are recommended to use CPM method instead of RM methods in when balance between treatments is important. And biostatisticians are recommended to carry out more researches to investigate the performance of CPM.

REFERENCES

1. Chow, S.C., Chang, M., and Pong, A. (2005). Statistical consideration of adaptive methods in clinical development. *Journal of Biopharmaceutical Statistics*,**15**: 575–591.

2. Pocock, S. J. and Simon, R. (1975). Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trials. *Biometrics*,**31**: 103–115.

3. Proschan, M. A. (2005). Two-stage sample size re-estimation based on a nuisance parameter: A review. *Journal of Biopharmaceutical Statistics*, **15**: 539–574.

4. Williams, G., Pazdur, R., and Temple, R. (2004). Assessing tumor-related signs and symptoms to support cancer drug approval. *Journal of BiopharmaceuticalStatistics*,**14**: 5–21.

5. Gallo, P., Chuang-Stein, C., Dragalin, V., Gaydos, B., Krams, M., and Pinheiro, J. (2006). Adaptive design in clinical drug development - An executive summary of the PhRMA Working Group (with discussions). *Journal of Biopharmaceutical Statistics*, **16**, 275–283.

6. Coad, D. S. and Rosenberger, W. F. (1999). A comparison of the randomized play-the-winner and the triangular test for clinical trials with binary responses. *Statistics in Medicine*,**18**: 761–769.

7. Shih, W. J. (2001). Sample size re-estimation - A journey for a decade. *Statistics in Medicine*, **20**: 515–518.

8. Zelen, M. (1974). The randomization and stratification of patients to clinical trials. *Journal of Chronic Diseases*, 28: 365–375.

9. Atkinson, A. C. (1982). Optimum biased coin designs for sequential clinical trials with prognostic factors. *Biometrika*, **69**: 61–67.

10. Birkett, N. J. (1985). Adaptive allocation in randomized controlled trials. *Controlled Clinical Trials*, **6**:146–155.