CHAPTER THREE

CRITICAL PERCENTAGE METHOD

3.1 Introduction:

In this chapter a new method in covariate adaptive randomization is introduced. The method which will be called critical percentage method (CPM) will be then compared with the MIN method referred to earlier.

3.2 Description of 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.

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 $\leq 60\%$ 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:

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 $k = 1\ ,\ 2, 3\ , \ldots, n - 1$ 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:

$n_{k i_j 1} \equiv$ The number of patients in level j of covariate i who are assigned to treatment T_1 after k assignments.

$n_{k i_j 2} \equiv$ The number of patients in level j of covariate i who are assigned to treatment T_2 after k assignments.

Compute:

$$p_{ij\,1} = \frac{n_{k i_j 1}}{n_{k i_j 1} + n_{k i_j 2}} \qquad (3.1)$$

$$p_{ij\,2} = \frac{n_{k i_j 2}}{n_{k i_j 1} + n_{k i_j 2}} \qquad (3.2)$$

c. Compute the r_i values defined as:

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

$$r_2 = \begin{cases} 1 & if \quad n_{k i_j 1} < n_{k i_j 2} \\ 0 & otherwise \end{cases}$$

$$r_3 = \begin{cases} 1 & if \quad p_{ij\,2} > \lambda_{ij} \;, \qquad \exists_{ij} \\ 0 & otherwise \end{cases}$$

$$r_4 = \begin{cases} 1 & if \quad p_{ij\,2} \ge \lambda_{ij} \;, \qquad \forall_{ij} \\ 0 & otherwise \end{cases}$$

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

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

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

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

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

$$p_{k+1,1} = \begin{cases} 1 \; if \; r_1 = 1 \; or \; (r_2 = 1 \; and \; (r_3 = 1 \; or \; r_4 = 1)) \\ \frac{1}{2} \; if \; r_5 = 1 \; and \; (r_6 = 1 \; or \; (r_7 = 1 \; and \; r_8 = 1)) \\ 0 \quad otherwise \end{cases} \quad (3.3)$$

3.3 Comparison of CPM, MIN and RM Methods:

Comparison of the CPM, MIN and RM methods reveals the following points.

1. Both of CPM and MIN work to reduce the imbalance in the number of patients between treatments in total assigning.
2. CPM work to reduce the imbalance in number of patients between treatments in each single layer.

3. CPM is more flexible, whence allows to increase or decrease λ_{ij} values according to the importance of covariate variable in the trial.
4. A new patient would be assigned to each treatment temporarily before the final assigning in MIN, whereas would be assigned just one time in CPM.
5. The first patient in the trial would be assigned to treatments as random with equal probabilities in both of CPM and MIN.
6. RM has the most imbalances compared with CPM and MIN in both single strata and total assigning.