RANDOMIZATION IN A TWO-ARMED CLINICAL TRIAL: AN OVERVIEW OF
DIFFERENT RANDOMIZATION TECHNIQUES

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ABSTRACT

Randomization is the key element of any sensible clinical trial. It is the only way we can be sure that the patients have been allocated into the treatment groups without bias and that the treatment groups are almost similar before the start of the trial. The randomization schemes used to allocate patients into the treatment groups play a role in achieving this goal. This study uses SAS simulations to do categorical data analysis and comparison of differences between two main randomization schemes namely unrestricted and restricted randomization in dental studies where there are small samples, i.e. simple randomization and the minimization method respectively.

Results show that minimization produces almost equally sized treatment groups, but simple randomization is weak in balancing prognostic factors. Nevertheless, simple randomization can also produce balanced groups even in small samples, by chance. Statistical power is also improved when minimization is used than in simple randomization, but bigger samples might be needed to boost the power.

Keywords: Blinding, Placebo, Power, Randomization, Treatment.
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Last but not least, I thank my dearest parents and family for loving me and having confidence in me and leading by example. I wouldn’t have finished without your support, I love you all.
DECLARATION

I hereby declare that all the contents of this research work are my original work. All references are truthfully acknowledged unless otherwise stated.

Signature……………………

Date……11 April 2011.
PREFACE

The following is the structure of this dissertation:

- Chapter 1 has the introduction, research problem, aims and objectives.
- Chapter 2 gives the literature review of randomization methods used in clinical trials, and an overview of some of the related articles to this study.
- Chapter 3 gives statistical methodology used in the study as well as methods for data analysis. A SAS Simulation is also done in this chapter.
- Chapter 4 focuses on results and data analysis and interpretation.
- Chapter 5 presents the conclusions, discussions, recommendations and areas of future research.
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CHAPTER ONE

INTRODUCTION

1.0 Randomization in Clinical Trials

In Phase III of a Randomized Clinical Trial (RCT), the efficacy of two different treatment interventions is compared. These two treatments can be either of a new treatment against a standard treatment, which is already on the market, or of a new treatment against a placebo which is done in a case where there is no effective standard treatment that already exists. The patients who receive the standard treatment or the placebo are referred to as the control group.

Two groups of patients are used to compare these two treatment effects, namely the treatment group and the control group. In the first case, the treatment group receives the new treatment whilst the control group receives the standard treatment and in the second case, the treatment group receives the new treatment whilst the control group receives the placebo. Patients are selected from heterogeneous populations, which means that the two treatment groups may have many differences in covariate factors i.e. baseline characteristics, such as gender, age, race, history of disease, environment, HIV awareness. These factors may influence the comparison between the treatment group and the control group. At the beginning of the study, the treatment groups should be fairly equal in their covariate factors, so that given the same treatment they
should produce the same results. Thus we can conclude that any difference in the results is due to treatment differences only.

1.1 What is randomization?
To try to make the treatment groups as similar as possible, by balancing out the covariate factors between them, patients are allocated at random to either of the treatment groups, so that they receive either of the treatments—a process called randomization. This as well helps guard against any use of judgment or systematic arrangements that can lead to bias. Randomization is therefore, defined as a technique for randomly allocating patients by chance rather than by choice, into the two treatment groups of a clinical trial and is mainly done to balance out conscious or unconscious prognostic factors. This achieves balance and reduces bias respectively.

1.2 Purpose of randomization

- Randomization eliminates the source of bias, since it is employed in the presence of equipoise. In other words it prevents the confounding effects which are external variables that are related to one or more of the variables defined in the study and affect the outcome of the study
- It allows the use of probability theory to express the likelihood of chance as a source for the difference between outcomes.
Moreover, it facilitates blinding of the treatment type, single or double. According to [35], trials with inadequate or unclear randomization tend to overestimate treatment effects up to 40% compared with those that used proper randomization.

- It provides a basis for standard methods for statistical analysis, like significance tests. Randomized allocation is easy to implement and it enables trial conclusions to be more believable than other forms of treatment allocation.

[5] stated that, if a difference occurs in outcomes between the two treatment groups at the end of a clinical trial, possible explanations for this difference would be:

- Difference in outcome is simply by chance; or
- The intervention exhibits a genuine effect;
- Due to factors apart from the intervention, there can be bias (or a systematic difference) between the two groups.

Randomization is done to prevent the third possibility.

[17] confirmed that the process of randomization tends to generate study groups comparable with respect to known and unknown risk factors, removes investigator bias in the allocation of participants, and guarantees that statistical tests will have valid significance levels. If randomization is done in a proper manner, it ensures strengthening of the internal and external validity. Internal validity is strengthened by minimizing bias, whereas external validity is ensured by providing a correct basis for generalization.
1.3 Problems with non-randomized trials

To appreciate the effects of randomization, we first look at what happens if no randomization has been applied. The following two examples were extracted from [32].

*Example 1:*

There is a report on a study of Anticoagulant therapy for myocardial infarction by Wright *et al* from [32]. There were 442 patients who had been admitted on the even days of the month and these were allocated to the control group, whilst 589 patients were admitted on odd days of the month and they were allocated to the treatment group. This produced an imbalance between the numbers of patients between the two groups. The groups also were not comparable, which therefore means the validity of results could be questioned.

Another problem with this allocation procedure was that, if a patient was admitted on an odd day of the month, he/she could easily predict that he/she will be allocated to the treatment group. That could result in some patients refusing to participate in the study, or having a biased attitude because they would have guessed that they were receiving the new treatment. This distorts the results of the study.

Therefore non-randomized trials suffer from selection bias because they will be depending on some judgmental or systematic assignment. This weakens the results of the study. It is also essential that the clinician is unaware of the treatment allocation so that he/she is unable to
predict what the next allocation will be. An independent person to the study, like a statistician should prepare the randomization list, do the randomization and documentation of randomization procedures.

Example 2:

Another report extracted from [32] from Smith ells et al was that of a trial of Vitamin supplementation for prevention of neural tube defects (NTD) that was given to high risk women who were planning further pregnancy. Patients were allowed to choose the treatment group that they wanted to be in. The control group which remained untreated comprised of those women who had refused to take the tablets, as well as the already pregnant women. Because there was no randomization, it was difficult to conclude whether the reduction in the number of NTD infants was due to the treatment itself or due to the bias in the selection of patients.

Therefore, from these two examples, it showed that in non-randomized trials, the treatment group and the control group differ in more than just the treatment they received. It becomes difficult to conclude that the improvement or reduction in the new treatment is genuinely due to the treatment effect alone.

To this date, most clinicians have used randomization to allocate participants in their clinical trials. Each patient will be having a non-zero, usually an equal, probability of receiving any of the treatments under study. In carrying out a clinical trial, therefore, the treatment groups are
made as homogeneous as possible before the treatment commences. The only difference is that they will be receiving different treatments.

Patients arrive sequentially in the trial over a prolonged period, which makes clinical trials differ from other experimental studies. Because of this, randomization is not easy to do in a clinical trial and balance is also not easy to ensure. Randomization is very compatible with the ethics in medicine.

1.4 Randomization schemes

Randomization is one of the important assumptions that are supposed to be satisfied to draw inferences about the population when studying a sample. It is the only means to guarantee that the participants who come into the trial are not assigned to the treatment arms in a biased way. Therefore, many methods of allocating patients into the treatment arms of a clinical trial have been suggested in the last century. These can be:

- Tossing a coin
- Random number table
- Computer generated tables
- Chit method
- Random number producing algorithms provided on internet.
There are also randomization schemes that have been developed and they will be discussed in detail in chapter 2. These include simple randomization, stratified randomization, block randomization and minimization.

1.5 Restricted randomization

Restricted randomization was introduced and is a method that has been developed to prevent unwanted patterns whilst maintaining the validity of randomization for subsequent analysis of variance. It was introduced by [38] and [39]. They developed restricted randomization in agriculture, to avoid the problem that nearly neighboring plots were receiving the same treatment. [39] referred to it as constrained randomization. Restriction ensures balance in numbers and prognostic factors between the two treatment groups in the trial as a whole, as well as when interim analysis is done before the end of the study. It is determined in advance that for every $n$ participants, $n/2$ of them will be allocated to the treatment group and the other $n/2$ will be allocated to the control group. Restriction also guards against imbalances due to time trends.

A randomization scheme can be restricted so as to avoid the problems associated with bad patterns. It also has to be unbiased and valid, so as to permit the usual analysis of variance to be done. A scheme is considered unbiased if the expectation of the simple estimator of every treatment difference is equal to the true value of the treatment difference, the expectation being taken over the randomization. If the treatments are equally replicated, a restricted randomization scheme is unbiased if and only if every patient in the trial has equal probability of being allocated to each of the arms in the trial.
Restricted randomization has been extended to clinical trials. Stratification and blocking are some of the examples of restricted randomization schemes. The use of restricted randomization can have a disadvantage of increasing the risk of technical error, as well as subversion. [9] referred to block randomization as restricted randomization, which helps increase the comparability of treatment groups, mainly when patient characteristics may modify in due course.

### 1.6 Reporting of randomization

Randomization is an important aspect of any good clinical trial, therefore it must be well specified in the protocol whether it is going to be used to assign the participants in the treatment group or not. A protocol is a formal document which documents the purpose, design and how the clinical trial is going to be conducted, eligibility criteria for participants, treatment regimes and the proposed data analysis methods. It has to be strictly followed (observed) for the trial to be successful.

The final report should also clearly specify how randomization was implemented in the trial. For example, in their report, [28] reported in their Figure1, that ‘the 73 subjects accepted for participation in the study were sorted into pairs matched for fasting serum insulin, BMI, age, and sex. The resulting matched groups were randomly assigned to either the low-fat, high-protein (LF-HP) diet or the high-fat, standard-protein (HF-SP) diet’. They went on to report that “no
significant differences existed in subject characteristics between treatment groups at baseline” in their results.

According to [30], only 16% of the randomized clinical trials that were done clearly reported the use of randomization procedures according to their protocols. This shows that most researchers are still reluctant to report randomization. It is very crucial to understand what randomization is, why it is done, as well as the randomization techniques and which ones are perfect for particular studies.

1.7 Research Problem

Differentiation between randomization methods should be done so as to decide the most optimal randomization scheme for a particular clinical trial. This is an intimidating job for some researchers. Limited work has been done on randomization methods used in prosthetic treatment of jaws where all molars are lost so as to make it easy for researchers to choose the randomization methods which go well with their studies. Shortened Dental Arch trials have been done, and fewer participants can be found to be eligible in these studies. Randomization still needs to be done even if the sample size is small with categorical responses, such that reasonable results are obtained. This mini-dissertation therefore will focus on small sampled trials.
1.8 Aim and Objectives

This mini dissertation focuses on the different schemes of randomization. The main objective of this study is to compare restricted and non-restricted techniques of randomization. This will compare Simple randomization for non-restricted methods to minimization method, as restricted methods. This will be enhanced by:

- Data simulation in SAS, so as to

1) Compare the advantages and disadvantages of simple randomization and minimization.
2) Calculate the variance of the estimated difference between two treatment means for the each randomization scheme.
3) Compare the means between two treatment groups for the different randomization schemes.
4) Analyze the statistical differences between Simple, and minimization method, i.e. the type I error.
5) Perform the logistic regression model and power calculation using the logistic regression model.
6) Determine which of the techniques produces equal distribution of prognostic factors
7) Determine which of the techniques produces equal distribution in numbers of patients between the two treatment arms.
CHAPTER TWO

LITERATURE REVIEW

2.0 Introduction

Randomization has been proved to be the best technique to reduce bias and to ensure balance between treatment groups in clinical trials. Some clinicians agree that it could be the most significant advance in scientific medicine in the 20th century, according to [36]. [21] referred to randomization as a critical component of a clinical trial which strengthens results. In many areas of medical research, there has been an increased demand for randomly controlled trials over the past years and the need to randomize has now been widely accepted by many experimental scientists in almost every other field of research.

“An experimenter who does not use randomization with variable material is widely (not necessarily correctly) regarded as incompetent”, according to [22]. In statistical literature, many randomization schemes have been suggested and recommended to balance out the treatments within strata and/or numbers in treatment groups. To mention the most common ones, Simple randomization, Block randomization and Stratified randomization are some of the methods that have been dealt with in the literature. This chapter will review literature on randomization in clinical trials.
2.1 Background

Randomization has been used in many clinical trials for over 50 years now. [15] introduced the concept of randomization at Rothamstead Agricultural Station in 1926 to safeguard against the effect of mysterious heterogeneity. By randomization, treatments were allocated to the plots of land; therefore every plot had an equal chance of being treated with all the treatments that were being studied.

[38], in 1948, found quality not needed of ordinary randomization, which is the non-zero probability of getting layouts in which the pattern of treatments is unduly like the spatial pattern of the plots. That was when he came up with the idea of restricted randomization as a method to avoid unwanted patterns but at the same time the validity of randomization is retained. [39] also suggested restricted randomization though he termed it constrained randomization. [23] and [39], established solutions for t treatments in a single block of 2t plots using a different restricted randomization method, and a solution for 3 treatments in a block of 9 plots was found, following Youden’s suggestion.

In clinical trials, randomization was first used by [1] in 1931. They tested the gold compound (sanocrysin) value that was in a pulmonary TB treatment and they used randomization for the first time in a clinical study of 24 participants. They flipped a coin so that the participants would be allocated to either the treatment or the control group. In their study, the treatment group received the treatment, but the control group was given an injection which had distilled water. In
In this case distilled water acted as a placebo, though the word placebo was first used by [10] in 1938 in a study of influenza virus vaccine.

2.2 Placebo

For most diseases, there does not exist an effective standard treatment which can be administered to the control group of the trial. For the sake of comparison, the control group should receive something, so that it can be interpreted whether any response improvement in the treated group is genuinely attributable to the new treatment or it will just be the psycho physiological (psychosomatic) effects of the treatment. Therefore the control group is given an inert substance which looks exactly as the new treatment in color, size, shape, taste and everything, except that it does not include the active substance for treatment. This inert substance is called the placebo. It is used to make participants’ psychosomatic perception to the trial be as similar as possible in both the control and the treatment groups.

2.3 Blinding

A trial must have adequate allocation concealment. This means that the researcher should not be able to predict the group which a patient will be randomized into; until the patient is unambiguously registered onto the study and also that the researcher should not be able to change a patient’s allocation once they are randomized.
Randomization too, is characterized by unpredictability. In the case where blinding is implemented, the participant will not even know which of the treatment under study they are receiving at all, until the end of the study. **Blinding** is another way of further reducing bias. [1] introduced blinding. The participants in the trial did not know whether they received Sanocrysin or distilled water. Blinding can be classified into single blinding and double blinding.

1) Single blinding is whereby it is only the participant who does not know which of the treatments they are receiving. This is done to control the Hawthorne effect, which is a situation when individuals tend to change their attitude/behavior because they will be knowing that they are targets of interest, irregardless of the true effect of the intervention they are receiving. For example if a patient knows that he/she is receiving a placebo, it can have a negative psychological effect on him/her. Injured soldiers in the World War II were treated with saline just because there was not enough morphine to give them. They experienced a significant pain relief because they thought they were on the proper treatment of morphine.

The same applies if patients know that they are receiving a new treatment, they may tend to like it, or to want to impress the doctor, hence yielding the wrong result on the trial. Therefore to eliminate such possibilities, it is better if the participants do not know to which treatment arm they belong.

2) Double blinding is when both the participant and the physician (the one who evaluates and/or administers the treatment to the participants) do not know which participant is receiving which treatment. If the physician knows which treatment a participant is receiving, there can be a situation where he will decide to increase or decrease a dose for a patient, or change some more things because he knows which treatment the patient is
on. The physician might unconsciously allocate a patient to the treatment group, with a more hopeful prognosis. That could make the new treatment seem more effective than it really is. This can affect the outcome of the clinical trial. To suppress that possibility, double blinding is incorporated.

Blinding may however not always be applicable. There are some treatments that cannot be blinded because of their nature. This is notable especially in cases where the patient has to participate actively for example in a chemotherapy surgery, a physical therapy, or on a dieting treatment. Therefore, before implementing blinding, it should be considered whether or not it is practical to do a blinded trial. Also, it has to be clear that blinding will not cause harm to anyone. It has to be ethical when implementing the blinding procedure.

One needs to assess just how serious the bias might be without blinding; otherwise it would not be of much importance to blind the study. Sometimes it will be better off with just single blinding rather than double blinding.

2.4 Methods of randomization

There are different schemes of randomization which have been developed which can be restricted randomization, or unrestricted randomization. Restricted randomization refers to any procedure that is done to control randomization to balance prognostic factors or size between the two treatment groups. Randomization schemes include simple randomization which is unrestricted, and stratified randomization, block randomization which are restricted.
Minimization is a covariate adaptive method but can also be classified under restricted randomization. Each method has its own advantages and disadvantages, and these have to be carefully considered before using the methods. It is wise to choose a method which produces results that are valid for the study and easy to interpret.

2.4.1 Simple randomization

Simple randomization is the randomization where there are no restrictions imposed on the nature of the allocation sequence except that there can be pre-specification of the overall sample size. It is based on a single sequence of random assignments where participants are randomized with a known probability. For equal allocation, each participant will have an equal probability (1/number of treatment groups) of being allocated to each of the treatment groups. In a two armed trial, each patient will be having a 0.5 probability of being selected into the treatment arms. Generally simple randomization is equivalent to tossing a coin, though coin tossing is not practiced in the real sense, especially when the sample size is large. Instead, random numbers are used from the statistical random number tables or computer generated random numbers. These numbers are random digits between 0 and 9 or random integers between 0 and 99.

Simple randomization has the advantage of complete unpredictability of the next treatment allocation. It is also not discoverable i.e. if anyone uses exactly the same method and same command; there is no guarantee of obtaining the same allocation. [25] pointed out that, if the sample is large (n >200), simple randomization produces well balanced treatment groups by
chance. Probability theory guarantees that the size of both treatment groups will not be completely different in the long run. Also simple randomization is easy to implement.

2.4.2 Replacement randomization
Simple randomization has a drawback that there can be dissimilarities in numbers of participants, which can arise between the two treatment groups. These imbalances may influence the statistical properties of the study including a reduction in the precision of the estimators for treatment group differences as well as a reduction in the power of a statistical test. Large imbalances may reduce credibility of the trial results. Replacement randomization can be done to try to produce almost equal sized groups. It should be specified in advance that, if the simple randomization list produces serious unsatisfactory imbalances, then a completely new simple randomization list can be generated to replace the first one. This can be done until satisfactorily balanced sized groups are produced.

2.4.3 Unequal randomization
There can be situations, though, where the number of patients in the two treatment groups is intentionally unbalanced, for specific reasons, for example to reduce costs. It can be a ratio of 2:1 (New treatment: Standard treatment). This is called unequal randomization. It has a disadvantage of reducing the statistical power. [11], mentioned that the significant reduction in power is more apparent for randomization ratios of 3:1 or more. [11] went on to give a number of situations like costs, learning curves and ethics where unequal assignment of group sizes might be
advantageous. An extensive list of clinical trials where unequal randomization was practiced was

[32], showed that unequal randomization reduces the power as follows:

Let $N_T$ and $N_C$ denote the number of patients assigned to the treatment and control group
respectively, with $N_T + N_C = N$ being fixed. Let $r = \frac{N_T}{N}$ denote the proportion of the new
treatment to the total number of patients. Suppose the response is normally distributed with
known variance $\sigma^2$ on both treatments, so that the difference between treatment means is

$$
\overline{X}_T - \overline{X}_C \text{ has a variance of } \frac{\sigma^2}{N_T} + \frac{\sigma^2}{N_C} = \sigma^2 \frac{1}{[N_r(1-r)]}.
$$

This changes relatively slowly as $r$ increases from $\frac{1}{2}$.

He furthermore considered that alternative hypothesis $H_1: |\mu_T - \mu_C| = \delta$ which can be detected
at significance level $2\alpha$ with power $1-\beta$ for the case $r = \frac{1}{2}$. He considered the extent to which
power is lost by choosing $r > \frac{1}{2}$. For any $r$, the power under the alternative hypothesis is given
by:

$$
\text{Power} = \Phi \left[ 2[\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)] \times \sqrt{r(1-r)} - \Phi^{-1}(1-\alpha) \right], \text{ where } \Phi \text{ is from tables.}
$$

Table provided in their Appendix A shows how this power varies for $\alpha = 0.5$, or 0.95 and $2\alpha =
0.01$ or 0.05. Same results can be anticipated for non-normal responses. Loss of power appears to
be substantial once $r = 0.75$ or greater, i.e. for randomization ratio of 3:1 or bigger.
Unequal Randomization together with the randomization ratio should also be clearly specified in the report if it was used.

2.4.4 Block randomization

Blocking also helps overcome the problem of imbalances in numbers between treatment groups. Blocks with equal numbers of A’s and B’s are used where the order of treatments within the block are randomly permuted (where for example, A = intervention and B = control.). Usually, four or six treatment assignments are randomly ordered as blocks, such that within each block, there will be equal number of patients to be allocated to each of the treatment arms. A sample size must be chosen which is divisible by the chosen block size and also the block size should be divisible by the number of treatment groups. The block size has to be big enough to prevent predictability of the treatment allocation but at the same time small enough to prevent imbalance.

Example 3: With two treatments A and B under study, 6 permuted blocks of four treatment allocation can be obtained, namely BABA, AABB, ABAB, ABBA, BBAA and BAAB. Each successive participant who enters the trial will be allocated to the next treatment in that block that will be in use. This means that there won’t be much difference in the numbers in each treatment, since number of participants that are allocated to each of the treatment arms within each block will never differ by more than two participants. In general number of participants will never differ by $P/2$ where $p$ is the length of the block.
[12], mentioned that simple randomization also has a disadvantage of chronological bias where one of the treatment could have more participants at the beginning of the study whilst another treatment could have more participants at the middle or end of the study. Blocking is known to help eliminate this kind of bias as it ensures that treatment groups are almost equally distributed in each block. It is considered as a guard against unknown time trends in the characteristics of incoming participants. Though blocking balances out treatment group numbers in the end of each block, it may lead to the allocation being unconcealed (reduced unpredictability). This is because if the physician discovers the block size, he/she can easily predict to which arm the next participant is going to be allocated. To try to eliminate this, three things can be done, namely

- Double blinding
- Using blocks of bigger sizes
- Varying the block size randomly and not using the same block size throughout the allocation process.

Block sizes and how they were generated should be clearly specified in the report, as well as whether the blocks were varied in size or not. However, the block sizes must not be specified in the protocol if the trial is supposed to be blinded. This helps that no-one can know or predict treatment allocation.

2.4.5 Stratified Randomization

Another drawback of simple randomization is that, it can produce unbalanced treatment groups in terms of prognostic factors, which can be inefficient when estimating the treatment effect. This however can be solved by stratifying. Stratified randomization is done so that comparison
of treatments can be done within relatively homogenous groups at baseline. Important prognostics factors which may influence the outcome are identified before the beginning of the study and participants must have baseline measurements taken prior to randomization. Stratified randomization is done to prevent imbalance of known prognostic factors between the treatment groups, such as age, gender, center (In the case of multi-centre clinical trials), etc. This is achieved by grouping participants with the same characteristics in the same stratum, and then performing separate block randomizations for each stratum (random permuted blocks) or simple randomization for each stratum. By so doing, we make sure that the sample is representative.

*Example 4:* A clinical trial on heart diseases for patients from 3 different clinics will have a number of covariates. It is well known that the patient’s age, gender and the environment they come from may affect the speed of recovery. Therefore, age and gender could be a confounding factor and affect the outcome of the clinical trial. Stratified randomization can balance the control and treatment groups for age or gender or clinic. Participants are to be stratified according to their age, gender, and centre where

- Age has 2 levels i.e. <18 years and ≥ 18 years,
- Gender has 2 levels, Male and Female,
- There are 3 Clinics A, Clinic B and Clinic C, from which the participants are getting treatment. This means that in total, there are 2 X 2 X 3 = 12 Strata which can be represented in table 1 as follows:
Participants are then allocated to each of these 12 strata according to their age, gender and the treatment centre. And then simple randomization or block randomization will be done in each of the 12 strata to allocate them between the two treatment groups. If a participant registered is less than 18 years of age, a female and is coming from clinic B, she will go to strata 5 and will be allocated to the treatment group or the control group as per list generated for strata 5. This happens for all participants who register for the study. Once allocation is over, those participants who had been allocated to treatment group say, from all the 12 strata will receive the new treatment and those who had been allocated to the control group from all the strata will receive the standard treatment or placebo. The statistical method used in the analysis stage should take into account that stratification had been used.

Stratification is a technique which partitions participants into mutually exclusive subsets defined by initial covariates which are thought to influence the outcome and it is done to reduce accidental bias. The number of participants in each stratum is not guaranteed to be balanced. If the prognostic factors are strong in smaller samples, stratification has shown to increase the
power by up to 12%. Stratification has a weakness that, if there are too many prognostic factors that are identified, it may result in chance imbalances between the treatment groups. It weakens in balance as the total number of strata is > (n/2). According to [19], the number of strata should be less than (total sample size) / (block size). In other words, stratification requires parsimony.

[9] pointed out that some of the strata will end up being empty or sparse if the strata are too many, relative to the target sample size. In some cases, each stratum could end up consisting of just one participant each, and this would yield a same result as simple randomization. Therefore the number of strata should be kept to a minimum for good effect.

Another weakness of stratified randomization lies in its need to identify all the participants in the study, so that they can be allocated to their strata. This becomes a problem since participants come into the study successively. There is hardly a case where they arrive in the study at the same time.

Stratifying has another disadvantage that the confounding factor used to stratify may not be important to the outcome of the study and some more factors may be identified later to be of more importance.

[24], stated that, “Stratification is a simple method of restricted randomization that is harmless always, useful frequently, and important rarely. It is harmless because it will not cause greater
imbalance in the distribution of stratification factors among treatment groups than would be expected by chance in a non-stratified scheme. It is normally helpful because it decreases both type I error and type II error, improves trial efficiency, as well as it facilitates both subgroup analysis and interim analyses”.

If stratification was used for randomization, it should be taken into account when analyzing the results. The particular logical procedure is simply to include the stratification factor as a covariate in the multivariate model that is chosen. Not accounting for stratification in the analysis may result in overestimation of the $P$-value for a difference between endpoint rates in treatment groups. The finding of a large $P$-value (>0.05) may cause an investigator to erroneously accept the null hypothesis (type II error).

2.4.6 Blocking within strata

Simple randomization may result in imbalances of numbers and important prognostic factors between the treatment groups. Blocking balances out the number but still does not balance the prognostic factors. Stratification balances the important prognostic factors but does not balance number, which is why it is used together with blocking within strata. Stratified randomization requires blocking within strata for it to be effective, so that it increases efficiency, facilitates subgroup and interim analysis, and may also protect against type I and type II errors where type II error is the increase in power. Apart from that, randomization has a disadvantage that patients might be reluctant to enter into a trial where chance mechanism is used to decide the treatment group they will be allocated to.
2.4.7 Minimization

This is a covariate adaptive random allocation method which balances the marginal distribution of each prognostic factor, balances several prognostic factors between the 2 treatment arms, as well as the number of participants throughout the trial. It is called minimization because the unevenness in the distribution of prognostic factors is minimized. Minimization is a non-random method of allocation, even though the first person is randomly allocated. It has been recommended by several researchers as a valid alternative randomization method for clinical trials. Each subsequent participant’s treatment allocation is determined so as to even out size and prognostic factors between the treatment arms, depending on the participants who were already allocated to the treatment groups.

Minimization method was proposed by [32] and then by [37]. [32] suggested the method of minimization using absolute differences among the groups. They also suggested the variance approach whereby variance among arms of the trial is calculated. Although the variance method performs similarly to the absolute difference method, both approaches have disadvantages of handling categorical covariates only.

[16], introduced a method of minimization for both continuous and categorical types of variables. His method made use of $P$-values to identify the difference among treatment groups. More imbalances among treatment groups are represented by a smaller $P$-value. The participant is temporarily allocated to both the treatment control groups, then the $P$-values for every covariate is calculated by means of a $t$ test and analysis of variance (ANOVA) for continuous
variables. Categorical variables use the $\chi^2$ test goodness-of-fit. The smallest $P$ value for every control or treatment group is determined. This will indicate more imbalances among treatment arms. To try to avoid more imbalances in groups, a participant is then assigned to the group with the larger minimum $P$-value.

[37] method suggests that the participant be allocated to treatment group, so as to balance out the numbers and prognostic factors between the 2 arms of the treatment.

*Example 5:* Example from page 84-85, table 5.7 of [31].

Table 2 shows a table of assignments by the four factors for 80 patients in an advanced breast cancer trial, (4 X number of patients)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Level</th>
<th>Number on each treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Performance Status</td>
<td>Ambulatory</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Non-ambulatory</td>
<td>10</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;50</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>≥ 50</td>
<td>22</td>
</tr>
<tr>
<td>Disease-free interval</td>
<td>&lt;2 years</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>≥ 2 years</td>
<td>9</td>
</tr>
<tr>
<td>Dominant metastatic lesion</td>
<td>Visceral</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Osseous</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>soft tissue</td>
<td>13</td>
</tr>
</tbody>
</table>

*Table 2: Table of assignments by the four factors for 80 patients*

Table 2 shows the allocation status at that moment, for advanced breast cancer trial after 80 patients have been entered. The next patient to be randomized is ambulatory, age <50, disease
fee interval ≥ 2 years, visceral metastasis. For the corresponding stratum, the sum of patient numbers is:

For A: $30+18+9+19=76$

For B: $31+17+8+21=77$.

[37] method suggests that the next patient will therefore be allocated to treatment A so that balance of the marginal totals of prognostic factors are balanced.

Minimization method has an advantage that it is easy to carry out even by hand. When compared to stratification, minimization has an advantage that it may put in a little additional power if stratification does not comprise all of the covariance, but given the same prognostic factors, minimization and stratification produce similar power levels. In small trials, minimization can also decrease the imbalance into the minimum level. It has a drawback that it is a bit complex procedure as compared to the simple randomization.

2.4.8 Biased coin randomization

A method which is related to urn models was suggested by [13]. It is done so as to balance treatment numbers. At each point in the trial, it is observed which treatment has the least patients so far, such that it is then assigned with probability $p > 0.5$ to the next participant. If two treatments have the equal numbers, then simple randomization is used for the next participant.
2.4.9 Urn randomization

In the family of adaptive biased-coin designs, the urn design is the most broadly studied member. It forces a trial of smaller size to be balanced but it tends to complete randomization as the sample size of the trial, $n$ increases. Therefore, urn randomization is not as vulnerable to experimental bias as the other restricted randomization procedures are. It may be difficult to assume that the participants constitute a random sample from a well-defined uniform population in a clinical trial. Here, a randomization model gives a better foundation for statistical inference.

Post stratified subgroup analyses can also be performed on the basis of the urn design permutational distribution. Urn randomization, therefore gives a foundation to analyze a subset of participants who will have experienced responses when other patients' responses are assumed missing at random.

Whichever randomization method that was used in the study, should be clearly stated in the final report. Also the sequence generating method should be well specified. Therefore it is very important to fully understand the methods of randomization and see which one is suitable for the particular study. [7], reported that, “Eligible patients were invited to participate study with a four month follow-up period and got some written consent. After baseline assessments, we randomly allocated those who consented to transfer to the transitional care facility or to remain in hospital and receive usual care. Each patient was assigned the same day as they had given consent. Allocations were computer generated, stratified by referring hospital, and randomized in blocks of 12. 2:1 (intervention: control) was the allocation ratio which was used to allow the facility to be entirely operational throughout winter.”
According to [5], the final report should also specify who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups as suggested in their consort statement. It is advisable that the randomization sequence be generated by the statistician or someone who is not directly involved in recruiting the participants into the trial.

2.5 Post-stratification

Some researchers argued that stratification is unnecessary labor since one can do simple randomization and then perform post adjustment procedure. Covariate imbalances can be adjusted in the analysis stage of the clinical trial by statistical techniques like ANCOVA and/or multivariate ANCOVA. [26] stated that, “It is better to avoid randomization, as far as possible, by blocking with respect to any factor thought to influence the results: randomization is only a last resort”.

On the other hand, some argue that ‘problem prevention is better than cure”. This is because ANCOVA doesn’t exactly adjust for the prognostic factors very well, since it assumes a specific model which may be wrong. Also the problem with ANCOVA is that the investigators may not be completely aware of all prognostic factors. [3], stated that randomization is needed to validate the usual model assumptions and the usual analysis of variance.

According to [21], there are some statistical techniques which are frequently used to adjust for covariate imbalance in the analysis stage of the clinical trial. These are analysis of covariance
(ANCOVA), multivariate analysis of covariance MANCOVA. They are referred to as post adjustment approach and their interpretation is usually difficult because covariate imbalances frequently lead to unexpected interaction effects, like unequal slopes among subgroups of covariates. ANCOVA has a serious assumption of homogeneity of regression slopes (i.e. the slopes of regression lines are the similar for every group of covariates). Unfortunately, there can be a problem of adjustment required for each covariate group which may differ since ANCOVA uses the average slope across the groups to adjust the outcome variable. Therefore, the only perfect way to balance the covariates among groups is to apply randomization in the design stage of a clinical trial (before the adjustment procedure) instead of after data collection. In such instances, random allocation is essential and it assures validity for statistical tests of significance that are used for comparison of treatments.

There has been a wide range on opinion on the use of randomization but according to [2], Roger Mead commented that randomization is used for validity and blocking is used for control.

2.6 Previous related research

The main aim behind this study is to look into the different randomization schemes that are used in randomized clinical trials (RCT’s). Some research has been done and below are some of those that are related to the present study:
2.6.0 A study on Comparison of Balanced and Random Allocation in Clinical Trials

[34], did a study on Comparison of Balanced and Random Allocation in Clinical Trials. This was done prior to the analysis of results of a randomized controlled clinical trial in which 200 children were balanced over five prognostic factors namely, gender (with two categories), season (with four categories), age (with two categories), hospital (with thirteen categories) and educational level of mother (with three categories).

In this study, they wanted to know the efficiency of a balanced allocation as compared to simple randomization in a clinical trial with two treatments. Balanced allocation referred to the minimization method by [32] where the subjects were balanced in their 5 prognostic factors. The effect on validity and precision of univariate and multivariate analysis, in simple randomized trials and in trials with balanced allocation was assessed. In addition, the effect of an unmeasured covariate which is either correlated or uncorrelated with another covariate was studied.

Four contrasting options for the design and analysis of randomized controlled trials presented themselves to see which of them is the best in terms of validity, precision, and width of the confidence interval depending on the distribution of the prognostic factors, number of patients, and the prognostic importance of the factors:

- Simple randomization with simple univariate analysis of the treatment effect.
- Simple randomization with multivariate modeling including the prognostic factors in the model.
• Balanced allocation with the prognostic factors as balancing factors and simple analysis of the treatment effect afterwards.
• Balanced allocation with multivariate modeling including the same prognostic factors in the model as used in the balancing procedure.

A simulation study with 1000 replications of each treatment allocation was done for both small sample (n = 20) and for relatively large sample (n = 100). Mean was calculated as a measure of validity. Standard deviation of the mean was calculated as a measure of precision, and mean was calculated as a measure of width of CI.

It was shown by simulations of 1000 replications that a mixture of multivariate analysis and balanced allocation leads to extra valid and precise treatment effects and to smaller confidence intervals, mainly in small trials (n=20) as compared to multivariate analysis and simple randomization.

2.6.1 A study to review and describe randomization techniques used in clinical trials, including simple, block, stratified, and covariate adaptive techniques.

[21] did a study the randomization techniques that can be used in athletics training researchers. By making use of these techniques, power and validity of findings will be increased for athletic medicine clinical trials. This will eventually improve the excellence of care provided.
2. 6.2. A study to review common randomization techniques often used in substance abuse research

[20], conducted a study to assess common randomization techniques that are frequently used in substance abuse research. They used an application from a National Institute on Drug Abuse (NIDA)-funded clinical trial in substance abuse to demonstrate several choices faced by investigators when designing a clinical trial.

The study was aimed at reviewing and elaborating on the properties linked with a number of randomization schemes which are commonly considered in designing a substance abuse clinical trials. Distinguishing features of these randomization schemes were presented so that substance abuse researcher will be guided selecting a suitable randomization scheme.

They classified randomization schemes into restricted and unrestricted. Furthermore, restricted randomization has two types, namely,

- Restrictions which imposes balance on covariate factors between treatment groups,
- Restrictions which impose balance on treatment allocations throughout the length of the trial so as to accomplish equal numbers of participants within each treatment allocation.

Familiar schemes used in the literature of substance abuse are: complete, simple, permuted block, urn and covariate adaptive randomization. These randomization schemes were Compared and contrasted in terms of deterministic and balancing properties. To investigate the balancing nature of randomization techniques for fairly sized clinical trials, Monte Carlo simulation was
used. For complete randomization, results revealed big treatment imbalance and for the urn or adaptive scheme, small treatment imbalance was revealed. The urn and adaptive randomization methods show lesser treatment imbalance as demonstrated by the small variability of treatment allocation imbalance. For all randomization schemes, with moderate to large sample size, imbalance of prognostic factors between the treatment arms was small but there was a small variation between stratified schemes, adaptive schemes, and unstratified schemes.

2.6.3. Statistical comparison of random allocation methods in cancer clinical trials

[18], did a study on the comparison of Simple randomization, stratified randomization and minimization method. Simulation was done based on a hypothetical population of 2158 rectal cancer patients from seven Japan randomized colorectal clinical trials.

Four main prognostic factors were considered, namely, Age, Sex, Histological depth of tumor invasion, and Lymph node metastasis. For stratified randomization, there were two types of stratification that was done one, (STR4), had four factors, Lymph node metastasis, Histological depth of tumor invasion, Sex and Age. The other type, (STR2), had the former two factors only. Stratification was also blocked with blocks of size four, to ensure balance in number between groups within strata.

Minimization was found best in balancing the number of patients between groups, followed by STR2, then STR4 and lastly simple randomization. Balancing in prognostic factors was high in minimization, followed by STR2, then STR4 and lastly simple randomization. They discussed that when four allocation factors exist, stratified randomization does not perform too well
On the performance of statistical tests, they found that simple unadjusted tests have conservative type I error while minimization is conducted. Conversely, adjusted tests for allocation factors have the high power up to 5-6%, because they can attain an almost normal significance level.

2.7 Conclusion

From the literature review, it has been shown that usually if the sample size is large, then simple randomization is expected to produce equal size among the treatment groups due to chance. For smaller sized samples, blocking averages out the numerical sizes of the two treatment groups. Stratification randomization by centre is suitable for a multicentre studies. When there are many prognostic factors, minimization is more appropriate to use than stratification. This chapter showed some literature based on the randomization schemes used in clinical trials.
CHAPTER THREE

RESEARCH METHODOLOGY

3.0 Introduction

This chapter presents and justifies the methods that were used in designing and implementing the study. Since this study is motivated by the study analyzed by [29], the two randomization schemes, namely simple randomization and minimization, will be compared in a number of criteria. Definitions of the required terminology will also be presented in this chapter, where chapter 4 will present the results of the comparisons. The logistic regression is also going to be discussed in this chapter since the responses are independent and categorical; therefore it is going to be used in data analysis.

3.1 Hypothesis

The null hypothesis of no difference in treatment effects is compared against the alternative hypothesis that the new treatment has an improved effect is the key hypothesis to be tested. This can be denoted by:

\[ H_0 : \beta_1 - \beta_2 = 0 \]

\[ H_1 : \beta_1 - \beta_2 \geq 0, \]
where $\beta_1$ is the effect due to the new treatment and $\beta_2$ is the effect due to standard treatment or placebo where the mean response is being measured for treatment effect.

### 3.2 Research design

The uniform distribution was used to simulate a sample of size 32 in SAS version 9.2, in line with the sample size used by [29] in an unblinded pilot study of the randomized shortened dental arch (RaSDA). In the actual study, randomly permuted blocks were used to allocate patients into two treatment groups, A, treatment with removable dental prostheses for molar replacement, and B, treatment limited to the replacement of all missing anterior and premolar teeth using fixed bridges. The primary outcome in their study was time to first tooth loss after prosthetic treatment, because of its big influence on oral health.

In this study, the simulated sample was randomized using simple randomization, with three main prognostic factors set to be age, following the actual study, ($\geq 50$ and $<50$ years old), gender (Male and Female) and smoking status (non-smoker, smoked only once, smokes once in a while and chain smoker). The primary outcome is a categorical response equal to the number of teeth lost after the treatment (0, 1, 2, 3, 4 and $\geq 5$ teeth).

The simulated sample was then randomized using the minimization method following Frane’s method [16] and these two were then compared by the following:

a) Type I error,
b) Power using the Logistic regression,
c) Difference between treatment means
d) Difference between variances between the two groups and
e) Range between the two randomization schemes.

In simulation, dummy variables were used to differentiate the treatment groups and the probability of allocation to the treatment groups was set from 0.1 to 1. The behaviors of odds ratio output and contrast statement were used to determine the differences between the treatment groups. This was enhanced by the procedure of PROC LOGISTICS.

3.3 Uniform Distribution

Since the subjects are independent, each subject in the sample has an equal chance of being randomized, thus the uniform distribution was chosen to generate the treatment groups for the samples in this study. For a continuous uniform distribution on the interval \([a, b]\), the probability density function of a uniform distribution is defined as:

\[
f(x) = \begin{cases} 
\frac{1}{b-a} & \text{for } a \leq x \leq b \\
0, & \text{elsewhere}
\end{cases}
\]

A range of \((0, \infty)\) was used in this study.

3.4 Sample size

[31], stated that in order to make inferences about its effectiveness, the new treatment for the population with a particular disease must be administered to an adequately big and representative sample of participants. The sample size must be sufficiently large to reveal a true difference between treatment groups. According to [14], the number of participants to be recruited should
be large enough to produce a sensibly precise estimation of response to every treatment involved. However, this study considers a sample of size 32 following the pilot study by [29].

3.5 Effect size
Effect size specifies the traditional difference between two treatments to be observed in the trial. Past literature, performing a pilot study or using clinical expectations are some ways that can be used to estimate the effect size of the treatments.

3.6 Type I error
The significance of a test is in its probability of making a Type I error. Generally in Clinical Trials, type I error is defined as the possibility of observing a difference in the outcome rates between two treatment arms when in fact the two treatments are equal. In statistics, it is denoted by \( \alpha \).

3.7 Type II error
Type II error is the possibility of failing to detect a difference that truly exists between two treatment groups. [27], stated that if sample size is small, then randomized trials are subject to type-II errors (beta errors). They went on to conclude that type II error rates can be reduced by performing power and sample-size calculation before conducting a trial where Type II error is denoted by \( \beta \). These can be summarized in tabular form in Table 3 as:
### Table 3: Tabulation of the definition of type I and II errors

<table>
<thead>
<tr>
<th></th>
<th>No difference exists</th>
<th>Difference exists</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_0$ True</td>
<td>OK</td>
<td>Type II error</td>
</tr>
<tr>
<td>$H_0$ Rejected</td>
<td>Type I error</td>
<td>OK</td>
</tr>
</tbody>
</table>

#### 3.8 Statistical power

Power of a statistical test is the probability that it will detect correctly a significant effect if it is present. It is a complement of the type II error and is denoted by $1-\beta$ where $\beta$ is the type II error. Tests which have a statistical power of greater than 0.8 are considered to be statistically powerful. [4] pointed out that as the sample size increases, power also increases. A test has to be adequately powered to identify a significant difference. Therefore a sample should be chosen that it neither over-powers the test, which is expensive nor under-powers the test, which does not identify a difference if it exists. In simulations, power is given by:

$$\text{Power} = \frac{\text{Number of times the Null Hypothesis is Rejected}}{\text{Total number of replications}}.$$

#### 3.9 Power calculation using the Logistic Regression

The logistic regression model is used to predict the probability of an event’s occurrence by fitting data to a logit function, logistic curve. PROC LOGISTIC was used to fit proportional odds model, because response variables are categorical and have got more than 2 levels which are ordinal. The logistic regression is appropriate for describing and testing hypotheses about relationships between a categorical response variable and one or more categorical or continuous predictor variables. The simple logistic model has the form:
\[ \log(it(Y)) = \ln\left(\frac{\pi}{1-\pi}\right) = \alpha + \beta x. \] \hspace{1cm} (1)

Antilog of (1) on both sides gives an equation to predict the probability of the occurrence of the outcome of interest as follows:

\[ \pi = \Pr(\text{outcome needed} | X = x, a\ specific\ value\ of\ X) = \frac{e^{\alpha + \beta x}}{1 + e^{\alpha + \beta x}}. \] \hspace{1cm} (2)

where \( \pi \) is the probability of the outcome of interest or event \( \alpha \) is the \( Y \) intercept and \( \beta \) is the regression coefficient. \( X \) can be continuous or categorical but \( Y \) is always categorical.

Considering \( n \) independent Bernoulli random variables \( Y_1, \ldots, Y_n \) having observed values \( y_0 = (y_{01}, \ldots, y_{0n})' \).

Each observation \( i = 1, \ldots, n \), \( x_i = (x_{i1}, \ldots, x_{ip}, x_{i,p+1}, \ldots, x_{i,p+q})' \) be a vector of \( p + q \) explanatory variables, and denote \( X = (x_1, \ldots, x_n)' \). \( \pi_i = \pi(x_i) = \Pr(Y_i = 1/ x_i) \) be the event probability for each \( i = 1, \ldots, n \) and denote \( \pi = (\pi_1, \ldots, \pi_n)' \). \( E(y_0) = \pi_0 \)

Then the logistic regression model is \( g(\mu) = g(\pi) = \logit(\pi) = X\beta \), or

\[ \logit(\pi_i) = \log\left(\frac{\pi_i}{1 - \pi_i}\right) = x_i' \beta, \] where \( \beta = (\beta_1, \ldots, \beta_{p+q})' \) is the unknown parameter vector.

The joint probability of the observed \( y_0 \) is a product of \( n \) Bernoulli functions:

\[ L(\beta) = \prod_{i=1}^{n} \pi_i^{y_{0i}} (1 - \pi_i)^{1-y_{0i}} \]
Because \( \pi_i = \frac{e^{x_i \beta}}{1 + e^{x_i \beta}} \) we obtain
\[
L(\beta) = \frac{\exp(y'_0 X \beta)}{\prod_{i=1}^n [1 + \exp(x'_i \beta)]}
\]

A large positive regression coefficient means that the risk factor strongly influences the probability of that outcome; while a near zero regression coefficient means that the risk factor has little influence on the probability of that outcome. The goal of the logistic regression is to correctly predict the category of outcome using the most parsimonious model. There are many distinct available options which can be used during model selection.

Odds ratios were also used and it can be defined as follows:

Given that a response variable is \( Y \), the odds that a response is in the \( j \)th level of \( Y \) rather than the \( k \)th level, \( j \neq k \), within the \( i \)th level of the predictor \( X \) is

\[
\Omega_i = \frac{(\pi_{j/i})}{(\pi_{k/i})} = \frac{(\pi_{j})}{(\pi_{k})} , j \neq k, \text{ different levels of response.}
\]

- \( \Omega_i = 1 \), means that the \( j \)th and the \( k \)th responses are likely to occur equally
- \( \Omega_i < 1 \), means that the \( j \)th response is less likely to occur than the \( k \)th response.
- \( \Omega_i = 1 \), means that the \( j \)th response is more likely to occur than the \( k \)th response

Interpretations are based on the same level of predictor:

- \( \Omega_i = \frac{(\pi_{j/1})}{(\pi_{k/1})} \), implies the odds of \( j \) vs \( k \) at 1st level of \( X \)
- \( \Omega_i = \frac{(\pi_{j/2})}{(\pi_{k/2})} \), implies the odds of \( j \) vs \( k \) at 2nd level of \( X \)
The Odds Ratio: $\theta = \Omega_1 / \Omega_2$, where $\theta \in [0, \infty)$, measures the likelihood of a predictor Y between X levels.

- $0 < \theta < 1$, implies that the particular level of Y is less likely in the 1st level of X compared to the 2nd level of X.
- $\theta = 1$, implies equal likelihood of 1st and 2nd level, thus independence.
- $\theta > 1$, implies less likelihood in the 2nd level than the 1st level.

Testing the significance of the measure can be done using the hypothesis that we reject $H_0$ if 1 is not in the confidence interval.

OR can also be written as $\theta_{ij} = [((\pi_{ij}) (\pi_{i+1,j+1})) / (\pi_{i,j+1}) (\pi_{i+1,j})]$.

Therefore for $I*J = 3*2$,

- $\theta_{11} = [((\pi_{11}) (\pi_{22})) / (\pi_{12}) (\pi_{21})]$
- $\theta_{21} = [((\pi_{21}) (\pi_{32})) / (\pi_{22}) (\pi_{31})]$
- $\theta_{12} = [((\pi_{12}) (\pi_{23})) / (\pi_{13}) (\pi_{22})]$

The SAS code used for power simulation, odds ratio and contrast statement is given in Appendix D.
3.10 Censoring

Observations which do not experience the event of interest are censored and are usually given a censor value of 0, otherwise if they experience the event, the censor value is 1. There are four types of censoring, namely right truncation, left truncation, right censoring, interval censoring and left censoring, the latter two are the most commonly used. Left censoring is when the patient experiences the event of interest prior to the study, whereas interval censoring is when the patient experiences the event of interest between two check-up times, but the exact time is not known. Right censoring is when the patient leaves the study before experiencing the event of interest.

The two graphs given in Appendix A show examples of censoring, where figure 1 shows a situation when all patients entered the study at the same time, and figure 2 illustrates a situation where they enter the study at different times. Subjects with dots at the ends were censored and those in circles at the ends experienced the event. In this study censored observations are treated as they have not experienced tooth loss, hence they have a response of 0.

3.11 Data Simulation

The 32 patients were simulated with the following distribution of prognostic factors as shown in table 4:
<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Level</th>
<th># of patients</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥50</td>
<td>21</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>&lt;50</td>
<td>11</td>
<td>34</td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>18</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>14</td>
<td>43</td>
</tr>
<tr>
<td>Status</td>
<td>1</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>4</td>
<td>13</td>
</tr>
</tbody>
</table>

**Table 4: Table showing the distribution of prognostic factors**

To start the simulation, the code in Appendix A was used to generate the 32 patients at random using a uniform distribution. The output for the distribution of variables as well as the frequencies for the prognostic factor is given in Appendix B. For all replications done to estimate balances in numbers between treatment groups, prognostic factors, logistic regression and power calculation, the SAS code is given in Appendix A.

### 3.12 Range of imbalance

For each randomization scheme, range of imbalance was computed. A simulation of 5000 simulation was performed to achieve this. Range was the difference between the numbers of patients in the bigger treatment arm compared to number of patients in the smaller treatment arm. If \( N_a \) is the number of patients administered to treatment A and \( N_b \) is the number of patients administered drug B, then the range of imbalance is given by:

\[
\text{Range} = \max(N_a, N_b) - \min(N_a, N_b).
\]
3.13 Conclusion

This chapter highlighted the various methods that were used to generate data; methods implemented on performing the analysis of data as well as performed the simulation of data. The next chapter does the analysis of data.
CHAPTER FOUR

DATA ANALYSIS

4.0 Introduction
In this chapter, the results of the study are displayed and analyzed using the methods mentioned chapter three. The interpretation of these results is also given in this chapter with tabular presentations giving clear visual interpretations.

4.1 Degree of imbalance in numbers between groups
5000 simulations were performed to compare the balance in the numbers in treatment groups obtained using the simple randomization and the minimization method. The means procedure from SAS had Simple randomization producing the mean and standard deviation with the following output:

<table>
<thead>
<tr>
<th>N</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>5000</td>
<td>0.50034</td>
<td>0.089761</td>
<td>0.218750</td>
<td>0.812500</td>
</tr>
</tbody>
</table>

The Minimization method produced the following mean differences and standard deviation:

<table>
<thead>
<tr>
<th>N</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>5000</td>
<td>0.49936</td>
<td>0.031252</td>
<td>0.375000</td>
<td>0.625000</td>
</tr>
</tbody>
</table>

These outputs showed means which are almost the same where simple randomization produced a slightly higher mean of 0.5003375 than the minimization method which had a mean 0.4993625. The variances between the treatment groups are also slightly different for the two randomization
schemes, where simple randomization produced a standard deviation of 0.0897606 and minimization method produced a smaller standard deviation of 0.0312529.

4.2 Range of imbalance
As discussed in chapter 3, range was calculated as \( \max (Na, Nb) - \min (Na, Nb) \). In simple randomization range was 17-15=2. In minimization, range was still 2, which shows that the difference is not too big for the two randomization schemes.

4.3 Imbalances in prognostic factors
The important prognostic factors in this study were age, gender and smoking status. 5000 replications were done to estimate the balance on prognostic factors. Results in appendix D were produced by the simulations and table 5 below is a summary of the means.

<table>
<thead>
<tr>
<th>P. Factor</th>
<th>Level</th>
<th>B %age</th>
<th>A %age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1</td>
<td>76.3</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>26.7</td>
<td>53</td>
</tr>
<tr>
<td>Gender</td>
<td>1</td>
<td>47.6</td>
<td>58.8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>53.3</td>
<td>41.2</td>
</tr>
<tr>
<td>Status</td>
<td>1</td>
<td>26.6</td>
<td>17.7</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>13.3</td>
<td>47.1</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>53.3</td>
<td>23.5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>6.7</td>
<td>11.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P. Factor</th>
<th>Level</th>
<th>B %age</th>
<th>A %age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1</td>
<td>58.8</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>41.2</td>
<td>40</td>
</tr>
<tr>
<td>Gender</td>
<td>1</td>
<td>58.8</td>
<td>46.7</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>41.2</td>
<td>53.3</td>
</tr>
<tr>
<td>Status</td>
<td>1</td>
<td>17.6</td>
<td>26.7</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>29.4</td>
<td>33.3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>41.2</td>
<td>33.3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>11.8</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Table 5: Table of means produced by imbalances in prognostic factors

From the table of means for imbalances in prognostic factors above, the percentages of age under treatment B of simple randomization produced an imbalance of 76.3% against 26.7%, which is far from the original distribution of age of 59.38% against 40.63% as compared to minimization method which had an imbalance of 58.8% against 41.2%. For treatment A under simple
randomization, the original distribution of prognostic factor, age, is 59.38% against 40.63%, but simple randomization produced an imbalance of 47% against 53% while minimization method produced an imbalance of 60% against 40%. The other imbalances can be found in a similar manner. This shows that minimization method is better method in balancing out prognostic factors.

Means for the balancing in prognostic factors are also presented in Appendix D. Simple randomization has mean age of 1.267 in treatment B compared to 1.529 in treatment A. This is a slight difference. Gender differs as 1.53 and 1.41. Smoking status differed as 2.4 and 2.29.

Minimization produced slight differences in prognostic factor balance as well. Age had 1.41 vs. 1.4, gender had 1.41 vs. 1.53 and smoking status had 2.47 vs. 2.2. These are also small.

4.4. Logistic regression
Table 6, was produced when the logistic procedure was performed in the simulated dataset using simple randomization. Minimization results were simulated in the same way.

<table>
<thead>
<tr>
<th>Score Test for the Proportional Odds Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-Square</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>119.1398</td>
</tr>
</tbody>
</table>

Table 6: Table showing scores for the proportional odds assumptions

The assumption of proportional odds holds, since p-value is 0.001 < 0.05 and the Chi-Square is large, having a value of 119.13. From the Testing Global Null Hypothesis Table 7 below, the likelihood ratio test is 43.9676, which is a bigger value.
Testing Global Null Hypothesis: BETA=0

<table>
<thead>
<tr>
<th>Test</th>
<th>Chi-Square</th>
<th>DF</th>
<th>Pr&gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likelihood Ratio</td>
<td>43.9676</td>
<td>6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Score</td>
<td>35.9457</td>
<td>6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Wald</td>
<td>36.989</td>
<td>6</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Table 7: *Table of the global null hypothesis

<table>
<thead>
<tr>
<th>Effect</th>
<th>DF</th>
<th>Wald Chi-Square</th>
<th>Pr&gt;ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1</td>
<td>14.3762</td>
<td>0.0009</td>
</tr>
<tr>
<td>Gender</td>
<td>1</td>
<td>0.6649</td>
<td>0.8827</td>
</tr>
<tr>
<td>Sstatus</td>
<td>3</td>
<td>26.0993</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Trt</td>
<td>1</td>
<td>5.6468</td>
<td>0.02743</td>
</tr>
</tbody>
</table>

Table 8: *Table showing the type 3 Analysis of Effects

From the Type 3 Analysis of Effects in the table above, age and smoking status had a Pr< 0.05, so it is a significant factor. Gender is not significant since its p-value is >0.001

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>Wald Chi-Square</th>
<th>Pr-ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0</td>
<td>-2.765</td>
<td>0.4768</td>
<td>67.49</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Intercept</td>
<td>1</td>
<td>-1.6741</td>
<td>0.3524</td>
<td>43.45</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Intercept</td>
<td>2</td>
<td>-1.4376</td>
<td>0.3564</td>
<td>23.476</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Intercept</td>
<td>3</td>
<td>-0.3746</td>
<td>0.2234</td>
<td>0.2273</td>
<td>0.5766</td>
</tr>
<tr>
<td>Intercept</td>
<td>4</td>
<td>0.4682</td>
<td>0.1565</td>
<td>5.4682</td>
<td>0.0044</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>0.9847</td>
<td>0.3425</td>
<td>14.3762</td>
<td>0.0009</td>
</tr>
<tr>
<td>Gender</td>
<td>1</td>
<td>-0.0987</td>
<td>0.2565</td>
<td>0.6649</td>
<td>0.8827</td>
</tr>
<tr>
<td>SStatus</td>
<td>1</td>
<td>1.7446</td>
<td>0.3986</td>
<td>32.476</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SStatus</td>
<td>2</td>
<td>0.9746</td>
<td>0.2221</td>
<td>0.3568</td>
<td>0.5265</td>
</tr>
<tr>
<td>SStatus</td>
<td>3</td>
<td>-0.3654</td>
<td>0.4367</td>
<td>0.9973</td>
<td>0.4365</td>
</tr>
<tr>
<td>COL77</td>
<td>0</td>
<td>0.5642</td>
<td>0.1623</td>
<td>5.6468</td>
<td>0.02743</td>
</tr>
</tbody>
</table>

Table 9: *Table of the Analysis of maximum Likelihood Estimates
Treatment A is 2.765 more effective than treatment B, according to the results of the analysis of maximum likelihood estimates. Level 1 of Smoking status is 32 times likely to be more effective than level 4 of those who smoke. This is shown from the result of 1.7446 in the output above.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Point Estimate</th>
<th>95% Confidence Limit</th>
<th>Wald Confidence Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 1 vs 2</td>
<td>4.384</td>
<td>1.857</td>
<td>10.348</td>
</tr>
<tr>
<td>Gender 1 vs 2</td>
<td>0.901</td>
<td>0.432</td>
<td>1.877</td>
</tr>
<tr>
<td>Sstatus 1 vs 4</td>
<td>26.042</td>
<td>6.553</td>
<td>103.499</td>
</tr>
<tr>
<td>Sstatus 2 vs 4</td>
<td>5.772</td>
<td>1.521</td>
<td>21.9</td>
</tr>
<tr>
<td>Sstatus 3 vs 4</td>
<td>3.624</td>
<td>0.98</td>
<td>13.4</td>
</tr>
<tr>
<td>COL77 0 vs 1</td>
<td>2.229</td>
<td>1.063</td>
<td>4.676</td>
</tr>
</tbody>
</table>

Table 10: Table showing the Odd Ratio Estimates

4.5 Power using the Logistic Regression
Power was calculated using the logistic regression in the code given in Appendix D. The power generated by making use of the chi-square test when simple randomization was used to allocate patients into the treatment groups was 0.01968 and that of minimization was 0.0204. These are both small values since the best power should be at least 0.8.

4.6 Conclusion
Chapter 4 showed the results of the study where comparisons have been done on the balances of numbers and prognostic factors as well as behavior of power in small scale trials. Results confirmed that when trials are small, simple randomization and minimization do produce a less power. According to literature in chapter two, simple randomization produces balanced samples in numbers when samples are large, due to chance. Also, by chance, this study has shown that
simple randomization produces low imbalances in the distribution of prognostic factors as it did with the minimization method.
CHAPTER FIVE

CONCLUSIONS, DISCUSSIONS AND RECOMMENDATIONS.

5.0 Introduction
The main aim of this study was to compare the statistical differences between some randomization schemes used in clinical trials. Simple randomization and minimization method were compared, where simple randomization is unrestricted randomization and minimization is restricted randomization. This chapter abridges all the work done in this study according to research goals. Discussions, recommendations and final conclusions are also done in this chapter.

5.1 Discussion
Simple randomization produced reasonably unbalanced sized treatment groups where whereas minimization produced slightly the same as simple randomization. This could have happened by chance.

By use of the statistical methods in chapter 3, of using the range, distribution of prognostic factors was shown to be balanced in the minimization method whereas simple randomization produces a range of 2 participants. The estimated treatment effect however, was shown to be
almost the same for the two randomization schemes. This means that the randomization scheme used does not change the effect of the treatment administered to each participant.

Power was shown to be extremely small in both randomization schemes, though minimization method had a bigger value than simple randomization. This could have been caused by the size of the sample. In chapter two, literature had proved that bigger sized samples have a better power than smaller sized. This was confirmed in this study and conclusion can still be made that minimization is better than simple randomization, although the practicality of the minimization scheme can be questioned for largest sized samples.

5.2 Recommendations
Even in smaller sample sized trials, restriction on the numbers of patients within and between treatment groups is preferred. Shortened Dental Arch trials also need a balance in the prognostic factors. These like most other trials for different diseases, have been proved in this study to increase the power of the chi-square test, hence most statistical tests.

5.3 Areas of future research
Other randomization schemes apart from simple, minimization and randomly permuted block, that was used in the actual study, that can be used in Shortened Dental Arch can also be studied. Studies can be done using other statistical tests and biggest samples to test the practicality of the minimization scheme.
5.4 Conclusion
A proper randomization scheme should be chosen that maximizes the output of any clinical trial, as well as strengthen the results. Restriction is most preferred in a small sized trial, so as to achieve balance on the trial as a whole, and when interim analysis is done.
BIBLIOGRAPHY


APPENDIX A
Graphs showing examples of censoring for time to event

Figure 1: Graph showing censoring when patients enter the study at the same times

Figure 2: Graph showing censoring when patients enter the study at different times

Example extracted from Statistical Computing Seminars. Survival Analysis with SAS. [Online].
http://www.ats.ucla.edu/stat/sas/seminars/sas_survival/default.htm
**APPENDIX B**

Output from Code jes, showing the distribution of variables.

The SAS System  
20:43 Tuesday, December 14, 2010

<table>
<thead>
<tr>
<th>age</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative Frequency</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>59.38</td>
<td>19</td>
<td>59.38</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>40.63</td>
<td>32</td>
<td>100.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>gender</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative Frequency</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>53.13</td>
<td>17</td>
<td>53.13</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>46.88</td>
<td>32</td>
<td>100.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>status</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative Frequency</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>21.88</td>
<td>7</td>
<td>21.88</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>31.25</td>
<td>17</td>
<td>53.13</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>37.5</td>
<td>29</td>
<td>90.63</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>9.38</td>
<td>32</td>
<td>100.00</td>
</tr>
</tbody>
</table>
APPENDIX C

SAS CODES

DATA jes(keep=pat trt_A trt_B age gender sstatus);
DO i=1 TO 32;
    pat=i;
age=ranbl(20.0 65 0.35);
gender=ranbl(21.0 55 0.45);
sstatus=ranbl(22.0 30 0.31 0.26 0.13);
slope=-0.47469*age-0.9259*gender-0.9819*sstatus;
f1=1.5434+slope; p1=exp(f1)/(1+exp(f1));
f2=3.0177+slope; p2=exp(f2)/(1+exp(f2));
f3=3.66417+slope; p3=exp(f3)/(1+exp(f3));
f4=4.4565+slope; p4=exp(f4)/(1+exp(f4));
f5=5.5567+slope; p5=exp(f5)/(1+exp(f5));
    odds=2;
a1=p1/(odds-odds*p1+p1);
a2=p2/(odds-odds*p2+p2);
a3=p3/(odds-odds*p3+p3);
a4=p4/(odds-odds*p4+p4);
a5=p5/(odds-odds*p5+p5);
trt_B=ranbl(24.a1.a2-a1.a3-a2.a4-a3.a5-a4.1-a5)-1;;
OUTPUT;
ODS RTF FILE='outputjes';
END;
RUN;
ODS RTF CLOSE;
PROC PRINT DATA=jes;
RUN;
proc freq data=jes;
run;
/*
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ ~~~~~~~~~~~
Creating Dummy Variables
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ ~~~~~~~~~~~
*/
DATA dummy;
SET jes;
KEEP pat trt_A trt_B p trt
   a1 a1_a a1_b
   a2 a2_a a2_b
   b1 b1_a b1_b
   b2 b2_a b2_b
   c1 c1_a c1_b
   c2 c2_a c2_b
   c3 c3_a c3_b
   c4 c4_a c4_b
   a_bal b_bal
END;
age gender sstatus;
trt=0; p=0;
a1=0; a1_a=0; a1_b=0;
a2=0; a2_a=0; a2_b=0;
b1=0; b1_a=0; b1_b=0;
b2=0; b2_a=0; b2_b=0;
c1=0; c1_a=0; c1_b=0;
c2=0; c2_a=0; c2_b=0;
c3=0; c3_a=0; c3_b=0;
c4=0; c4_a=0; c4_b=0;
IF age=1 THEN a1=1;
IF age=2 THEN a2=1;
IF gender=1 THEN b1=1;
IF gender=2 THEN b2=1;
IF sstatus=1 THEN c1=1;
IF sstatus=2 THEN c2=1;
IF sstatus=3 THEN c3=1;
IF sstatus=4 THEN c4=1;
a_bal=0; b_bal=0;
PROC SORT;
BY pat;
RUN;
PROC PRINT DATA=dummy;
RUN;
/*
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ ~~~~~~~~~~~~~~~~~~~~~~~~~
Allocation patients into Treatments groups using simple randomization.
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ ~~~~~~~~~~~~~~~~~~~~~~~~~
*/
%MACRO alloc;
PROC iml;
A=shape(0,32,5000);
B=shape(0,5000,34);
do k=1 to 5000;
use dummy;
read all var {pat age gender sstatus
  trt_A trt_B p trt
  a1 a1_a a1_b
  a2 a2_a a2_b
  b1 b1_a b1_b
  b2 b2_a b2_b
  c1 c1_a c1_b
  c2 c2_a c2_b
  c3 c3_a c3_b
  c4 c4_a c4_b
  a_bal b_bal
} into m;
do i=1 to 32;
do j=9 to 30 by 3;
m[i,33]=m[i,33] + ABS(m[i,j]*(m[i,j+1]-m[i,j+2]+1));
m[i,34]=m[i,34] + ABS(m[i,j]*(m[i,j+1]-m[i,j+2]-1));
end;
m[i,7]=ranuni(0);
if m[i,33]>m[i,34] then do;
if m[i,7]>0.5 then A[i,k]=0; else
if m[i,7]<=0.5 then A[i,k]=1;
end; else
if m[i,33]<m[i,34] then do;
if m[i,7]>0.5 then A[i,k]=1; else
if m[i,7]<=0.5 then A[i,k]=0;
end; else
if m[i,33]=m[i,34] then do;
if m[i,7]>0.5 then A[i,k]=1; else
if m[i,7]<=0.5 then A[i,k]=0;
end;
if i<32 then do;
do j=9 to 30 by 3;
m[i+1,j+1]=m[i,j+1];
m[i+1,j+2]=m[i,j+2];
if A[i,k]=0 then m[i+1,j+1]=m[i+1,j+1]+m[i,j]; else
if A[i,k]=1 then m[i+1,j+2]=m[i+1,j+2]+m[i,j];
end; end;
if i=32 then do;
do j=1 to 34;
B[k,j]=m[32,j];
end; end;
CREATE A FROM A;
APPEND FROM A;
CREATE B FROM B;
APPEND FROM B;
quit;
run;
run;
%MEND;
%alloc;
/*
----------------------------------
Creation of the Dataset Simple.
----------------------------------
*/
DATA SIMPLE;
MERGE jes A;
ARRAY col{5000} col1-col5000;
ARRAY response{5000} response1-response5000;
DO i=1 to 5000;
IF col[i]=0 THEN response[i]=trt_A;
ELSE
IF col[i]=1 THEN response[i]=trt_B;
END;
RUN;
PROC PRINT DATA=SIMPLE;
RUN;
/*----------------------------------
ALLOCATION USING THE MINIMIZATION METHOD
----------------------------------*
*/
%MACRO alloc;
PROC iml;
A=shape(0,32,5000);
B=shape(0,5000,34);
do k=1 to 5000;
use dummy;
read all var {pat age gender sstatus trt_A trt_B p trt_i a1 a1_a a1_b a2 a2_a a2_b b1 b1_a b1_b b2 b2_a b2_b c1 c1_a c1_b c2 c2_a c2_b c3 c3_a c3_b c4 c4_a c4_b a_bal b_bal} into m;
do i=1 to 32;
do j=9 to 30 by 3;
m[i,33]=m[i,33] + ABS(m[i,j]*(m[i,j+1]-m[i,j+2]+1));
m[i,34]=m[i,34] + ABS(m[i,j]*(m[i,j+1]-m[i,j+2]-1));
end;
m[i,7]=ranuni(0);
if m[i,33]>m[i,34] then do;
if m[i,7]>0.75 then A[i,k]=0; else
if m[i,7]<0.75 then A[i,k]=1;
end; else
if m[i,33]<m[i,34] then do;
if m[i,7]>0.75 then A[i,k]=1; else
if m[i,7]<0.75 then A[i,k]=0;
end; else
if m[i,33]=m[i,34] then do;
if m[i,7]>0.5 then A[i,k]=1; else
if m[i,7]<0.5 then A[i,k]=0;
end;
end;
if i<32 then do;
do j=9 to 30 by 3;
m[i+1,j+1]=m[i,j+1];
m[i+1,j+2]=m[i,j+2];
if A[i,k]=0 then m[i+1,j+1]=m[i+1,j+1]+m[i,j]; else
if A[i,k]=1 then m[i+1,j+2]=m[i+1,j+2]+m[i,j];
end;
end;
if i=32 then do;
do j=1 to 34;
B[k,j]=m[32,j];
end;
end;
end;
CREATE A FROM A;
APPEND FROM A;
CREATE B FROM B;
APPEND FROM B;
quit;
run;
run;
/* Creation of the Dataset Minimization. */
DATA minimization;
MERGE Jes A;
ARRAY col{5000} col1-col5000;
ARRAY response{5000} response1-response5000;
DO i=1 to 5000;
IF col{i}=0 THEN response{i}=trt_A;
ELSE IF col{i}=1 THEN response{i}=trt_B;
END;
RUN;
PROC PRINT DATA=minimization;
RUN;
/*
Using 5000 replications estimate treatment balances after simple randomization
*/
ODS LISTING CLOSE;
%MACRO simple (dt);
%DO i=1 %TO 5000;
proc means data=SIMPLE n mean std;
var col{i};
output out=balance mean=means std=deviation ;
run;
data &dt;
SET &dt balance;
it=&i;
run;
%end;
%mend;
data testsimple;
set _null_;
run;
%simple(testsimple);
data balance1(keep=means);
set testsimple;
run;
ODS LISTING;
PROC MEANS DATA=BALANCE1;
VAR means;
RUN;
/*
Using 5000 replications estimate treatment balances after minimization method
*/
ODS LISTING CLOSE;
%MACRO minimization (dp);
%DO i=1 %TO 5000;
data testminimization;
set _null_;
run;
%minimization(testminimization);
data balance11(keep=means);
set testminimization;
run;
ODS LISTING;
PROC MEANS DATA=balance11;
VAR means;
RUN;
/*
Balanced Prognostic Factors within Treatment Groups Using 5000 Replications after simple randomization
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
DATA ballas_pf_trtA (keep=age gender sstatus col77);
SET SIMPLE;
IF col77=0 THEN DELETE;
ELSE col77=1;
RUN;
PROC FREQ DATA=ballas_pf_trtA ;
RUN:
DATA ballas_pf_trtB (keep=age gender sstatus col77);
SET SIMPLE;
IF col77=1 THEN DELETE;
ELSE col77=0;
RUN;
PROC FREQ DATA=ballas_pf_trtB;
RUN;
PROC MEANS DATA=ballas_pf_trtA mean;
VAR age gender sstatus;
RUN;
PROC MEANS DATA=ballas_pf_trtB mean;
VAR age gender sstatus;
RUN;
/*
Balanced Prognostic Factors Within Treatment Groups Using 5000 Replications after minimization method
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
DATA ballam_pf_trtA (keep=age gender sstatus col77);
SET minimization;
IF col77=0 THEN DELETE;
ELSE col77=1;
RUN;
PROC FREQ DATA=ballam_pf_trtA; RUN;
DATA ballam_pf_trtB (keep=age gender sstatus col77);
SET minimization;
IF col77=1 THEN DELETE;
ELSE col77=0;
RUN;
PROC FREQ DATA=ballam_pf_trtB; RUN;
PROC MEANS DATA=ballam_pf_trtA mean;
VAR age gender sstatus;
RUN;
PROC MEANS DATA=ballam_pf_trtB mean;
VAR age gender sstatus;
RUN;
/* ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ ~~~~~~~~~~~~~~~~~
Logistic Regression using 5000 Replications for simple randomization
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~ ~~~~~~~~~~~~~~~~~*/
/*ODS RTF FILE='output1';*/
ODS LISTING CLOSE;
%macro lregs (df);
%DO i=1 %TO 5000;
proc logistic data=SIMPLE;
title2 'Logistics Regression Model under Simple randomization';
class age gender sstatus col&i;
model response&i=age gender sstatus col&i/*selection=forward expb */;
oddsratio=OR_S;
run;
data &df;
set &df OR_S;
if=&i;
run;
%end;
%mend;
data testlregs;
set _null_; run;
%lregs(testlregs);
%macro logregs (dg);
%DO i=1 %TO 5000;
/*ods graphics on;*/
proc logistic data= SIMPLE; /*plots(only)=(effect(polybar)
oddsratio(range=clip))*/;
class age gender sstatus col&i /*para=ref*/;
model response&i = age gender sstatus col&i /
oddsratio col&i;
oddsratio age;
oddsratio gender;
oddsratio sstatus;
contrast ' col&i =1 vs col&i =0' col&i 1 -1/ estimate=exp;
odds noresults;
odds output contrastestimate=contrast;
run;
data &dg;
Logistic Regression using 5000 Replications for minimization method

/*ODS RTF FILE='output1';*/
ODS LISTING CLOSE;
%macro lregm(dx);
%do i=1 %to 5000;
proc logistic data=minimization;
title2 'Logistics Regression Model under minimization method';
class age gender sstatus col&i; 
model response&i=age gender sstatus col&i /*selection=forward expb */ ;
ods output oddsratios=OR_M;
run;
data &dx;
set &dx OR_M;
ix=&i;
run;
%end;
%mend;
data testlregm;
set _null_; 
run;
%lregm(testlregm);
%macro logregm(dy);
%do i=1 %to 5000;
/*ods graphics on;*/
proc logistic data= minimization; /*plots(only)=(effect(polybar) oddsratio(range=clip))*/;
class age gender sstatus col&i /*para=ref*/;
model response&i = age gender sstatus col&i /;
oddsratio col&i;
oddsratio age;
oddsratio gender;
oddsratio sstatus;
contrast 'col&i =1 vs col&i =0' col&i 1 -1/ estimate=exp;
ods noresults;
ods output contrastestimate=contrast;
run;
data &dy;
set &dy contrast;
iy=&i;
run;
/*ods graphics off;*/
data testlogregm;
set _null_;
run;
%logregm(testlogregm);
/*
  power simulation using simple randomization.
  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
*/
DATA powers (keep=probchisq contrast waldchisq) ;
set testlogregs;
run;
data powers1 (keep=lowercl uppercl) ;
set testlregs;
if variable in ('age','gender','sstatus') or
effect in ('age 1 vs 2','gender 1 vs 2','sstatus 1 vs 4',
'sstatus 2 vs 4','sstatus 3 vs 4') THEN DELETE;
RUN:
DATA powers2;
SET powers;
SET powers1;
DO i=1 TO 5000;
powerchisqs = 0;
powercls = 0;
powerwldsqs =0;
IF probchisqs < 0.05 THEN powerchisqs = powerchisqs + 1;
ELSE powerchisqs = powerchisqs;
IF lowercls > 1 THEN powercls = powercls + 1;
ELSE powercls = powercls;
IF waldchisqs > 3.8415 THEN powerwldsqs = powerwldsqs + 1;
ELSE IF probchisqs < 0.05 THEN powerwldsqs = powerwldsqs + 1;
ELSE powerwlds = powerwldsqs;
end;
run;
proc print data=powers2;
run;
ODS LISTING;
PROC MEANS DATA=POWERS2;
VAR powerchisqs powercls lowercls uppercls probchisqs;
run;
/*
  power simulation using Minimization method.
  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
*/
DATA powerm (keep=probchisq contrast waldchisq) ;
set testlogregm;
run;
data powerm1 (keep=lowercl uppercl) ;
set testlregm;
if variable in ('age','gender','sstatus') or
effect in ('age 1 vs 2','gender 1 vs 2','sstatus 1 vs 4',
'sstatus 2 vs 4','sstatus 3 vs 4') THEN DELETE;
RUN;
DATA powerm2;
SET powerm;
SET powerm1;
DO i=1 TO 5000;
powerchisqm = 0;
powerclm = 0;
powerwldsqm = 0;
IF probchisqm < 0.05 THEN powerchisqm = powerchisqm + 1;
ELSE powerchisqm = powerchisqm;
IF lowerclm > 1 THEN powerclm = powerclm + 1;
ELSE powerclm = powerclm;
IF waldchisqm > 3.8415 THEN powerwldsqm = powerwldsqm + 1;
ELSE IF probchisqm < 0.05 THEN powerwldsqm = powerwldsqm + 1;
ELSE powerwldm = powerwldsqm;
END;
run;
proc print data=powerm2;
run;
ODS LISTING;
PROC MEANS DATA=POWERM2;
VAR powerchisqm powerclm lowerclm upperclm probchisqm;
run;
APPENDIX D
Results of estimation of frequency tables per prognostic factor and treatment group for the simulated dataset.

The FREQ Procedure

<table>
<thead>
<tr>
<th>Cumulative</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>age Frequency</td>
<td>Percent</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cumulative</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender Frequency</td>
<td>Percent</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cumulative</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>sstatus Frequency</td>
<td>Percent</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
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<tr>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
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</table>

<table>
<thead>
<tr>
<th>Cumulative</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL77 Frequency</td>
<td>Percent</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
</tr>
</tbody>
</table>

The FREQ Procedure

<table>
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<th>Cumulative</th>
</tr>
</thead>
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<tr>
<td>age Frequency</td>
<td>Percent</td>
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<td>1</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
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<table>
<thead>
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<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender Frequency</td>
<td>Percent</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cumulative</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>sstatus Frequency</td>
<td>Percent</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cumulative</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL77 Frequency</td>
<td>Percent</td>
</tr>
<tr>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>
The MEANS Procedure

Variable        Mean

age             1.2666667
gender          1.5333333
sstatus         2.4000000

The MEANS Procedure

Variable        Mean

age             1.5294118
gender          1.4117647
sstatus         2.2941176

The FREQ Procedure

<table>
<thead>
<tr>
<th>age</th>
<th>Frequency</th>
<th>Percent</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>58.82</td>
<td>10</td>
<td>58.82</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>41.18</td>
<td>17</td>
<td>100.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>gender</th>
<th>Frequency</th>
<th>Percent</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>58.82</td>
<td>10</td>
<td>58.82</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>41.18</td>
<td>17</td>
<td>100.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>sstatus</th>
<th>Frequency</th>
<th>Percent</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>17.65</td>
<td>3</td>
<td>17.65</td>
</tr>
<tr>
<td>2</td>
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<td>29.41</td>
<td>8</td>
<td>47.06</td>
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<tr>
<td>3</td>
<td>7</td>
<td>41.18</td>
<td>15</td>
<td>88.24</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>11.76</td>
<td>17</td>
<td>100.00</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>COL77</th>
<th>Frequency</th>
<th>Percent</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>100.00</td>
<td>17</td>
<td>100.00</td>
</tr>
</tbody>
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The FREQ Procedure

<table>
<thead>
<tr>
<th>age</th>
<th>Frequency</th>
<th>Percent</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>60.00</td>
<td>9</td>
<td>60.00</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>40.00</td>
<td>15</td>
<td>100.00</td>
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</table>

<table>
<thead>
<tr>
<th>gender</th>
<th>Frequency</th>
<th>Percent</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>46.67</td>
<td>7</td>
<td>46.67</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>53.33</td>
<td>15</td>
<td>100.00</td>
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</tbody>
</table>

Cumulative  Cumulative
<table>
<thead>
<tr>
<th>sstatus</th>
<th>Frequency</th>
<th>Percent</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>26.67</td>
<td>4</td>
<td>26.67</td>
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<td>33.33</td>
<td>9</td>
<td>60.00</td>
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<td>3</td>
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<td>93.33</td>
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</table>

Cumulative Frequency Percent

<table>
<thead>
<tr>
<th>COL77</th>
<th>Frequency</th>
<th>Percent</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>0</td>
<td>15</td>
<td>100.00</td>
<td>15</td>
<td>100.00</td>
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</tbody>
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The MEANS Procedure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>1.4117647</td>
</tr>
<tr>
<td>gender</td>
<td>1.4117647</td>
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<tr>
<td>sstatus</td>
<td>2.4705882</td>
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</tbody>
</table>

The MEANS Procedure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>1.400000</td>
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<tr>
<td>gender</td>
<td>1.533333</td>
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<tr>
<td>sstatus</td>
<td>2.200000</td>
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