# CHAPTER TWO

# LITERATURE REVIEW

## 2.1 Introduction:

Several designs are usually available for use in a clinical trial. So, appropriate design selection is important and necessary to conduct any experiment.

An Adaptive Design (AD) is an adaptive randomized design, which has been used by biostatistician in clinical trials instead of random design for many decades. Since its inception, it captured the attention of researchers, and became the focus of their interest.

The first researches about AD were in the seventies of the last century which discussed adaptive randomization. Many approaches were suggested to make adaptations on randomization methods, at that time. Other types of adaptations, such as, adaptive sample size, hypotheses, dose escalation and treatment switching were addressed after that.

“Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial” (Pocock, Simon 1975) is one of

the famous papers that discussed AD. The paper, addressed a new method to reduce imbalance between treatments. The authors has pointed out disadvantages of previous randomization methods in clinical trials such as “purely random assignment”, “random permuted blocks” and “permuted blocks within stratum”

According to the paper, purely random assignment completely neglects the effects of covariate variables. And this could lead to maximal imbalance between treatments. A permuted block is one method which leads to equal numbers of patients in treatments. But in this design, for each patient’s blocks are formed as they enter the trial and random permutation of treatments is determined. This makes the same treatment numbers offered after each block of patients. But this procedure makes the last treatment that has been assigned in a block pre-determined.

This can be a considerable source of bias, especially where the block size is small. “Permuted within stratum” is a design whereat the permutation used in all the strata are distributed in a specified manner derived from consideration of fraction factorial designs. This procedure is more effective as compared with permuted blocks if the number of strata is somewhat less than the number of patients, and

the numbers of patients are very evenly distributed across strata. But the last condition is rarely met in actual clinical trials.

Pocok's design was suggested to avoid disadvantages of the three designs which were mentioned above. The method depended on dividing the prognostic factors into strata. This procedure leads to achieve minimum imbalance between each strata, and the total patients in treatments at the same time.

A simulated data was used to make a comparative between Pocock's method and traditional methods. The major advantage of the new method is that it enables treatments balance across several prognostic factors more than the other methods. That approach is especially useful in a small trial (when the number of patients less than 100) according to simulation study.

The paper by Zelen(1974) "The randomization and stratification of patients to clinical trial" is one of the most important designs in adaptive randomization method.

Wei(1978) 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. "Atkinson Optimal Model" is a

model which considered a linear regression model to obtain the same above advantage. Atkinson(1982)

Berry(1985), Blackwell(1957), Brophy(1995), Chaloncr(1989), Chen(2000), Chang(2006), Faries(1994), Gallo and others (2006), Hardwick and Stout(2002) and Jennison(2005) had written different topics, under various conditions about adaptive design.

Aickin(2009) has compared adaptive design with random design to two regression model. The study depended on simulation data. The data was generated with various conditions, different numbers and types of covariates. The study conducted at different sample sizes also.

In each case, two regression models have been estimated. The first one was with adaptive allocation and another with random allocation. The study concluded that, in many cases, adaptive allocation is better than random allocation. In other instances no different between them. Also, there is no evidence of any bias in either marginal or joint regression model estimators using adaptive allocation.

## 2.2 Adaptive Design Definition:

As any other science, adaptive design has been defined with more than one definition. But the difference between all those definitions is not significant.

Gallo(2006) has defined adaptive design as a design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial. The goal of this procedure is to learn from the accumulating data and to apply what is learned as quickly as possible.

Adaptive design is a trial design that allows modifications to some aspects of the trial after its initiation without undermining the validity and integrity of the trial. This definition has addressed by Chang(2005).

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. Chow and others(2005)

Liu and Pledger (2002) has 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.

According to Chow and Chang (2007) 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.

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. FDA (2010)

By depending on all previous definitions, adaptive design could be defined as a flexible design allows to make some modifications or changes of a trial or statistical procedures on ongoing trial based on accumulating data from the trial, without undermining the validity and integrity of the trial. The modifications and changes ought to lead to get some benefits or avoid harm.

Majority of researchers, pointed that the modifications and changes must not be allowed generally. Have to be planned before the trial starting. But this condition sometimes might be constrained. But pre-planning to some manners which would happen is desirable.

Adaptations which could be occurred of a trial typically are caused by one of three reasons. The first one is ethic. Sometimes, research team may notice that particular treatment has side effect on determined group of people. In this case, adaptations are needed ethically. The second reason is cost. When research team kwon that the trial could be conducted with less cost than that determined, have not done it with higher cost. Here adaptations are desired to achieve benefit in cost. The last reason is legalization. If a researcher learns that some

aspects are illegal after a trial started, can make some adaptations to avoid illegal things.

## 2.3 Adaptive Design Types:

Based on adaptations which would employ, adaptive design is branched into many types. The main classifies of AD are adaptive randomization, adaptive treatment switching, adaptive dose escalation, drop the loser design, group sequential design, sample size re-estimation, adaptive biomarker, adaptive hypotheses, seamless phase $II/III$ trial and multiple adaptive designs. Chow and Chang (2007).

1. **Adaptive randomization:**

Adaptive randomization design allows making unequal probabilities in patient's allocations. This design aimed to get either minimum imbalance between treatments or to add more patients to treatment which has higher successful. This design is classified into two categories. First one is "covariate adaptive randomization". This focused on minimization of covariate variables imbalance between treatments. Many methods have been described to achieve this purpose. This design will be discussed in detailed in the next section.

The second type of adaptive randomization is “response adaptive randomization”. This method aims to compute the probability of success in each treatment, and allocate majority of patients to that treatment. Coad and Rosenberger (1999).

2. **Adaptive treatment switching:**

A comparison studies between two or more treatments such as control and test treatments are common in clinical trials. Often the goal of a trial is to assess the effect of a treatment on one disease. Patients are allocated to treatments randomly. But, if the researcher noticed that, one treatment has high positive or negative effect on particular group of patients, the researcher could switch a patient from treatment to another. When this switching is allowed, the design called “adaptive treatment switching”. More than one model to make this switching is suggested such as “latent event time” and “proportional hazard rate”. Sommer and Zeger(1991), Branson and Whitehead (2002), Kalbeisch and Prentice(1980)

3. **Adaptive dose escalation:**

In early phases in clinical trials, the main objective is to determine the optimum dose. In dose efficacy studies, the primary goal is indentify

the minimum effective dose. In dose toxicity studies, the primary goal is to determine the maximum tolerable dose.

The traditional methods to achieve these goals called “traditional escalation rule (TER) or “3+3”. “Continued reassessment method” and “Hybrid Frequents-Baysian Adaptive Design” are adaptive methods addressed to obtain the same purposes with less sources and fewer time. Bretz and Hothorn (2002),Crowley (2001)

4. **Drop the loser design:**

In many clinical trials, some treatment arms have been compared. Where a trial aimed to compare treatment arms on one disease, one or more arms could be dropped, if its effect is weak. Additional arm could be added at this stage too. The assessment of arms effect must be at pre-determined stages. In this instance the design called “drop the loser design”. A lot of models to make the dropping have been suggested. Chow(2008)

5. **Adaptive sample size re-estimation:**

Sample size is one of important manners in any trial. In random designs, sample sizes have to be computed before a trial started. Sample size based on many measures like population variability. In practice studies, the variance in study data may be different from that

in previous study which was used in sample size calculation. In cases like this, test power and type *I* error rate might not be accurate. In adaptive sample size re-estimation, a trial divided into some stages. Desired sample size has been calculated after each stage. “Sample size re-estimation without unblinding data”, “Cui-Hung-Wang’s method” and “Proschan-Hunsberger’s method” methods are widely used in this design. Gould(1992), Shih(2001), Proschan(2005)

**6. Group sequential design:**

Group sequential design considered one of more flexible designs. In this design a trial can be stopped prematurely for safety or efficacy issues. After the analyzing of interim data, additional modifications are allowed. The trial could be stopped at this stage or continue with new aspects. The modifications may be concluded patient population or treatments. The main challenge in this design is controlling the difference between “target patient population” and “actual patient population”. It is too difficult to control type *I* error rate also. “General approach for sequential design” and “early stopping boundaries” methods are useful to apply this design. Jennison and Turnbull (2005), Wang and Tsiatis (1987)

7. **Adaptive biomarker:**

   In adaptive biomarker, adaptations could be made on continues trial based on an outcome of various biomarkers associated with the disease under consideration. This design has been used for three reasons. First one is selection the right patient population. The determination of disease nature is the second one. The last reason is early detection of disease. Many models to achieve this aim have been suggested.

8. **Adaptive hypotheses:**

   It is common in clinical trials that, a data which collected from a trial be insufficient to test the main hypothesis in the trial. Adaptive hypotheses design allows making modifications or changes of a hypothesis. “Switching from a superiority hypothesis to non-inferiority hypothesis” is extremely used in this design. Hommel(2001), Williams and Temple (2004)

9. **Adaptive seamless phase $II/III$ trial:**

   In clinical trial there are five phases. In phase $II$, a researcher aimed to achieve two objectives. Selection the best dose of a new treatment, and determine the effect of this dose. In phase$III$, the objective is to compare a new treatment with a control or a placebo treatment.

Adaptive seamless phase $II/III$ trial makes a combination of separated phases (phase $II$ and phase $III$) to obtain the same objectives in one phase (phase $II/III$). In practical trials, this design achieves significant benefits. By this design the both phases are done in shorten time and less cost. Carefulness is desired in this design because it's expected effect on sample size and validity of the trial. Gallo and others (2006), Macal and others(2006)

**10. Multiple adaptive design:**

Any combination includes two or more of above adaptive designs called multiple adaptive designs. Combination of adaptive seamless phase$II/III$ and adaptive drop the loser or groups sequential are common in clinical trial.

## 2.4 Covariate Adaptive Randomization Methods:

Adaptive randomization is one of the most important and earliest braches of adaptive designs. It is classified into two categories: the response adaptive randomization and covariate adaptive randomization. This section will be focus on the second one.

Covariate adaptive randomization has been suggested to avoid an imbalance which may be carried out by pure randomization methods. Two benefits could be obtained by covariate adaptive randomization design. The first is the balancing of numbers of patients across treatments. The second one is balancing of patient's characteristics between treatments also.

Many methods have been addressed to achieve these purposes. In this section, previous covariate adaptive randomization methods will be presented. In chapter three a new method of covariate adaptive randomization will be introduced.

**1. Zelen's method:**

This method has been addressed by Zelen (1974) to reduce imbalance between treatments across the number of patients.

In the method, patients must come to a clinical trial sequentially. To assign a new patient to a treatment, do the following:

Compute $D_i(n)$ where:

$$D_i(n) = N_{i1}(n) - N_{i2}(n)$$

where: $N_{i1}(n)$ is the number of patients who have been assigned to treatment 1.

$N_{i2}(n)$ is the number of patients who have been assigned to treatment 2.

If $|D_i(n)| < c$ , then the new patient would be assigned to a treatments randomly.

If $|D_i(n)| \geq c$ , the patient would be assigned to the treatment which has a fewer patients. Where $c = 2, 3, 4$.

**2. Pocock-Simon's method:**

This method has been suggested by Pocock and Simon (1975). The use of this method leads to balance the number of patients between treatments. The method supposed that patients are entered to a clinical trial sequentially.

Assume there are $T$ treatments and $C$ covariates with covariate $i$ ($i = 1, \dots, c$) having $l_i$ levels. Let $n_{ijk}$ be the number of patients with level $j$ of covariate $i$ who have been assigned treatment $k$ at arbitrary point during the trial for:

$j = 1 \dots, l_i$ ; $i = 1, \dots, c$ ; $k = 1, \dots, T$.

Consider the next patient entering the trial, let $r_1, r_2, r_3, \dots, r_c$ be level of covariates $1, 2, 3, \dots, c$ respectively for this patient. The

choice of treatment for the new patient is determined in the following manner.

**The choice of variation function:**

Let $D(\{z_t\}_{t=1}^{T})$ measures the amount of variation (amount of imbalance) in any set of non-negative integers $\{z_t\}_{t=1}^{T}$. Four possible formulas for $D$ are considered:

a. The standard deviation or variance of $\{z_t\}$.

b. The range of $\{z_t\}$ this is a simple measure. If one is essentially interested in comparing pairs of treatment in analysis it may be preferable since $D$ would then be measuring the most imbalance in any pair.

c. An upper limit of acceptable treatment imbalance could be defined for each level of each factor. This limit could depend on the factor, but consider the case where it is a constant $U$. Then,

$$D = \begin{cases} 0 & if\ range\ of\ \{z_t\} \leq U, \\ 1 & if\ range\ of\ \{z_t\} > U. \end{cases}$$

d. A sign rule can be used in the case of two treatments. This need to be defined in terms of each actual $d_{ik}$ rather than defining a general function $D$. Thus,

$$d_{i1} = \begin{cases} 1 & if\ n_{ij1} > n_{ij2} \\ 0 & otherwise \end{cases}$$

$$d_{i2} = \begin{cases} 1 & if\ n_{ij2} > n_{ij1} \\ 0 & otherwise \end{cases}$$

**The choice of total imbalance function:**

Let $G_k = G(d_{1k}, \dots, d_{Tk})$ where $G$ is some function from $R^T \to R$ which combines the $d_{ik}$.

The $G_k$ represents the total amount of imbalance in treatment numbers which would exist at all the factor levels of the new patient treatment $k$ were assigned to that patient. One reasonable way of combining $\{d_{ik}\}_{i=1}^{T}$ is to sum them. That is,

$G_k = G(d_{1k}, \dots, d_{Tk}) = \sum_{i=1}^{T} d_{ik}$

The situation may arise where some covariates are considered more important than others. Other can then make $G_k$ a weighted sum of $\{d_{ik}\}$ so that $G_k = G(d_{1k}, \dots, d_{Tk}) = \sum_{i=1}^{T} w_i d_{ik}$

where $\{w_i\}$ are constants, that sum to one.

**The choice of $\{\boldsymbol{p_k}\}$:**

To compute the probabilities of treatment to assign a new patients, treatments must be ranked according to their $G_k$ values (ascending ranking).

The assigning to treatment $k$ can be determined from the following set of probabilities:

$p_{(T=k)} = p_k$ where $p_1 \geq p_2 \geq \cdots \geq p_T$ and $\sum p_k = 1$.

The following formulas are suggested for $\mathrm{p_k}$:

a. Let $p_1 = p$ and $p_k = \frac{1-p}{N-1}$ for $k = 2,3,\ldots,T$ where $p$ is some constant which must be greater than $\frac{1}{T}$.

b. A formula which would take into account the complete ranking of $\{G_k\}$ is:

$$p_k = q - \frac{2(Nq-1)}{N(N+1)}\ k \quad \text{for} \quad k = 1,2,3,\ldots,T$$

where $q$ is some constant between $\frac{1}{T}$ and $\frac{2}{T-1}$.

c. A formula for $p_k$ which depends not only on the ranking of (1) to $(T)$, but also on the values of $\{G_k\}$:

$$p_k = \frac{1}{T-t}\left[1 - \frac{t(G_k)}{\sum G_k}\right], \qquad k = 1,\ldots,T$$

where $t$ is a constant, $0 < t < 1$.

**3. Atkinson Optimal Method:**

Atkinson (1982) 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.

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

Let $y_j = x_j^{'}\beta + e_j$ general linear regression;

where $e_j, (j = 1,2,3, \dots, n)$ are independent random errors with mean (0) and variance ($\sigma^2$). $x_j$ is a $(p+1) \times n$ fixed matrix and $\beta$ a $p+1$ vector of constants. The variance of the least square estimate of $\beta$ is:

$cov(\hat{\beta}) = \sigma^2 (x^{'}x)^{-1}$

Let $M(\varepsilon) = x^{'}x$ where, $\varepsilon$ is a measure over the design region $x = \{\binom{1}{0}, \binom{0}{1}\}$.

The method aims to minimize the determinant of the generalized variance $M^{-1}(\varepsilon)$.

Let $d(x_i, \varepsilon) = x_i^{'}(x^{'}x)^{-1}x_i\ ,\ i = 1,2$

where $x_1 = (1,0)^{'}\ ;\ x_2 = (0,1)^{'}$.

Let $var(e_j \,|x_j = (1,0)^{'}) = \sigma_1^2$

And $var(e_j \,|x_j = (0,1)^{'}) = \sigma_2^2$

In this case:

$$var(\hat{\beta}) = (x'x)^{-1}\, x' \sum_{y} x(x'x)^{-1} = \begin{pmatrix} \frac{\sigma_1^2}{n_{l,1}} & 0 \\ 0 & \frac{\sigma_2^2}{n_{l,2}} \end{pmatrix}$$

Following this procedure, the probability of assigning the $(l+1)st$ patients to treatment 1 is:

$$p_{l+1,1} = \frac{d(x_1, \varepsilon)}{d(x_1, \varepsilon) + d(x_2, \varepsilon)} = \frac{\frac{\sigma_1^2}{n_{l,1}}}{\frac{\sigma_1^2}{n_{l,1}} + \frac{\sigma_2^2}{n_{l,2}}}$$

In practical cases, where the variances are unknown, we substitute estimator for the unknown variances. Let $\hat{\sigma}_{l,j}^2$ be an estimate of $\sigma_i^2$ under the $i-th$ treatment after $l$ responses have been observed. The probability of assigning the $(l+1)st$ patient to treatment is:

$$p_{l+1,1} = \frac{\frac{\hat{\sigma}_{l,1}^2}{n_{l,1}}}{\frac{\hat{\sigma}_{l,1}^2}{n_{l,1}} + \frac{\hat{\sigma}_{l,2}^2}{n_{l,2}}}$$

**4. 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. The method has been addressed by Birkett (1985).

Suppose 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:

$d_i = n_{ir_j 1} - n_{ir_j 2}$

where, $n_{ir_j 1}$ be the number of patients with covariate $i$ in level $j$ who have been assigned to treatment 1.

$n_{ir_j 2}$ be the number of patients with covariate $i$ in level $j$ have been assigned to treatment 2.

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

$Step\ 3$:

Add a new patient to treatment $A$ or $B$ which one leads to minimum imbalance $(G)$.

5. **Marginal Urn Method:**

The marginal urn design suggested by Wei (1978) is one of the most important methods in adaptive randomization.

This method leads to more balance between treatments across the number of patients and their characteristics too. A new patient will be assigned in this method as follows:

Let an urn contain $\alpha$ white balls and $\alpha$ red balls. Each color meant specific treatment. When a new patient arrives, a ball is drawn and replaced. If the ball is white, the new patient would be assigned to treatment $A$; if the ball is red then the new patient would be assigned to treatment $B$. In addition, additional $\beta$ balls of a color opposite to that chosen ball of the ball which be chosen are added to the urn. Where $\alpha, \beta \geq 0$.

This drawing procedure would be repeated for each assignment. Either treatment $A$ or $B$ will be chosen with probability $\frac{1}{2}$ for the first assignment.

Let $n_A$ and $n_B$ be the number of prior assignment to $A$ and $B$ after $n$ patients. Thus, the $(n+1)st$ patient will be assigned to $A$ with probability:

$$p_{n+1,A} = \frac{n_b}{n}$$