CHAPTER ONE

INTRODUCTION

1.1 Introduction:

In clinical research, the primary goal of the experiment is usually to assess the effectiveness and safety of the treatment whose impact is to be tested compared with a control treatment. To ensure the success of a clinical experiment, an appropriate design should be used. There must be a detailed plan of how to perform a clinical experiment, how data should be collected and analyzed. Data collection is considered a basic and essential stage in the experiment. If data were collected incorrectly, that makes the results of the analysis unreliable and may be biased or misleading.

Adaptive randomization is an allocation that uses all previous assignments in the trial to influence the allocation of the current experimental unit. 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 covariates to make units allocations, and it is a flexible design.

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 research, 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 and other covariate adaptive allocation methods under varying conditions.

1.2 Research Problem:

Several problems may emerge when pure randomization is used in clinical trials. Examples are: all or most of males in the trial be assigned to one treatment and females to the other one, or the youngest people be assigned to one treatment and the eldest to the other treatment.

The earliest methods in adaptive randomization, attempted solving this problem in each single layer in the trial, but ignored the total assigning in the trial. Imbalance minimization method (MIN)

addressed solution to the imbalance in total assigning, without catering for imbalance inside layers.

So, the problem remains of how to reduce both types of imbalance at the same time. This is the motivation of this research. An attempt will be made to reduce the imbalance in both single layers and total assigning at the same time.

1.3 Research Significance:

The significance of this research comes from two sides, statistical and clinical. In the statistical side, the research introduces a new statistical method in covariate adaptive randomization topic, and this is considered an original knowledge. In the clinical side, the research will provide researchers in clinical trials by a method that is expected to achieve maximum balance (minimum imbalance) between treatments in term of number of patients and their characteristics.

1.4 Research Objectives:

This research aims to introduce a new method in covariate adaptive randomization topic. The objective of the new method is to decrease the imbalance between treatments in term of patient's number and

their characteristics in clinical trial which is usually produced by pure randomization and other covariate adaptive randomization methods.

1.5 Research Hypotheses:

The following hypotheses will be tested:

1. Imbalance mean of single layers in CPM is less than RM when sample size is less or more than layers number, at significance level $\propto = 0.05$.
2. Imbalance mean of total assigning in CPM is less than RM when sample size is less or more than layers number, at significance level $\propto = 0.05$.
3. Imbalance mean of single layers in CPM is less than MIN when sample size is less or more than layers number, at significance level $\propto = 0.05$.
4. Imbalance mean of total assigning in CPM is not more than MIN when sample size is less or more than layers number, at significance level $\propto = 0.05$.

1.6 Research Methodology:

The research adopts both analytical and descriptive approaches. Simulation is also used in certain parts of the research. The statistical package $STATA_{12}$ was used in the execution of the simulation. And $SPSS_{20}$ is used to analyze data and create figures also.

1.7 Research Plan:

This thesis contains eight chapters. Chapter one is an introduction to the research. In the second chapter, literature review in adaptive design topic is covered. Chapter three introduces a new method of adaptive covariate randomization and an evaluation of it is carried out through a simulation experiment. The data which is generated by the simulation is summarized and discussed in chapters five, six and seven. Finally, chapter eight is devoted to the results and recommendations.

1.8 Research Terminology:

Below are brief definitions to the main terms used in the study.

1. Clinical trial: is a type of research study that assesses medical questions in people. These studies often test new methods of screening, prevention, diagnosis, or treatment of a disease.
2. Covariate variable: is a variable that has effect on the trial, but not included in the study.
3. Imbalance: is the absolute difference between numbers of patients who are assigned to two treatments.
4. Adaptive design: is a flexible design that allows making some modifications or changes of a trial or statistical procedures on ongoing trial based on accumulating data from the trial.
5. Adaptive randomization: is a restricted random allocation of experimental units to treatments.
6. Covariate adaptive randomization: is the usage of covariate variable data for all previous patients to assign a new patient to treatments.
7. MIN: imbalance minimization method (important method in adaptive randomization designs).

8. CPM: critical percentage method (a new method in adaptive randomization designs)
9. RM: pure randomization method.