

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

UNIVERSITY OF FORTHARE

FACULTY OF SCIENCE AND AGRICULTURE



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Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique.

By

Chioneso Show Marange

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Supervisor: Prof J.C. Tyler

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DECLARATION

I would like to acknowledge that all references are truthfully recorded and that, unless otherwise stated, all work herein is my own.

Signed by Author / / 20

ABSTRACT

Background: Generally the primary goal of randomized clinical trials (RCT) is to make comparisons among two or more treatments hence clinical investigators require the most appropriate treatment allocation procedure to yield reliable results regardless of whether the ultimate data suggest a clinically important difference between the treatments being studied. Although recommended by many researchers, the utilization of minimization has been seldom reported in randomized trials mainly because of the controversy surrounding the statistical efficiency in detecting treatment effect and its complexity in implementation. **Methods:** A SAS simulation code was designed for allocating patients into two different treatment groups. Categorical prognostic factors were used together with multi-level response variables and demonstration of how simulation of data can help to determine the power of the minimization technique was carried out using ordinal logistic regression models. **Results:** Several scenarios were simulated in this study. Within the selected scenarios, increasing the sample size significantly increased the power of detecting the treatment effect. This was contrary to the case when the probability of allocation was decreased. Power did not change when the probability of allocation given that the treatment groups are balanced was increased. The probability of allocation $\{P_k\}$ was seen to be the only one with a significant effect on treatment balance. **Conclusion:** Maximum power can be achieved with a sample of size 300 although a small sample of size 200 can be adequate to attain at least 80% power. In order to have maximum power, the probability of allocation should be fixed at 0.75 and set to 0.5 if the treatment groups are equally balanced.

Key Words: Minimization, Randomization, Power, Logistic regression, Allocation probability

PREFACE

This dissertation is structured as follows:

- Chapter one (1) gives the introduction, research problem together with the research aims and objectives
- Chapter two (2) gives the detailed description on the implementation of the minimization treatment allocation technique as well as the literature review and overview of this technique. This chapter also highlights on power and sample size consideration in randomized clinical trials.
- Chapter three (3) gives the statistical methods and designs used in this study and their justifications. This includes the simulation procedures using SAS programming and categorical data analysis using logistic regression models.
- Chapter four (4) gives the methods for data analysis and the interpretation of results.
- Chapter five (5) presents the discussions, conclusions, recommendations and areas of future research that can be drawn from the study.

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Acronyms

ABPM	Ambulatory Blood Pressure Monitoring
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BP	Blood Pressure
DP	Difference of Proportions
ICH	International Conference on Harmonization
OP	Office Pressure
OR	Odds Ratios
PROC IML	Matrix Based SAS Command
PROC	SAS Command Prompt
RANUNI	Uniform Distribution Random Number Generating Command
RCT	Randomized Clinical Trials
RR	Relative Risk
SAS	Statistical Programming/Analysis Software
SD	Standard Deviation
SP	Self-Pressure
STATISTICA	Statistical Analysis Software

CHAPTER ONE (1)

INTRODUCTION/BACKGROUND INFORMATION

1.1 GENERAL INTRODUCTION

In a randomized clinical trial subjects should be assigned to comparison or treatment groups on the basis of a random process which should be unpredictable. In such studies, several methods of randomization are available to create comparable intervention groups. Randomized controlled trials generally use some form of constraints when allocating subjects for example; blocking, stratification, or minimization. The main purpose behind this is to attain a better balance of known prognostic factors. Achieving balance on prognostic factors between treatment groups in a clinical trial is essential to make sure that any observed treatment outcome may be accredited to the treatment itself. Improving the balance on prognostic factors also potentially increases the statistical power attained in a trial (Weir CJ and Lees KR, 2003).

The design of a clinical trial which involves the choice of a method of allocating treatments to subjects can contribute to the prevention of selection bias and minimizing the precision and validity of the estimates of treatments by minimizing bias and ensuring an efficient comparison (Kalish and Begg, 1985). It is desirable that any method of treatment allocation exhibits unpredictability and balance between treatment groups with respect to the available treatment numbers and major prognostic variables. Being a cornerstone in the design and conduct of clinical trials, randomization is the bias of most treatment allocation methods. Randomization prevents most clinicians from consciously or unconsciously assigning particular subjects to a treatment they believe to be superior hence treatment allocation is not based on subject's prognostic factors. Randomization also prevents confounding and ensures comparability with respect to known and unknown factors that may affect the response.

Since the requirements of randomization and balancing of prognostic factors conflict with one another, in practice investigators have to come to a compromise and use a procedure which suites that specific trial to be conducted. This study intends to describe current knowledge about the implementation of minimization as a form of restrictive measure of randomization in clinical trials and try to investigate its behavior in terms of maximizing power. Since power and

efficiency are directly correlated, thus for a particular treatment difference and significance level, a more highly powerful trial will require more patients and a larger trial will have more power. Because of this direct relationship, this study also intends to focus on statistical efficiency.

1.2 DEFINITION OF TERMS/CONCEPTS

1.2.1 Effect Size or Treatment Size

The sample size of a clinical trial depends on the size of the difference to be detected. The larger the desired detectable difference the more patients required for the study. It is usually best to make sure that there is an adequate number of subjects to detect the minimal “clinically” significant difference to avoid the need for astronomically large numbers of patients. Considering the rule above, it makes sense that studies, in which strong treatment effects and large differences between groups are anticipated, require a smaller number of subjects.

1.2.2 Power

The power of a study is defined as its ability to detect a true difference in outcome between the treatment arms. It can also be defined as the ability of a test to detect a statistical difference between two different treatments, when the difference in fact exists. Power is correlated to the possibility of finding a clinically relevant effect for any given drug or treatment and this may be termed “clinical effect,” which is not always the same as statistical effect.

1.2.3 Prognostic Factors

Prognostic factors are factors that have a greater effect on the response variables. They are usually categorized in different levels. Categorizing prognostic variables is vital for their use in clinical decision-making. Often a single cut point that stratifies patients into high-risk and low-risk categories is sought. These categories of prognostic factors may be used for making treatment recommendations, determining study eligibility, or to control for varying patient prognoses in the design of a clinical trial. Methods used to categorize variables include biological determination, arbitrary selection of a cut point at the median value, graphical examination of the data for a threshold effect and exploration of all observed values for the one

which best separates the risk groups according to a chi-squared test. Prognostic variables can be continuous or categorical and they are usually independently distributed.

1.3 METHODS OF TREATMENT ALLOCATION

1.3.1 The Method of Minimization

Minimization is considered not to be a method of randomization. In fact it is the only non-random technique which is an acceptable option to randomization. Minimization can be classified as a “dynamic allocation” or “covariate adaptive” method as the allocation depends on the characteristics of patients previously recruited. This is different from “response adaptive” methods where the allocation can depend on the interim results of the study. Minimization ensures balance between treatment groups for a number of patient factors. Randomization lists are not set up in advance. The first patient is strictly randomly allocated; for each successive patient, the treatment allocation is identified, which minimizes the imbalance between groups at that instance. Minimization makes a sequential assignment of subjects to treatments by minimizing the total imbalance between treatment groups over significant prognostic variables.

1.3.2 Block Randomization

The basic idea of block randomization is to divide potential patients into m blocks of size $2n$, randomize each block such that n patients are allocated to treatments A and B then choose the blocks randomly. It is used to ensure close balance of the numbers in each group at any time during the study. After allocating in every block the number of participants in each group would be equal. Blocking tends to diminish the unpredictability of randomization, as a result it is recommended to use random block sizes when using block randomization. This method ensures equal treatment allocation within each block if the complete block is used. The example given below illustrates how block randomization is implemented.

Example 1(Beller M et al, 2002).

The permuted block method of randomization for a block size of four, with A and B being treatment groups (A = new treatment and B = control/placebo, for example)

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Table 1-1

Random number sequence	Permuted blocks	Randomisation list
1	1. AABB	1 { A A B B
4	2. ABAB	
8	3. ABBA	
6	4. BBAA	
5	5. BABA	4 { B B A A
(etc)	6. BAAB	
		6 { B A A B
		5 { B A B A

A random number sequence is generated from a statistical textbook or computer. Each possible permuted block is assigned a number (1 to 6 in the above example). Using each number in the random number sequence in turn selects the next block, determining the next four participant allocations. Numbers in the random number sequence greater than the number of permuted block combinations (7, 8, 9 and 0 in the above example) are not used to select blocks.

Block size depends on the number of treatments, it should be short enough to prevent imbalance, and long enough to prevent guessing allocation in trials. The block size should be at least 2 times the number of treatments. The block size is not stated in the protocol so the clinicians and investigators are blind to the block size. If blocking is not masked in open-label trials, the sequence becomes somewhat predictable. This may possibly lead to selection bias. The solution to avoid selection bias is not to reveal blocking mechanism and to use random block sizes. If treatment is double blinded, selection bias is highly not to be expected. Note, if only one block is requested, then it produces a single sequence of random assignment, that is simple randomization.

1.3.3 The Method of Stratification

Stratification ensures that the numbers of participants receiving each treatment are closely balanced within each stratum. Stratified randomization is achieved by performing a separate randomization method within each of two or more subsets of participants. Stratified randomization has quite a number of potential advantages which include as outlined below.

i. Greater assurance of homogeneity

One of the advantages is of providing greater assurance that compared groups are similar with respect to known prognostic features other than treatment (R. Simon, 1979; S.J. White and L.S. Freedman, 1978; M. Zelen, 1974; A.B. Hill, 1951; R. Simon, 1982; P. Armitage and E.A. Gean, 1974). For small trials (that is with $n < 100$) (S.J. White and L.S. Freedman, 1978), stratification is cited to assure a valid comparison (P. Armitage and E.A. Gean, 1974).

ii. Protection against type I error

It also protects against type I error. A falsely positive trial could occur if the randomization schedule allocates patients between treatment groups such that those patients in the active group have a better prognosis than those in the control group. Thus stratification reduces the probability of finding statistically a significant difference between two treatment groups when none exists.

iii. Improvement of power

Stratification also helps to protect against type II error (increased power) (Walter N. Kernan et al, 1999). Investigators refer to the quantity, $1 - \beta$ as statistical power and a highly powered study is known to have a greater probability of detecting a specific treatment effect at any given level of alpha (significance level). Power is inversely related to variance of the difference between two means, thus stratification reduces that variance (J.E. Grizzle, 1982 and O.S. Miettinen, 1976) and theoretically should increase power and, also when stratification improves power, it also reduces sample size.

iv. Improvement of efficiency

Efficiency is referred to as the number of patients that are required to detect a difference between two treatments at a pre-specified power and level of significance, and increased efficiency is one other potential advantage of stratified randomization. The magnitude of the benefit of stratified randomization on efficiency has been examined and demonstrated in only a limited number of studies (J.M. Nam, 1995 and M. Palta, 1985). Power and efficiency are directly related; hence for a specific treatment difference and significance level, a more highly powered trial will require more patients and a larger trial will have more power (Walter N. Kernan et al, 1999).

Other advantages include; facilitation of subgroup analysis, facilitation of interim analysis and, protection against effects of recruitment center drop-out. Provided that the number of strata is kept small, relative to the size of the study, there is generally no disadvantage to stratification. However one problem which is associated with too many strata and incomplete filling of blocks is termed overstratification. The maximum number of strata that is acceptable for any trial cannot be fixed easily. Investigators have proposed that more than three to four strata are seldom advisable (Pocock SJ, Simon R, 1975); the maximum appropriate number of strata depends on;

- i. The total number of subjects in the trial,
- ii. The expected number of subjects who will be in each strata, and
- iii. The significance of the stratification factors.

The number of strata required in a trial is the product of the number of levels of each factor (for example; with just 16 factors, each having 2 levels, 32 strata are possible.). To assure parsimony, investigators are encouraged to consider only those clinical variables that have a known and important effect on outcome risk or treatment responsiveness (Walter N. Kernan et al, 1999).

1.4 RESEARCH PROBLEM

The greatest determinant of the power of a study is its design (Treasure T, MacRae KD., 1998). Thus for any particular study, special considerations on the sample size, the effect size and alpha (α) should be practiced since they are so essential in determining the power of a study. In studies with restrictions on randomization, imbalances may occur which will lead to power loss. It is of greater concern to go beyond older reviews that have focused on limited aspects of power maximization in studies with restrictive measures applied on treatment allocation schemes. From

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previous studies it can be noted that little work has been done by clinicians and clinical investigators on the effect of restricted randomization on the validity of significance tests.

The benefits of minimization have been debated recently (Altman DG., 2005; Buyse M., 2004) and a recent review of the usage of minimization recommended 'its wider adoption in the conduct of randomized controlled trials' (Scott NW et al., 2002). Some literature suggests that in very small trials where there is an insufficient patient population for algorithms to work minimization has less statistical benefits and stratification may be necessary. Nevertheless, for other trials, including very large trials, minimization is preferable to stratification.

Angie Wade et al (2006) stated that minimization could be used within treatment trials to ensure that prognostic factors are evenly distributed between treatment groups. The method is moderately straightforward to apply but does need running tallies of patient recruitments to be made and some simple calculations to be performed prior to every allocation. As computing facilities have become more widely available, minimization has become a more feasible option for many researchers. Although the technique has increased in popularity, more research needs to be done to ensure solid results in regard to the power achieved by this technique. Minimization improves power by comparing similar groups but randomized block design has even more power (Zar JC, 1996). Previous studies conducted by Tu et al. (2000) together with Weir and Less (2003) have compared the statistical power of minimization and random permuted blocks within strata using simulations but results have differed and McEntegart (2003) states that more research is needed before drawing conclusions regarding statistical efficiency of minimization.

Generally the primary goal of randomized clinical trials (RCTs) is to make comparisons among two or more treatments. In this sense clinical investigators require the most appropriate treatment allocation procedure to yield reliable information regardless of whether the ultimate data suggest a clinically important difference between the treatments being studied or the study is intended to measure the accuracy of a diagnostic test or the incidence of a disease. Having all this in mind the focus of this research is on finding the parameters within the minimization algorithm that yields the most statistical effect in maximizing power for the minimization technique, power in this sense refers to the power of a statistical test conditional on the particular restrictive measure achieved.

1.5 AIMS AND OBJECTIVES

The main aim of this study is to investigate the maximization of power in clinical trials where minimization treatment allocation technique is implemented (a simulation approach). The objectives of the study were as follows:

- i. To generate a dataset of size ≥ 50 with 3-4 prognostic factors and having two treatment groups.
- ii. To compare a measure of the maximum power and balance between treatment groups to be attained using different sample sizes under the null and the alternative hypotheses
- iii. To investigate a measure of the maximum power and balance between treatment groups to be attained with the effect of varying the probability of assignment $\{P_k\}$ to treatments 1 and treatment 2 using the minimization allocation algorithm.
- iv. To examine the effect of minimization parameters on the power of tests.

CHAPTER TWO (2)

LITERATURE REVIEW

2.1 INTRODUCTION

This chapter highlights the implementation of the minimization treatment allocation technique in clinical trials. In this context various formulations of power and sample size considerations and determination are also discussed. The effects of minimization on statistical efficiency will also be highlighted basing on the theoretical aspects, empirical evidence and evidence from previous researches.

2.2 IMPLEMENTATION OF MINIMIZATION TREATMENT ALLOCATION TECHNIQUE

Minimization makes a sequential assignment of subjects to treatments by minimizing the total imbalance between treatment groups over important prognostic variables. This section will present the ideas developed by Pocock and Simon on the implementation of the method of minimization.

2.2.1 General Description of Minimization

Some important prognostic factors are identified before the commencement of a clinical trial where the assignment of a new subject to a particular treatment group is determined so as to minimize the difference between the groups depending on these factors (Scott *et al.*, 2002). Suppose we have N treatments and M prognostic factors. Thus for a given arbitrary situation in a trial, we denote x_{ijk} as the number of subjects with factor i at level j assigned to treatment k . Let the next patient entering the trial have factor levels r_1, r_2, \dots, r_M . Therefore if the new patient is assigned to treatment k , then only x_{irik} for $i=1$ to N will change. That is, the number of patients assigned to treatment k will only change for the factor levels that the new patient exhibits. Pocock and Simon provided a generalized framework of Taves (1974) minimization scheme and treatment assignment that describes the following three functions:

- i. The amount of variation among assignments for any given factor level D , (where D is the individual factor balance function).

- ii. The measure of the total imbalance in treatment numbers G , (where G is an overall balance function).
- iii. Assignment probabilities to the k treatments of the trial $\{P_k\}$; where P_1 is the probability of assignment to the treatment that would lead to the least total imbalance p , (a set of treatment assignment probabilities).

Functions D and G are used to decide on which treatment assignment will result in the least overall imbalance in treatments based on the changed x_{irik} values.

2.2.2 The Choice of Individual Factor Balance Function, D

Consider $d_{ik} = D(x_{iri1}, \dots, x_{iriN})$ where d_{ik} measures the resulting “lack of balance” among treatment assignments for factor i at level ri if the patient is assigned to treatment k . Pocock and Simon considered four possible formulae for choosing D , the range, the standard deviation or variance, an upper limit of acceptable treatment imbalance and the sign rule (Pocock and Simon, 1975).

- i. **The Range** of ri , where i is a prognostic factor and r the factor level. If there are only two treatments the range is defined as $di = |NiA - NiB|$, where NiA is the number of subjects assigned to A for ri and NiB is the number of subjects assigned to B for ri .
- ii. **The Standard Deviance or Variance** of ri . Because of its squared component, the variance measure attaches relatively higher importance to more extreme imbalances, which sometimes can be considered appropriate. With only two treatments, the standard deviation is equivalent to the range method.
- iii. **An Upper Limit of Acceptable Treatment Imbalance** could be defined for each level of each factor.
- iv. **A Sign Rule**, this can be used in the case of two treatments.

2.2.3 The Choice of Overall Balance Function, G

Now consider $G_k = G(d_{1k}, \dots, d_{Mk})$ for $k = 1$ to N , where G is a function that calculates the resulting overall imbalance of the treatment assignments if the patient is assigned to treatment k . Then G might be chosen to simply sum up the d_{ik} values, or G could be a weighted sum of the d_{ik} values to reflect the desire to obtain balance for certain prognostic factors more than others (Pocock and Simon, 1975). The overall imbalance functions corresponding to each treatment k can then be ranked from the smallest overall imbalance value to the largest, with the motivation that one would assign a patient to a treatment with a low G score with a high probability so as to increase the chance of maximizing balance among the factors.

In a purely deterministic procedure, assuming that there are no ties in the scores for G , the treatment assignment k with the lowest G function would be picked with probability one. But, other values for $p = (p_1 \dots p_N)$ could be chosen. The patient is then assigned to a treatment based on the probabilities for p . The steps above are repeated for every patient that enters the trial (Pocock and Simon, 1975).

2.2.4 The Choice of $\{p_k\}$

Determining what values to use for $p = (p_1 \dots p_N)$ is important as it establishes the level of determinism of the minimization procedure; unpredictability in the treatment assignment process will help protect against selection bias. Let p_1 be the treatment assignment probability corresponding to the treatment yielding the smallest G value. Pocock and Simon suggest letting $p_1 = p$, where p is a constant greater than or equal to $1/N$, and

$$p_k = (1-p)/(N-1) \text{ for } k = 2 \text{ to } N. p = 1/N$$

which corresponds to random treatment assignment, while $p = 1$ corresponds to deterministically assigning the patient to the treatment yielding the lowest value of G (Pocock and Simon, 1975).

Example 1(Beller M et al, 2002).

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Example of randomisation using the minimisation method in a trial of chemotherapy for breast cancer, with stratification factors of clinic site, oestrogen receptor status (ER+ or ER-) and menopausal status

Table 2-1 Status after 34 participants have been randomised to the trial

Characteristic	Treatment A	Treatment B
Site 1	7	8
Site 2	10	9
ER+	5	6
ER-	12	11
Premenopausal	8	9
Postmenopausal	9	8
Total	17	17

The next participant (no. 35) is from Site 2, ER+, postmenopausal. Subtotals for treatment allocation to this profile of characteristics are $10 + 5 + 9 = 24$ for Treatment A and $9 + 6 + 8 = 23$ for Treatment B (note subjects are counted more than once). Participant no. 35 would therefore be allocated to Treatment B. When the tallies on A and B are equal within a profile, the next participant is randomly allocated. This process is equivalent to a permuted block size of two within the profile.

2.3 COMPONENTS FOR CONSIDERATION ON STATISTICAL POWER ANALYSIS

Power is calculated based on several components. Some are judgments made by investigators, others are calculated from samples. These components are:

- i. Sample size
- ii. Standardized effect size
- iii. Test Size or Significance level
- iv. Power of the test($1 - \beta$)
- v. Model(test)

2.3.1 Sample Size Calculations

To estimate a sample size which will ethically answer the research question of a randomized clinical trial (RCT) with a reliable conclusion, the following information should be available.

2.3.1.1 Type of Comparison

R Schall et al., (1998) noted that there are three types of comparisons and these include superiority trials which show that a new experimental therapy is superior to a control treatment. There are also equivalence trials which are aimed at showing that the test and control therapies are equally effective. Lastly there exist non-inferiority trials, and for these non-inferiority trials the aim is to show that the new therapy is as effective but need not be superior compared to the control therapy.

2.3.1.2 Type of Configuration

Two types of configuration were discussed in an article published by Chan YH. (1998). Firstly there is the parallel design which is the most commonly used design. In this design subjects are randomised to one or more arms of different therapies and treated concurrently. Secondly there is the crossover design, and in this design subjects act as their own control, and will be randomised to a sequence of two or more therapies with a washout period in between therapies. The crossover design is appropriate for chronic conditions which will return to its original level once therapy is discontinued.

2.3.1.3 Type I Error and Power

L Thomas and F Juanes, (1996) quoted that the type I error is usually set at two-sided 5% and power is at 80% or 90%. For the purposes of statistical testing, the major aim of this study is to use a feasible sample of data to evaluate a given hypothesis, H_1 , that the effect of treatment 1 (placebo) is better than the effect of treatment 2 (new drug). If the sample data leads to conclude that H_1 is true, but the contrary is actually the case, that is, if the (null) hypothesis H_0 is true that there is in actual fact no effect this is called a type I error. The probability of a type I error is typically designated by α , and statistical tests are intended to ensure that α is suitably small (for example, less than 0.05).

However it is also significant to have power over the probability β of making the opposite (type II) error that is, concluding H_0 , that there is no effect, when there really is one. The probability $1 - \beta$, of correctly rejecting H_0 when it is false is traditionally called the power of the test. However, another more scientific meaning of power is the probability of rejecting H_0 for any known set of conditions, even those matching to H_0 being true.

2.3.1.4 Effect Size of Therapies

The effect size specifies the accepted clinical difference between two therapies that a researcher wants to observe in a study. There are three usual ways to get the effect size:

- i. From past literature.
- ii. If no past literature is available, one can do a small pilot study to determine the estimated effect sizes.
- iii. Clinical expectations.

To calculate the sample size, besides knowing the type of design to be used, one has to classify the type of the primary outcome, which includes:

- i. Proportion outcomes: The primary outcome of interest is dichotomous (success/failure, yes/no). For example, 25% of the subjects on the standard therapy had a successful outcome and it is of clinical relevance only if we observe a 40% (effect size) absolute improvement for those on the study therapy (that is 65% of the subjects will have a successful outcome). Thus a simple formula to calculate the sample size is given by

$$m(\text{size per group}) = \frac{c \times \pi_1(1 - \pi_1) + \pi_2(1 - \pi_2)}{(\pi_1 - \pi_2)^2}$$

Where c (the required total sample size of the standardised effect size in steps of 0.1 for two-sided 5%) = 7.9 for 80% power and 10.5 for 90% power, π_1 and π_2 are the proportion estimates.

- ii. Continuous outcomes: There exist two scenarios; firstly a case in which we have two independent samples thus, the primary outcome of interest is the mean difference in an outcome variable between two treatment groups. For example, it is postulated that a good clinical response difference between the active and placebo groups is 0.2 units with a standard deviation (SD) of 0.5 units, how many subjects will be required to obtain a statistical significance for this clinical difference? A simple formula, for a two-sided test of 5%, is

$$m \text{ (size per group)} = \frac{2c}{\delta^2} + 1 \text{ where } \delta = \left| \frac{\mu_2 - \mu_1}{\sigma} \right| \text{ is the standardized effect size}$$

and μ_1 and μ_2 are the means of the two treatment groups, σ is the common standard deviation $c = 7.9$ for 80% power and 10.5 for 90% power. Secondly we have paired samples. In this case, we have the pre and post mean difference of the two treatment groups and a simple formula for the total sample size is;

$$n = \frac{c}{\delta^2} + 2$$

2.3.2 Relationship among the Components of Power

Basing on the arguments and specifications of the various components mentioned in this section, namely model (test), standardized effect size, sample size (n), significance level and power of the test, this sub-section will highlight the relationship among these components.

Considering the three parameters which characterize power of a study, that is sample size, effect size defined by the alternative hypothesis and significance level collectively with the power, fixing any three will permit determination of the fourth. Usually the most significant factor affecting statistical power is the sample size. In actual fact there is little room to alter a test size, and it is as well complex to have power over effect sizes in most cases (Jeeshim, 2004). Different statistical tests need different methods of calculating power for the reason that the sensitivity of

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the tests varies. Power is the ability to identify a difference in effect between treatments; if the test being used is not extremely sensitive, in that case a bigger sample will be desirable to attain sufficient power. Tests in which the data satisfy the assumptions of a normal distribution are usually fairly robust, meaning they can detect differences with high sensitivity, so their sample sizes might be moderately small. For the reason that tests for non-normal data (for example; Chi Square or the Mann-Whitney U) are comparatively insensitive, they need bigger samples. Multivariate tests over and over again need larger samples for the reason that they are looking for multiple relationships and interrelationships, hence have to be responsive as much as necessary to detect them all.

Effect size is a key consideration in power calculation. Just as a large object is easier to see than a small one, big effects are easier to notice in the data than small effects. To compute power, the investigator has got to predetermine the size of effect considered clinically important. A new drug that cures only 1% of the patients will on no account depart the pharmacy shelf, but one that cures 80% will fly off the shelves. The difficulty of clinical implication becomes more appealing if a cure rate of only 10%, 20% or 30% is clinically significant. Large effects can be detected by means of small samples, whereas subtle effects need large samples. Detecting rare side effects requires extremely large samples. Determining a significant effect size is a ruling call, but clinical expertise, historical studies, and patient responses possibly will all be considered.

The tolerable level of power is also set by the researcher. A power of 80% is considered the modestly satisfactory level, at the same time a number of researchers need much higher levels of power for their studies. Selecting an advantageous power level is achieved by balancing the need to detect a result with the difficulty in obtaining large sample sizes. The following elements of power calculation, which include, the precise statistical test, meaningful effect size, and level of power necessary are determined by the researcher prior to the commencement of the study.

Researchers usually report these elements in the methods section of an article by means of the discussion of sample size and power analysis. Additionally, elements of power calculation are not selected but somehow predictable by taking into consideration characteristics of the probable population. As a general rule, a highly heterogeneous population is not represented well by a small sample, and so will have less power. Heterogeneity can be assessed statistically via the standard divergence of key variables. If prior measurement of outcome variables shows an

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enormous deal of variability as represented by a moderately large standard deviation, then larger samples will be considered necessary.

The probabilities that a number of groups will be under or over-represented are greater in a diverse population, hence larger samples can aid guarantee that this does not take place. To institute population characteristics with whichever assurance, historical data or data from comparable studies is necessary. Unfortunately, these statistics are frequently unavailable for early-stage studies, hence when no historical data are available, precise power analysis is problematic. The main ordinary way to get hold of data is to carry out a pilot study. There are a lot of additional advantages of conducting pilot studies prior to full-scale randomized trials, these include, assessments can be tested, protocols refined, and measures experienced relatively quickly and economically with small numbers of subjects. On the other hand, if a pilot study is not possible and no historical data is accessible, the researcher can analyze data from the initial subjects to determine with restricted certainty whether the sample size is supposed to be modified. The diagrammatic representation of the relationship among the components is given in figure 2-1 below:

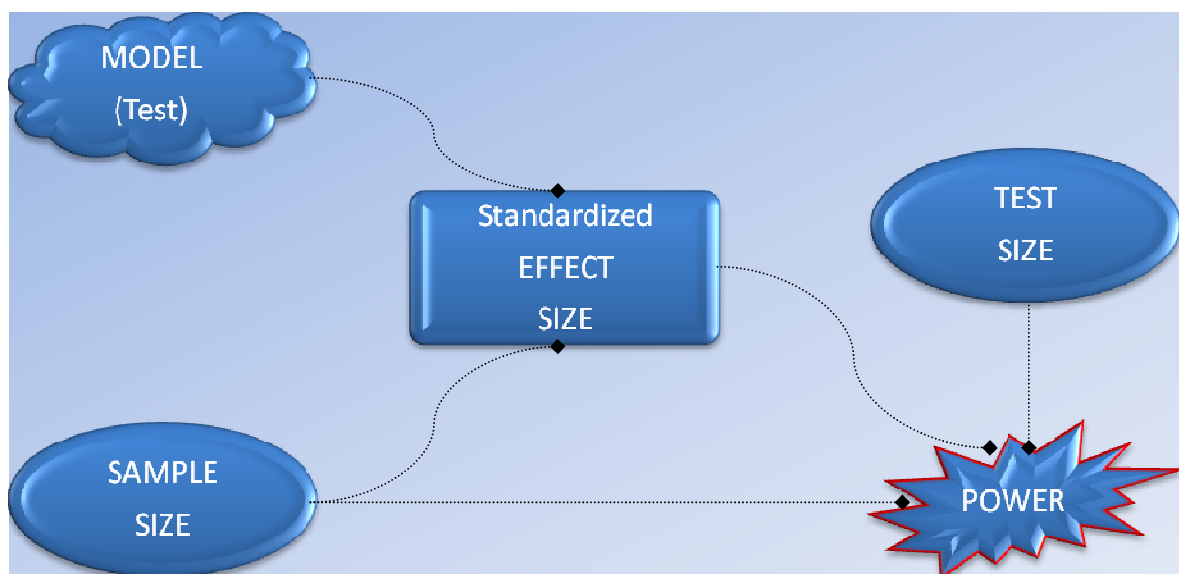


Figure 2-1 RELATIONSHIPS AMONG THE COMPONENTS OF POWER

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Model (Test): Due to variation of sensitivity of tests, different statistical tests require different methods of calculating power. If the test being used is not very sensitive, then a larger sample size is required to obtain adequate power. Also a model (or a test) dictates the formula for the standardized effect sizes (test statistics).

Standardized effect size: Effect size is a key consideration in power calculation (Houser J, 2007). Large effects can be detected with small samples, while subtle effects require large samples. Detecting rare side effects requires very large samples. If the standardized effect size is small, it is difficult to detect effects even when they exist, that is larger power is achieved by larger effect size (positive relationship).

Sample size (n): A larger sample size generally leads to a parameter with smaller variances, a larger standardized effect size and eventually a greater ability to detect a significant difference (positive relationship with power and standardized effect size).

Test size (Significance level): The lower the significance level, the lower the power hence there is a positive relationship between the two components.

2.4 OVERVIEW ON THE MINIMIZATION TECHNIQUE

2.4.1 History and Background

This method was introduced by Pocock and Simon in 1975 and they declared that it may finally be able to replace longer established procedures (Pocock SJ and Simon R, 1975). The minimization method was described separately by Taves (Taves DR, 1974) and Pocock and Simon (Pocock SJ and Simon R, 1975). Even though the term “minimization” can be applied to any of Pocock and Simon’s methods, it is most commonly used to refer to the special case described by Taves, which is less complex to use in practice. Begg and Iglewicz extended Pocock and Simon’s method by minimizing an estimate to the variance of the treatment effect (Begg CB and Iglewicz B, 1980). Begg and Iglewicz method allows chosen interactions to be incorporated. Atkinson also provided a method which uses optimum design theory, but here the probability of allocation to the underrepresented treatment responds to increasing imbalance rather than just being a random value (Atkinson AC, 1982). Smith proposed a modification of Atkinson’s method (Smith RL, 1984). Klotz’s method addresses the issue of a trade-off between

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uncertainty and imbalance which is similar to that of Pocock and Simon but is more computationally demanding and describes a function for calculating the best possible treatment randomization probabilities (Klotz JH, 1978). Titterington proposed a similar method that involves minimizing a quadratic criterion subject to a balance constraint and is said to be simpler than Klotz's method (Titterington DM, 1983). These proposed minimization methods and a variety of other allocation methods have been used in quite a number of studies.

The minimization method has been used since then and it is far from widely replacing other methods of randomization. The International Conference on Harmonization (ICH) support the use of dynamic allocation, and the CONSORT statement declares "trials that use minimization are measured methodologically equivalent to randomized trials, even when a randomization element is not included" (<http://www.consort-statement.org/statement/revisedstatement.htm>). On the other hand, when Altman and colleagues reviewed 80 randomized clinical trials from four journals in 1990, they found that only one used minimization (Scott et al. 2002). Scott et al reviewed all randomized clinical trials published in Lancet and the New England Journal of Medicine in 2001 and found that only 4% of the 150 trials used minimization (Scott et al. 2002). Scott et al did not mention the proportion of trials that they thought minimization would be appropriate for, however twenty nine percent of the trials used permuted block stratification and 13% used other stratification methods. The remaining articles did not evidently explain the alternative of allocation technique (Scott et al. 2002). The apparently minute percentage of minimization uptake in light of its public commendations may result from the analysis and practical issues. Tu et al speculate that minimization might be an additional well-liked alternative in academic world than in industry (Tu et al, 2000).

The major drawback of deterministic allocation procedures such as minimization is that in certain cases the next allocation can be predicted by means of assurance and knowledge of the characteristics of earlier patients. Therefore there is a potential for selection bias, which can have an effect on the validity of a trial's results. Even an understanding on which allocation is more likely to take place next can result in selection bias. It must be noted that the predictability issue is not just restricted to minimization. In randomized permuted block the allocation intended for the final patient in each block can also be predicted through assurance even if blocks of random length are used, and the most probable allocation can often still be guessed. Taves realized that

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the next assignment can usually be predicted if the exact system used in the minimization method is well-known (Taves DR, 1974). He showed that minimization can be considerably less predictable than restricted randomization but the subsequent allocation might still be guessed by means of knowledge of just the current group totals in nearly 70% of cases. Pocock and Simon and others have argued that the probability of assignment to the “optimal” treatment according to the minimization algorithm should be set at some value less than one to make sure that the next assignment can on no account be predicted by means of certainty (Pocock SJ and Simon R, 1975). On the other hand, they and others acknowledged that in many trials, mainly multicenter trials, it is acceptable to set this probability to one (White SJ and Freedman LS, 1978).

Additional methods have been planned that seek out a compromise between the conflicting aims of ensuring balanced groups and ensuring unpredictability of assignment. No more than one report had been identified that used simulations to investigate the effect of varying the probability of assignment to the treatment selected by the minimization algorithm. Pocock and Simon compared allocation systems where the probability of getting the optimal treatment be reduced from 1 to 0.75 (Pocock SJ and Simon R, 1975). Peto et al believed that the gains in effectiveness and balance comparative to complete randomization insignificant (Peto R et al, 1976). They also consider the use of any stratified method of randomization unnecessary as the added complexity is able to harm enrollment and adjustments for covariates can be prepared at the end of the trial. Their arguments have, nevertheless, been countered by a number of authors. Other potential drawbacks of using minimization were noted. Firstly minimization is fundamentally a deterministic scheme but statistical tests used in the analysis of the trial formulate the assumption of random allocation. Secondly, also arising from the nonrandom nature of minimization, are concerns concerning selection bias due to the fact that the next assignment might be predicted in a number of situations. Lastly, minimization can result in organizational complexity as a result of its potential to damage recruitment as well as raise expenditure.

The use of minimization can, on the other hand, also guide indirect benefits as well as increased persuasiveness and credibility by presenting data signifying that prognostic factors be closely balanced within each treatment group (Brown BW, 1978). It has furthermore been recommended that planning to use minimization is a good regulation for making trialists feel confident about

prognostic factors prior to a study and for helping guarantee loyalty to the protocol as the trial progresses (Day S, 1999). Additional benefits of the minimization technique have been anticipated, such as the ability to consist of more patient factors than for stratified randomization. This can be chiefly important in smaller trials in which quite a few factors are known to have an effect on outcome (Pocock SJ, Lagakos SW, 1982). Additionally, minimization can have power over confounding factors without the need of splitting the patient sample into too numerous strata (Kalish LA, Begg CB, 1985).

2.4.2 Practical and Theoretical Considerations in using Minimization

Taves acknowledged that the use of his technique does have implications for the analysis of the trial (Taves DR, 1974). He further suggested that modification should be made for factors used in the minimization using analysis of covariance, recognizing that minimization is not a random scheme. Many standard inferential measures necessitate that each series of treatment assignments is evenly probable. Only simple randomization has this property, on the other hand, concerns over the validity of the analysis surround not just minimization but all other allocation methods. As a result a disadvantage of adaptive methods like minimization is that the correct statistical analysis is compound and not yet obviously worked out (Halpern J and Brown BW, 1986; Lachin JM, Matts JP, Wei LJ, 1988). Quite a few authors have discussed how permutation tests can be conducted when analyzing trials where such methods have been used (Kalish LA and Begg CB, 1985),(Simon R, 1979),(Green H et al, 2001). Even though it is hypothetically achievable to carry out a suitable permutation test for minimization using simulation, this is in practice not straightforward and makes little distinction to the results obtained (Buyse M, 2000). Although Green et al. (2001) thinks that permutation tests be unnecessary provided that minimization factors be used as covariates in the analysis, they refer to a case where a U.S. regulatory organization requested that a trial that had used minimization be reanalyzed using permutation tests (Green H et al, 2001).

Pocock and Simon cite in brief the likelihood of accidental bias taking place when patients go into a trial in a nonrandom order (Pocock SJ and Simon R, 1975). Though the consequence of stratifying by a covariate and then ignoring it in the analysis may perhaps not be severe, accidental bias is able to result from using an erroneous hypothetical model for analysis. It is likely that accidental bias decreases whilst a random element is included into such a methodical

design (Simon R, 1979). Halpern and Brown have described how in the case of biased coin randomization the classical analysis will more often than not yield acceptable conclusions apart from specific conditions such as trends in outcome of low time frequency in the stratifying variables (Halpern J and Brown BW, 1986). Many authors have discussed the consequence of minimization on the nominal level of the significance test as well as on the power of the test. Forsythe and Stitt showed that if the analysis method ignores the fact that minimization has been used; this will result in p -values that are indistinct (Forsythe AB and Stitt FW, 1977). On the other hand, when analysis of covariance is used to evaluate treatments following adjusting for the upshot of the covariate, the significance level resulting from minimization is equivalent to the nominal level of the test.

Additionally, the analysis of covariance resulting from minimization is more influential than that resulting from randomization, though the differences were not great. Birkett used simulations to evaluate minimization by means of simple and stratified randomization (Kalish LA and Begg CB, 1987). Minimization resulted in conservative levels of significance using Student's t test, and even though minimization shaped improvements in power compared to stratification in opposition to chosen hypotheses, little or no increase in power has been seen except "actual" cut points were used. He suggests that the use of analysis of covariance in the analysis may additionally increase power. Kalish and Begg found that by simulating data from actual trials p -values resulting using permuted block randomization implementing Begg as well as Iglewicz's techniques were conservative but were not probable to be strictly unclear if the analysis is stratified by the covariates used as analysis prompts (Kalish LA and Begg CB, 1987).

Furthermore, the intrinsic conservativeness of exact methods due to discreteness tends to govern any extra conservativeness due to nonrandom designs. Tu et al conducted simulations using data from two actual trials (Tu D et al, 2000). They bring into being that minimization be inferior to stratified allocation in reducing alpha in addition to beta errors and be almost comparable to simple randomization in this regard. They affirm that the balance in marginal totals achieved by minimization will be adequate when the effects of prognostic factors do not interrelate. When such interactions do exist, as is frequently the case in actual trials, balance among individual strata is essential to decrease alpha errors. They believe that minimization enhances reliability by producing marginal balance, but whether it can increase accuracy depends on whether

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interactions exist between covariates. They have the same opinion that explanation should be taken of the covariates in the analysis. Senn argues that factors used in the minimization have got to also be incorporated in the analysis and that using minimization but not together with the covariates in the model is not justifiable (Senn S, 1995).

Fisher and Yates argued from a Bayesian viewpoint he argues that balancing for factors that are not incorporated in the model is worthless if not risky (Senn S, 2000). Even though Kalish and Begg states that the agreement is that factors used in the allocation process have to be accounted for in the analysis, they also admit that scientific audiences might find the results of simple, unadjusted treatment comparisons by means of demonstration of good balance of important factors extra realistic than the results of a covariate analysis (Kalish LA and Begg CB, 1985). Other authors have overlooked such abstract concerns in practice. Vaughan Reed and Wickham state that they do not regulate for covariates for the reason that the errors introduced be likely to be fewer than the errors resulting from imbalance among treatment groups (Vaughan Reed J and Wickham EA, 1988). Watson and Pearce also do not consider so as to the nonrandom allocation process invalidates the statistical assumptions to any large degree as it would still be likely for whichever individual to be allocated to any treatment (Rovers MM et al, 2000). Treasure and MacRae consider that attempts to regulate for imbalances in randomization might guide to ambiguity about the legitimacy of the conclusion (Treasure T and MacRae KD, 1998).

Even if the calculations required for assigning treatments using minimization be moderately straightforward as well as knowing how they are conducted by hand, they might exist difficult as well as unfeasible in numerous situations (Taves DR, 1974 ; Pocock SJ and Simon R , 1975),(Vaughan Reed J and Wickham EA, 1988). White and Freedman have exposed how this is capable of being cut down in practice using index cards (White SJ and Freedman LS, 1978). Despite the fact that several authors differ in that the implementation of the standard minimization technique increases the organizational burden, the use of various prognostic factors and extensions to the standard method (such as the use of weighting factors by means of diverse probabilities) put in additional difficulty. A lot of investigators have made use of computerized randomization, although the issue of computer downtime has been mentioned (Therneau TM, 1993). Additionally, a continuously updated centralized scheme is necessary since the allocation of every new patient entering the trial depends on information of prior patients entered being

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kept up to date. By means of conventional stratified randomization the whole randomization schedule can be formed and circulated to centers in advance (Kalish LA and Begg CB, 1985; Simon R, 1979). On the other hand, for multicenter trials central randomization has additional reward such as the capability to centrally regulate the trial as well as to watch alongside selection bias. Stratified minimization performed locally by every center is as well an alternative.

An additional practical thought in multicenter trials concerns precisely when patients come into view for randomization and how extended a gap linking recruitment and the need for an allocation is tolerable. The minimization may be logistically more difficult to put into practice in an emergency situation, in which patients can come in at any time as well as need instant allocation, than in situations where the allocation is non-urgent and an office hour's randomization service is adequate. It has been recommended that the use of more complex allocation methods may damage recruitment of clinicians as well as accrual of patients to the trial (Peto R et al, 1976). This is not the knowledge of Kalish and Begg, but they consider that the difficulty of the algorithm used may create practical problems for the administrators of the trial (Kalish LA and Begg CB, 1985). Programming errors are not infrequent when computerized randomization is used. As for example, one recent trial had to re-recruit over 1000 women when an error in the minimization algorithm caused severe imbalance (Lancet, 2001). This can be prevented by the routine integration of simulation exercises to make sure the minimization algorithm before recruitment commences (McPherson G and Campbell MK, Grant A, 2002).

The implementation of more compound allocation schemes such as minimization can be unreasonably expensive, even though it has been pointed out to facilitate even minute gain in effectiveness to save money, particularly for centers conducting many trials concurrently (Kalish LA and Begg CB, 1985). Hamilton demonstrated the advantage of minimization in a state where the supply of a drug at centers can be restricted (Hamilton SA, 2000). The issue of using withdrawals following randomization can also be significant (Zielhuis GA et al, 1990; Rovers MM et al, 2000; Vaughan Reed J and Wickham EA, 1988). Zielhuis et al have described such a situation when such dropouts caused an actual trial to turn out to be imbalanced whereas simulations had revealed ideal balance using minimization (Zielhuis GA et al, 1990). The most important cause for using minimization is the need to attain balanced groups by means of respect to both the numbers in each treatment arm and the uniqueness of each group.

It has been seen that the method of minimization has such a wider adoption by clinicians and investigators are so much eager to venture into having a more understanding in the use of this method. Much credibility has been given to this technique and in the light of this scope adequate literature is seen to be available for one to draw conclusive evidence and investigations regarding this new dynamic method of treatment allocation. However the next section will focus on the researches which were previously done subject to the aims of this study.

2.5 PREVIOUS RELATED RESEARCH

2.5.1 The Method of Minimization Proposed by Pocock and Simon -Properties with Regards to Balance and Inferential Validity.

This study focused on the minimization method developed by Pocock and Simon (1975), which is a somewhat controversial treatment allocation method proposed for sequential randomized trials that require balancing over several factors. The researcher pointed out that the main reason for this controversy concerns the validity of conventional analyses following minimization. Another aspect of statistical properties is power and it was not further investigated in this study. By use of simulations, the method's properties with regards to balance and inferential validity were investigated.

Results showed that minimization yields tight balance, which has also been shown in previous studies. Due to the limited number of replications used in the simulation study, the researcher found it difficult to draw extensive conclusions regarding the validity of standard inferential procedures following the use of minimization. However, nothing indicated that the standard tests used in the simulation study -ordinal logistic regression, and frequency table analysis does not have satisfactory properties. The researcher recommended that studies where minimization has been used should be analyzed using randomization tests.

2.5.2 The Method of Minimization for Allocation to Clinical Trials: a Review

The researchers defined minimization as a largely non-random method of treatment allocation for clinical trials, and conducted a systematic literature search to determine its advantages and disadvantages compared with other allocation methods. A total of articles which amount to 71 were assessed. Reviews on advantages and disadvantages of minimization as well as the comparison of minimization with other methods were carried out. It was clear that a number of

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authors have used computer simulations to prove that minimization is a better method as compared to other allocation methods such as *simple (unrestricted) randomization, restricted randomization, stratified allocation methods and other allocations*. Further reviews on the current status of minimization evidenced from published papers and empirical evidence was done. The most common design was permuted blocks within strata, minimization was considered as infrequently used and not a well-known technique.

Many authors discussed the effect of minimization on the nominal level of the significance test and on the power of the test (alpha and beta errors). Additionally, the analysis of covariance resulting from minimization was more powerful than that resulting from randomization, despite the fact that the differences were not enormous. Birkett used simulations to compare minimization with simple and stratified randomization (Birkett NJ, 1985). Minimization resulted in conservative levels of significance using Student's *t* test, and although minimization produced improvements in power compared to stratification against selected hypotheses, little or no increase in power was seen unless "actual" cut points were used. Birkett (1985) suggests that the use of analysis of covariance in the analysis may further enhance power. Tu et al. conducted simulations using data from two actual trials (Tu D *et al*, 2000). They established that minimization was inferior to stratified allocation in reducing alpha and beta errors and was almost comparable to simple randomization in this regard.

A recommendation on which allocation method to use was reviewed and it was found that few authors make unqualified recommendations as to whether minimization should be used in practice in preference to other methods. At least two articles came out wholly in favour of the minimization method, the other referring to minimization as the platinum standard if randomization is the gold standard (Vaughan Reed J and Wickham EA, 1988) (Treasure T and MacRae KD, 1998). Other authors cite minimization as the technique of choice (or one of a number of methods of choice) in smaller trials when it is desirable to attain balance in a number of prognostic factors (Simon R, 1979) (Campbell MK and McPherson G, 2001). Kernan et al. believe minimization preferable to stratification techniques when more than four such variables are used.

Despite the advantages of minimization and the recommendations by many commentators to use it, the research has showed that the use of the technique is still rarely reported in randomized

trials. This may possibly have resulted in a number of trials displaying significant treatment imbalance between groups unnecessarily. The researchers additionally urged that research into the efficiency of minimization in more complex designs is necessary. In summary, therefore, it was believed that the results of the review suggested that minimization is a highly effective method for treatment allocation, and advocated for a wider implementation of the technique within the clinical trial field.

2.5.3 Comparison of Randomization Techniques for Clinical Trials with

Data from the HOMERUS-Trial

Numerous methods of randomization are available to create comparable intervention groups in a study. W.J. Verberk et al. (2005) considered a HOMERUS-trial, where they compared the minimization procedure with a stratified and a non-stratified method of randomization in order to test which one is most suitable for use in clinical hypertension trials. The second aim of this article was to describe the baseline characteristics of the HOMERUS-trial.

The HOMERUS population consisted of 459 mild to-moderate hypertensive subjects (54% males) with a mean age of 55 years. These patients were prospectively randomized with the minimization scheme to either the office pressure (OP) group, where antihypertensive treatment was based on office blood pressure (BP) values, or to the self-pressure (SP) group, where treatment was based on self-measured BP values. Minimization was compared with two other randomization methods, which were performed post-hoc: (i) nonstratified randomization with four permuted blocks, and (ii) stratified randomization with four permuted blocks and 16 strata. Additionally, numerous factors that might influence outcome were investigated for their effect on BP by 24-h ambulatory blood pressure monitoring (ABPM). Minimization and stratified randomization methods did not lead to significant differences in 24-h ABPM values between the two treatment groups. Non-stratified randomization resulted in a significant difference in 24-h diastolic ABPM between the treatment groups. Factors that caused significant differences in 24-h ABPM values were: region, centre of patient recruitment, age, gender, microalbuminuria, left ventricular hypertrophy and obesity.

The researchers finally concluded that minimization and stratified randomization are appropriate methods for use in clinical trials. Several outcome factors must be taken into account for their

potential influence on BP levels. The author recommended that due to the large number of potential outcome factors that can influence BP levels, minimization should be the preferred method for use in clinical hypertension trials, as it has the potential to randomize more outcome factors than stratified randomization.

2.5.4 An Investigation of Minimization Criteria

Angie Wade et al (2006) developed an automated package for patient allocation which incorporated a simulation arm. They demonstrated how simulation of data can help to determine the input parameters to be used in a subsequent application of minimization. Several scenarios were simulated and within the selected scenarios, increasing the number of factors did not substantially adversely affect the extent to which the treatment groups were balanced with respect to the prognostic factors.

Weighting of the factors tended to improve the balance when factors had numerous categories with only a minor negative effect on the factors with a smaller number of categories. When interactions between factors were included as minimization factors, there was no major reduction in the balance overall. The researchers finally concluded that, with the advent of widely available computing facilities, researchers can be better equipped to implement minimization as a means of patient allocation. Simulations prior to study commencement can assist in the choice of minimization parameters and can be used to justify those selections.

2.5.4 New Algorithm for Treatment Allocation Reduced Selection Bias and Loss of Power in Small Trials

The researchers' objectives were focused on clinical trials where patients become available for treatment sequentially. Especially in trials with a small number of patients, loss of power may become an important issue, and also when treatments are not allocated equally or if prognostic factors differ between the treatment groups. They presented a new algorithm for sequential allocation of two treatments in small clinical trials, which are concerned with the reduction of both selection bias and imbalance.

With this algorithm, an element of chance is added to the treatment as allocated by minimization. The amount of chance depends on the actual amount of imbalance of treatment allocations of the

patients already enrolled. The sensitivity to imbalance may possibly be tuned. They performed trial simulations with different numbers of patients and prognostic factors, in which they quantified loss of power and selection bias.

With their method, selection bias was seen to be smaller than with minimization, and loss of power was lower than with pure randomization or treatment allocation according to a biased coin principle. The method combines the conflicting aims of reduction of bias by predictability and reduction of loss of power, as a result of imbalance. The technique might be of use in small trials.

2.5.6 Power of Minimization versus Stratification Methods (Previous Studies)

Various researchers have studied and compared stratification with minimization. Focusing on power, this section will concentrate mostly on previous researches done on power comparison for the minimization treatment allocation technique and stratification. In the light of this context, initial simulations studies comparing the power of minimization and stratification tended to use unrealistic datasets with normally distributed and independent variables. Only three recent studies have somehow shaded some light on overcoming this deficiency.

2.5.4.1 Adjustment of Treatment Effect for Covariates in Clinical Trials: Statistical Regulatory Issues

Tu et al (2000) sampled data from two datasets of actual subjects with known binary outcome and covariates. Taking sample sizes of 50, 200 and 400, they examined the type1 and type2 errors associated with the minimization technique, stratified randomization with a block size of two and simple unstratified randomization with a block size of two. With the assumption that the correct stratified analysis technique is used, the authors found that the performance of minimization largely depends on the presence or absence of covariate interactions that predict outcome. Minimization was overshadowed with stratification in datasets with interactions. In datasets without covariate interaction, minimization accounting for three or four prognostic factors was less powerful than stratified randomization for trials of size 50 and 200 but approached equality for trials of size 400. The seemingly poor performance of minimization in

one of the datasets was attributed to interactions between the covariates that are predictive of outcome.

2.5.4.2 Comparison of Stratification and Adaptive Methods for Treatment

Allocation in an Acute Stroke Clinical Trial

In contrast of the latter study, Weir and Less (2003) found advantages for minimization over stratified randomization in trials of 1000 subjects and a normally distributed outcome variable. The aim of this comparative study was to compare statistical power in stratification and adaptive methods for treatment allocation in an acute stroke clinical trial. The study was based on the following theoretical aspects, (i) Achieving balance on prognostic factors between treatment groups in a clinical trial is important to ensure that any observed treatment effect may be attributed to the treatment itself, (ii) Improving the balance on prognostic factors also potentially increases the statistical power attained in a trial, (iii) Substantial imbalances may occur by chance if simple randomization is used, (iv) Allocation of the treatment according to stratified random blocks based on clinical features is the conventional approach to obtain treatment groups that are as similar as possible.

Basing on this the researchers proposed an alternative approach known as minimization which is generally known as adaptive stratification. They assessed the feasibility of minimization in the context of a clinical trial of insulin in controlling plasma glucose level following acute stroke. Determination of suitable settings for the parameters in the adaptive stratification was done by implementation of simulation studies. The researchers further assessed; the optimal probability for allocating a patient to the preferred treatment group, the number of variables that could be incorporated in the adaptive stratification algorithm, the weighting that should be given to each variable, and whether interactions between variables should be included.

They then compared the statistical power across a range of simulated treatment effects between trials where treatments were allocated by stratified random blocks and by adaptive stratification. Finally they considered the importance of the method of analysis in realizing the gain in power which may potentially be achieved by allocating treatments using stratified random blocks or adaptive stratification.

2.5.4.3 Choosing an Optimal Treatment allocation Method in Randomized Clinical Trials (Poster)

Quinaux et al (2001) provided a comparison of stratified randomization and minimization in trials of size 400 and censored survival data sampled from real data. The simulations accounted for centre and additionally one, three and five prognostic variables. The main conclusion was that pre-stratification provided relatively little gain in power over post-stratification. In terms of the comparison between minimization and stratification, there was a little difference in power for the two randomization methods.

2.6 CONCLUSION

All aspects that govern the use, outcomes and nature of the minimization scheme have been discussed on a relatively wider perspective in this chapter. Introduced by Pocock and Simon in 1975 this method was aimed to replace other existing randomization methods. The method is seen to be usually preferred in academics than industry as mentioned by Tu et al. (2000).

Since this technique minimizes imbalances between treatment groups over important prognostic factors, many authors agreed that it yields tight balance as compared to other treatment allocation techniques. Few studies have investigated the effect of the probability of allocation $\{p_k\}$ but other investigators argued to keep it between 1 and 0.75. Though minimization has more advantages than disadvantages it has a potential of selection bias and it is advised to be implemented in small trials in which a few factors are known to have an effect on outcome.

In terms of power, quite a number of researchers have investigated the power of minimization compared to other randomization schemes using simulation studies. It has power over confounding factors without the need of splitting the individual samples into too numerous strata. Less power is noticed in datasets with interactions between covariates, having 3-4 prognostic factors and sample size of 50 and 200 but powerful at 400. Sample size was seen to be the most significant factor affecting statistical power. 80% power is considered to be the moderately acceptable level even though quite a number of investigators need much higher levels of power for a study. A few studies have focused on investigating the power of minimization and some researchers highlighted that more research needs to be done into the efficiency of minimization.

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The minimization method is seldom reported in trials and is seen to be used in small trials due to the conflicting aims of reduction of bias by predictability and reduction of loss of power as a result of imbalance. This chapter gave an insight on the vast amount of research that still needs to be done on this adaptive method in the academic world. In this context one can explore more since little has been done to investigate the statistical implications in using minimization treatment allocation technique in order to come up with decisive conclusions that can lead to a wider adoption of this method. With all this literature at hand, this study will just focus on ways to maximize power using the minimization technique as a method of treatment allocation.

CHAPTER THREE (3)

STATISTICAL METHODOLOGY AND DESIGN

3.1 INTRODUCTION

This chapter will present the statistical methods and designs used in this study and their justification. Since a simulation approach is to be implemented in this study, various forms of incorporating statistical techniques in SAS are to be described as well as the simulation of data and power calculation. The data to be simulated is categorical hence more aspects on categorical data handling will also be highlighted in this chapter.

3.2 HYPOTHESIS

The primary aim of this study is to test the null hypothesis that there is no difference in treatment effect against the alternative hypothesis that the effect of treatment 1 (new drug) is better than the effect of treatment 2 (placebo). This can be denoted as:

$$H_0 : \beta_1 - \beta_2 = 0$$

$$H_1 : \beta_1 - \beta_2 \neq 0$$

Where β_1 is the effect due to treatment 1 and β_2 is the effect due to treatment 2.

3.3 RESEARCH DESIGN

A simulation study was conducted using SAS programming language. Initially two ordinal categorical response variables having six levels each with higher levels representing better response was simulated, one for each treatment group together with three other categorical prognostic factors, where two were binary (two levels each) and one with four levels.

Dummy variables were used to distinguish different treatment groups. The probability of allocation to either treatments (P_k) was set to range from 0.1 to 1 and the minimization treatment allocation algorithm (given in the appendix B as code_3) was used to randomly assign subjects to either treatment 1 (new drug) or treatment 2 (placebo). The sample size was initially set at 50. Since the response variables were polytomous and ordinal, ordinal logistic regression using the PROC LOGISTIC procedure in SAS was used for determining the differences between the

treatment groups by taking note of the behavior of the odds ratio output and the use of the CONTRAST statement in SAS.

3.4 ANALYSIS ISSUES

Most standard tests which are used for statistical inference assume random treatment assignment. This assumption does not hold with dynamic allocation techniques; hence such tests are not necessarily valid from a statistical point of view. Permutation tests have been used to analyze data from trials which uses the minimization method (Scott N.W et al, 2002). Currently, conventional tests are being used to analyze data in most trials which uses dynamic allocation schemes. Regarding post-adjustment, the general consensus is that, if pre-adjustment methods (such as minimization) are employed, post-adjustment procedures should be used as well, by means of an analysis of variance or other methods of analysis. Post-adjustment procedures adjust imbalances in the analysis stage of the trial. Examples of such methods include, analysis of variance or covariance (when the primary outcome is quantitative), logistic regression (when the outcome is binary or polytomous), and Cox-regression (for time to event data). Any post-adjustment procedure used should be planned and stated before the trial begins. In this study the logistic regression approach was used since the outcomes were categorical. (<http://www.consort-statement.org/statement/revisedstatement.htm>.)

3.5 CATEGORICAL VARIABLES (SCALE OF MEASUREMENT)

In this study the data to be generated and used will be having measures that are categorical. Categorical data are the ones presented in tabular form, known as contingency tables. Categorical data analysis is concerned with the analysis of categorical response measures regardless of whether any accompanying explanatory variables are also categorical or continuous.

An important framework for consideration in determining the appropriate analysis of categorical variables is their scale of measurement. This section will describe the various scales of measurement that are related with categorical response variables. Categorical response variables include:

- i. Dichotomous response variables.
- ii. Ordinal response variables.

- iii. Nominal response variables.
- iv. Discrete counts.
- v. Grouped survival times.

Dichotomous responses are those that have two possible outcomes, for example yes and no. If the outcome from any clinical trial is dichotomous, then the analysis investigates the relationship between the responses and treatment groups.

When categorical responses represent more than two possible outcomes and often these possible outcomes take some inherent ordering, such response variables have an *ordinal* scale of measurement, for example low, medium and high. The order of the response levels is clear but there is no clue as to the relative distances between the levels. The outcomes can be analyzed using the proportional odds model to assess the relationship between the response variable, treatment groups and other prognostic factors. This study is concerned with this type of response variable.

One can also combine some of the levels to produce a dichotomous outcome. If there are more than two outcome categories, and there is no inherent ordering to the categories, then the resulting measurement scale is *nominal*, for example “which of the four presidential candidates did you vote for?” There is no underlying scale for such outcomes and no apparent way in which to order them. Here one can test for association in the categorical table.

Categorical response variables sometimes include *discrete counts*. Instead of falling into categories that are labeled (yes, no), the outcomes are numbers (1, 2) or (0, 1). The analysis in this case is concerned with modeling means of the responses as a function of other prognostic factors. Lastly, another type of response variable is one that represents *survival times* where tracking of the number of patients with certain outcomes over time is done.

3.6 DUMMY VARIABLES

A dummy variable is an arithmetical variable used in regression analysis to symbolize subgroups of the sample in a study. In this research, dummy variables are used to distinguish different treatment groups. In the simplest case, one would use a 0, 1 dummy variable where a patient is given a value of 0 if in the control group or 1 if in the treatment group. Dummy variables are useful because they enable the use of a single regression equation to represent multiple groups.

This means that there is no need to write out separate equation models for each subgroup. The dummy variables operate like 'switches' that turn a range of parameters on and off in an equation.

Another advantage of a 0, 1 dummy-coded variable is that even though it is a nominal-level variable one can treat it statistically like an interval-level variable. For instance, taking an average of a 0, 1 variable, this will result in having proportions of 1's in the distribution. Whenever one have a regression model with dummy variables, one can always see how the variables are being used to represent multiple subgroup equations by following the two steps described below (<http://www.socialresearchmethods.net/kb/dummyvar.php>):

- create separate equations for each subgroup by substituting the dummy values
- find the difference between groups by finding the difference between their equations

3.7 COMPARISON OF PROPORTIONS

3.7.1 Difference of Proportions (DP)

Given a response Y and a predictor X , one can compare two levels of X at a given level of Y using $DP = \pi_{j/h} - \pi_{j/i}, \forall h \neq i$ levels of X .

$$\Rightarrow -1 \leq DP \leq 1.$$

$DP = 0 \Rightarrow$ Independence if it happens for all pairs of rows h and i of X at all levels, j of the response Y . One can test the significance of DP by setting $H_0 : \pi_{j/h} = \pi_{j/i} (DP = 0)$. Suppose one have proportions 0.09 and 0.009, then $DP = 0.08$. For proportions 0.79 and 0.709, $DP = 0.08$. But DP for proportions 0.09 and 0.009 is actually more defined than that for 0.79 and 0.709. Therefore the difference of proportions is not the best measure for comparing proportions in all cases. In fact, for proportions close to 0 and 1, the DP is not a good measure; instead their ratio would be more appropriate.

3.7.2 Relative risk (RR)

The ratio of proportions, which is more preferable to the DP in some cases, is defined as:

$$RR = \frac{\pi_{j/h}}{\pi_{j/i}}, h \neq i$$

For the ratios of proportions above,

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$$RR_1 = \frac{0.09}{0.009} = 10$$

$$RR_2 = \frac{0.79}{0.709} = 1.11$$

0.09 is much larger than 0.009 than 0.79 is to 0.709. Using RR, the value of 1 implies independence of variables.

3.7.3 Odds Ratios

Suppose one has a response variable Y , the odds (chances) that the response is in the j^{th} level of Y instead of the k^{th} level, $j \neq k$, within the i^{th} level of the predictor X is:

$$\Omega_i = \frac{\pi_{j/i}}{\pi_{k/i}} = \frac{\pi_{ij}}{\pi_{ik}}, \quad j \neq k, \text{ different levels of the response.}$$

- $\Omega_i = 1 \Rightarrow$ the j^{th} and the k^{th} responses are equally likely to occur
- $\Omega_i < 1 \Rightarrow$ j^{th} response is less likely compared to the k^{th} response
- $\Omega_i > 1 \Rightarrow$ j^{th} response is more likely compared to the k^{th} response

Interpretations are based on the same level of the predictor.

- $\Omega_1 = \frac{\pi_{j/1}}{\pi_{k/1}} \Rightarrow$ odds of j vs k at 1st level of X
- $\Omega_2 = \frac{\pi_{j/2}}{\pi_{k/2}} \Rightarrow$ odds of j vs k at 2nd level of X

The Odds Ratio: $\theta = \frac{\Omega_1}{\Omega_2}$, $\theta \in [0, \infty)$, measures the likelihood of a predictor Y between X levels.

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

To test the significance of the measure, we use the following hypothesis:

Reject H_0 if $1 \notin CI$

$$OR = RR \left(\frac{1 - \pi_{1/2}}{1 - \pi_{1/1}} \right), \text{ In general, the } OR = \theta_{ij} \text{ for } I * J \text{ table is given by } \theta_{ij} = \frac{\pi_{ij} \pi_{(i+1)(j+1)}}{\pi_{i(j+1)} \pi_{(i+1)j}}$$

$$\text{For } I * J = 3 * 2, \quad \theta_{11} = \frac{\pi_{11} \pi_{22}}{\pi_{12} \pi_{21}}, \quad \theta_{21} = \frac{\pi_{21} \pi_{32}}{\pi_{22} \pi_{31}}, \quad \theta_{12} = \frac{\pi_{12} \pi_{23}}{\pi_{13} \pi_{22}}$$

3.8 LOGISTIC REGRESSION: Polytomous (Multinomial) and Ordinal Logistic Models

Logistic regression was implemented as a procedure to cater for the polytomous, ordinal nature of the response variables. It is part of a category of statistical models called generalized linear models. This extensive class of models consists of ordinary regression and ANOVA, as well as multivariate statistics such as ANCOVA and loglinear regression. The LOGISTIC and GENMOD procedures are used in SAS system to fit logistic regression models by specifying the response variable and the explanatory variables in a MODEL statement and it fits the model via maximum likelihood estimation.

Logistic regression allows one to predict a discrete outcome, such as group membership, from a set of variables that may be continuous, discrete, dichotomous, or a mixture of any of these. In general, the dependent or response variable is dichotomous, such as presence/absence or success/failure. Discriminant analysis is as well used to foretell group membership with only two groups. On the other hand, discriminant analysis can only be used with continuous independent variables. Thus, in instances where the independent variables are categorical, or a mixture of continuous and categorical, logistic regression is preferred.

3.8.1 Model Fitting

The dependent variable in logistic regression is usually dichotomous, that is, the dependent variable can take the value 1 with a probability of success p , or the value 0 with probability of failure $1 - p$. This type of variable is called a Bernoulli or better known as a binary variable. Although not as common and not discussed, applications of logistic regression have also been extended to cases where the dependent variable is of more than two cases, known as multinomial or polytomous, (Tabachnick and Fidell, 1996) used the term polychotomous.

As mentioned before, the independent or predictor variables in logistic regression can take any form. That is to say, logistic regression makes no assumption about the distribution of the independent variables. They do not have to be normally distributed, linearly related or of equal variance within each group. The relationship between the predictor and response variables is not a linear function in logistic regression, instead, the logistic regression function which is used, is the logit transformation of θ :

$$\theta = \frac{e^{(\alpha + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_i x_i)}}{1 + e^{(\alpha + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_i x_i)}}$$

Where α is the constant of the equation and, β is the coefficient of the predictor variables. An alternative form of the logistic regression equation is:

$$\log it [\theta(x)] = \log \left[\frac{\theta(x)}{1 - \theta(x)} \right] = (\alpha + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_i x_i)$$

The goal of logistic regression is to correctly predict the category of outcome for individual cases using the most parsimonious model. To achieve this objective, a model is formed that includes all predictor variables that are helpful in predicting the response variable. Quite a lot of different options are available during model formation. Variables can be entered into the model in the order specified by the researcher or logistic regression can test the fit of the model once each coefficient is added or deleted, called stepwise regression.

Stepwise regression is used in the exploratory phase of research but it is not recommended for theory testing (Menard and Scott, 1995). Theory testing is the testing of a priori theories or hypotheses of the associations among variables. Exploratory testing makes no a-priori assumptions concerning the associations between the variables, thus the objective is to determine relationships. Backward stepwise regression appears to be the most preferred method of exploratory analyses, where the analysis begins with a full or saturated model and variables are eliminated from the model in an iterative process. The fit of the model is tested after the removal of each variable to make sure that the model still sufficiently fits the data. After no more variables can be eliminated from the model, the analysis has been accomplished.

There are two main uses of logistic regression. The first is the prediction of group membership. Since logistic regression calculates the probability of success over the probability of failure, the results of the analysis are in the form of an odds ratio. For example, logistic regression is often used in epidemiological studies where the result of the analysis is the probability of developing the disease under study after controlling for other associated risks. Logistic regression as well provides information of the associations and strengths among the variables. Logistic regression consists of several types of regression models which include binary logistic regression, ordinal logistic regression, polytomous logistic regression and many others. The next section will discuss two of these regression models which are ordinal and polytomous since they were used in this study.

3.8.2 Ordinal Response: Proportional Odds Model

The proportional odds model extends logistic regression to hold with an ordinal response variable. If the response variable y is ordinal, the categories can be ordered in a natural way such as health status 'good/moderate/bad'. The polytomous logistic regression model can be applied but does not make use of the information about the ordering and use of cumulative probabilities, cumulative odds and cumulative logits. Considering $k + 1$ ordered categories, these quantities are defined by

$$P(Y \leq i) = p_1 + \dots + p_i$$

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$$odds(Y \leq i) = \frac{P(Y \leq i)}{1 - P(Y \leq i)} = \frac{p_1 + \dots + p_i}{p_{i+1} + \dots + p_{k+1}}$$

$$\log it(Y \leq i) = \ln \left(\frac{P(Y \leq i)}{1 - P(Y \leq i)} \right), i = 1, \dots, k$$

The cumulative logistic model for ordinal response data is given by;

$$\log it(Y \leq i) = \alpha_i + \beta_{i1}X_1 + \dots + \beta_{im}X_m, i = 1, \dots, k$$

Like the polytomous logistic regression model, we have k model equations and one coefficient β_{ij} for each category/covariate combination. Hence, the general cumulative logistic regression model contains a large number of parameters. However, in some cases a more parsimonious model is possible. It follows that the cumulative odds are given by:

$$odds(Y \leq i) = \exp(\alpha_i) + \exp(\beta_{i1}X_1 + \dots + \beta_{im}X_m), i = 1, \dots, k$$

This means that the k odds for each cut-off category i differ only with regard to the intercepts α_i in other words, the odds are proportional. Hence, McCullagh P, (1980) used the term proportional odds model. The relatively stringent proportional odds assumption may be especially valid in cases where the ordinal response y is related to an underlying latent continuous variable (McCullagh P, 1980). However, categories assessed by an observer are another important type of ordinal variables. Such variables frequently occur in biomedical research. Anderson JA, (1984) pointed out that for assessed ordinal response variables are proportional odds model which are not flexible enough to cover the range of problems. He proposed a general class of models for ordinal data called ‘stereotype ordered regression models’ which include the proportional odds model as a special case. The proportional odds model is now the most commonly used logistic regression model for ordinal response, for two reasons. Firstly, it has the convenient feature that the effect of a covariate on y can be quantified by one regression coefficient, and hence the calculation of one common odds ratio is possible; therefore, the presentation of results is short and simple. Secondly, standard statistical software with

additional features such as stepwise variable selection procedures is now available for calculations.

3.8.3 Polytomous Response: Nested Dichotomies

If the response variable y is discrete with more than two categories, for example y = marital status defined in 3 categories 'married, divorced, separated or widowed and single', then the standard binary logistic regression model is not applicable. One possible way to handle such situations is to split the categorical response y in several ways, for example y_1 ='married yes/no', y_2 ='single yes/no', and to apply binary logistic regression to each dichotomous variable. However this will result in several different analyses for only one categorical response. A more structured approach is to formulate one model for the categorical response by means of generalized logits. Suppose that y has $k+1$ categories and the probability for category i is given by $P(y=i) = p_i$ for $i=1, \dots, k+1$, then the k generalized logits are given by;

$$\log it(Y=i) = \ln \left(\frac{p_i}{1 - (p_1 + \dots + p_k)} \right) = \ln \left(\frac{p_i}{p_{k+1}} \right), i=1, \dots, k$$

This means that the generalized logits relate the probability p_i for the categories $i=1, \dots, k$ the reference category $k+1$. For m covariates the general polytomous logistic regression model becomes:

$$\log it(Y=i) = \alpha_i + \beta_{i1}X_1 + \dots + \beta_{im}X_m, i=1, \dots, k$$

Note that the polytomous logistic model is given by k equations if y has $k+1$ categories and that we have one logistic coefficient B_{ij} for each category/covariate combination. Hence, it is not possible to summarize the effect of a covariate on the response y by a single measure such as one odds ratio. Although the polytomous model offers the advantage of simultaneously testing the effect of a covariate on all response categories, polytomous logistic regression generates a cumbersome amount of statistical information which is difficult for physicians to understand. For

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example given a polytomous response with, say, three categories, we construct our model as follows:

➤ Let π_{i1} : the probability that response = 1 for subject i

π_{i2} : the probability that response = 2 for subject i

π_{i3} : the probability that response = 3 for subject i

For subject i and response choice j , let X_i be a column vector of the explanatory variables and β_j' be a row vector of coefficients for category j . The model is

$$\ln \left[\frac{\pi_{ij}}{\pi_{iJ}} \right] = \beta_j' X_i, j = 1, \dots, (J-1).$$

Each category is compared with the highest category $J = 3$, known as the reference category. The above equations can be solved to yield:

$$\pi_{ij} = \frac{\exp(\beta_j' X_i)}{1 + \sum_{j=1}^{J-1} \exp(\beta_j' X_i)}, j = 1, \dots, (J-1).$$

The proportional odds model is attractive if the response is ordinal, and the proportional odds assumption also holds. However, if the response is purely nominal (for example, vote Tory, vote Liberal, vote Reform, vote NDP), or if the proportional odds assumption is untenable, one particularly simple strategy is to fit separate models to a set of $m - 1$ dichotomies derived from the polytomous response.

- Each dichotomy can be fit using the familiar binary-response logistic model, and,
- the $m - 1$ models will be statistically independent (so that likelihood-ratio G^2 statistics will be additive) if the dichotomies are chosen as nested dichotomies.

Nested dichotomies: These are successive binary partitions of the response categories into nested sets. As for example, the response categories {1, 2, 3, 4} could be divided first as {1, 2} versus {3, 4}. Then these two dichotomies might be divided as {1} versus {2}, and {3} versus {4}. On the other hand, these response categories might be divided as {1} vs. {2, 3, 4}, then {2} versus {3, 4}, and lastly {3} versus {4}.

3.9 DATA SIMULATION

3.9.1 Simulation options

From previous studies by Angie Wade et al. (2006) it was estimated that 200 simulations would allow quantification of the 95th percentile of the distribution to within ± 0.2 standard deviations of that distribution with 95% confidence. Increasing the number of simulations to 2500 or 5000 would increase this precision substantially to ± 0.06 and 0.04 respectively. Further doubling of the number of simulations to 10000 would only further increase precision by less than 0.01 standard deviations. Angie Wade et al. (2006) finally concluded that 5000 simulations would be adequate for a comparison of minimization criteria. For further accuracy of results in this study, 10000 simulations were performed using a SAS program.

3.9.2 Generation of Variables

To randomly generate the study population, a simulation study was conducted using SAS. The program was implemented and developed from the ideas of Pocock and Simon. The simulated trial consisted of initial sample size of 50 patients having three categorical prognostic factors profactor_1, profactor_2 and profactor_3, where profactor_1 and profactor_2 were binary factors and profactor_3 having four levels. The response variables trt1_placebo and trt2_drug are ordinal and having six levels with higher levels representing better response (that is 3 to 5). The generation of these subjects, prognostic factors and response variables was done using the SAS codes provided in appendix B. The simulation trial was meant to initially distribute the covariates as shown in table 3-1 below; the output is provided in the appendix C:

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Table 3-1

PROGNOSTIC FACTOR	FACTOR LEVEL	# OF PATIENTS	PERCENTAGE
profactor_1	1	32	64
	2	18	36
profactor_2	1	27	54
	2	23	46
profactor_3	1	12	24
	2	11	22
	3	18	36
	4	9	18

3.9.3 Creating Dummy Variables

Dummy variables were defined to distinguish different treatment groups. In this case 0 and 1 were used as dummy variables, where a patient is given a value of 0 if in the placebo group and a value of 1 if in the treatment group (code provided in appendix B).

3.9.4 Allocation of Treatments

PROC IML was used to generate the algorithm for minimization allocation technique. It is a matrix-based programming language within the SAS statistical package. It contains numerous commands for performing a variety of common matrix operations. A total of 10000 replications were used in allocating patients to the two treatment groups. The minimization algorithm used in this study took into account the technique described by Pocock and Simon which is not an algorithm, but a methodology with recommended options for possible algorithms based on the minimization technique. The technique used in this study described three steps for the minimization.

- Determining the amount of variation. The function D - which measures the “amount of variation” at each level of each factor, was measured by the range method (difference between the highest and lowest value).
- Measuring the total imbalance for each treatment. The function G_k - which measures the “total amount of imbalance” in treatment numbers which would exist at all factor levels of the new patient if treatment k were assigned to that patient was used. G_k was

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measured by the sum of marginal imbalances, d_i . That is, let N_{rik} be the number of patients allocated to treatment k for factor level r of prognostic factor i . When there are two treatments, treatment 1 and treatment 2, the amount of imbalance for one factor level was measured as $|N_{ri1} - N_{ri2}|$. The overall amount of imbalance was measured as the summation of all $|N_{ri1} - N_{ri2}|$. (see Code 3-1 below)

SAS Code 3-1

```
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;
```

- iii. The code above was also used to assign an allocation probability to the ranked candidate treatments. The probability of assignment of each treatment in the list of treatments ranked on their value of G_k , denoted by $\{P_k\}$ was set to range from 0.1 to 1. For such $\{P_k\}$, the randomization method used a bias probability of allocating the treatments which minimizes the imbalance. In this study this method first checked to verify if there is a difference in lack of balance for each of the treatment assignments. If there is no difference, treatment allocation was random, that is, $\{P_k\}$ was set to range from 0.1 to 1. SAS provides several functions to work as random number generators, in this case

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RANUNI was used to generate random numbers between 0 and 1 which have a uniform distribution.

3.9.5 Generating the Dataset

For generating the dataset, arrays were used to merge code_1 which consisted of prognostic factors and response variables to A which consisted of just treatment groups. If the value in column {i} = 0 for dataset A then that particular subject will be assigned a response value corresponding to trt1_placebo in code_1, else a response value corresponding to trt2_drug code_1 will be assigned to that particular subject. This was achieved by the code 3-2 below:

SAS Code 3-2

```
DATA dataset_1;
MERGE code_1 A;
ARRAY col{10000} col1-col10000;
ARRAY response{10000} response1-response10000;
DO i=1 to 10000;
IF col{i}=0 THEN response{i}=trt1_placebo;
ELSE
IF col{i}=1 THEN response{i}=trt2_drug;
END;
RUN;
```

3.9.6 Investigating Balance of Treatment Groups

It is of interest to investigate the effect of varying parameters within the minimization algorithm on treatment balance. Macro 'balla', available in appendix B was used to test whether the two treatment groups are equally allocated or not by estimating the total number of subjects allocated to each treatment group.

A total of 10000 simulations were executed for each scenario and PROC MEANS was used to calculate the mean balance between the two treatment groups. The mean balance, the standard deviation together with the maximum and minimum values were observed and used to see the resulting imbalances which occurred for each particular simulation. Results were recorded and

they are available in appendix A. The next section will discuss and describe how power was calculated.

3.10 POWER CALCULATION

3.10.1 Background

Simulation has turned out to be a well known component of contemporary statistical study. In elements of Computational Statistics (2002) James Gentle reports that approximately half of the articles that are appearing in the Journal of the American Statistical Association incorporated simulation studies as part of the reported research (Gentle, 2002). Simulation can be used for a variety of purposes and a recent book by Fan and colleagues describes numerous simulation applications that can be implemented in the SAS system (Fan, Felsevalyi, Sivo et al., 2003).

A general and moderately simple application is the use of simulation for determining the power of a statistical test. Statistical power analysis characterizes the capability of a study to detect a significant effect size, for example, the difference among two population means. It also determines the sample size that is essential to provide a preferred power for an effect of scientific importance. Suitable planning reduces the possibility of conducting a study that will not create constructive results and determines the most responsive design for the resources on hand. Power analysis is now essential to the health and behavioral sciences, and its use is progressively growing wherever experimental studies are performed.

Quite a lot of power formulas are available for logistic regressions models. One formulated by Hsieh and colleagues is chiefly remarkable (Hsieh, Bloch, and Larsen, 1998). It is used in the PASS software and it has an extraordinary modification to the formula that adjusts the sample size for the impact of covariates. In this case, ρ is the multiple correlation coefficient among the main predictor variable and additional covariates. Hsieh and colleagues adjust the sample size according to the following formula:

$$N_{adjusted} = \frac{N_{unadjusted}}{1 - \rho^2}$$

Hosmer and Lemeshow proposed that this modification may be too conservative (Hosmer and Lemeshow, 2000). Another way to avoid this argument is to use a simulation approach to determine the power of logistic regression models. One can use either the p-values for a Wald statistic, a score statistic, or a likelihood ratio statistic in order to decide whether the chief predictor of a given model qualifies as statistically important according to some particular level of significance. This approach of using p-values is the one which was used in this study but in addition to the probabilities of the Chi-Square and the odds ratios confidence intervals. The section below will highlight how power was simulated using the logistic regression models.

3.10.2 Power Calculation Using the Logistic Regression Approach

The primary interest is to determine whether the effect in treatment 1 is different from the effect in treatment 2. Since the response variables were having more than two levels, PROC LOGISTIC was used to fit the proportional odds model. Furthermore the responses were ordinal; hence this fulfilled the assumption of the PROC LOGISTIC. The code below requests that PROC LOGISTIC fit a proportional odds model;

SAS Code 3-3

```
%DO i=1 %TO 10000;

proc logistic data=dataset_1;

TITLE2 'Logistic Regression Model with Polytomous Ordinal Response Variable';

class profactor_1 profactor_2 profactor_3 col&i;

model response&i=profactor_1 profactor_2 profactor_3
col&i/*selection=forward*/;
```

Macros were used (codes available in appendix B) to execute these commands for all the simulated datasets. The macros were aimed to fit the logistic models for all the simulated response variables against respective prognostic factors and treatment groups. PROC LOGISTIC produces various output including, parameter estimates, their standard errors, and statistics to assess model fit. In addition, it also provides several model selection methods which puts predicted values and other statistics into output data sets, and includes a number of options for controlling the model fitting process.

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The CONTRAST statement was used to compare the difference in effect in treatment 1 versus treatment 2. With satisfactory goodness of fit, it is appropriate to examine the odds ratio output as well as the Wald Chi-Square and probabilities of Chi-Square from the contrast estimate output. These parameters were taken from each set of output by the following SAS codes;

SAS Code 3-4

```
DATA powerr1(keep=lowercl uppercl);  
SET testlogreg;  
/*removing other variables(taking odds confidence limits for treatments)*/  
IF variable in (' profactor_1',' profactor_1',' profactor_1') or  
effect in ('profactor_1 1 vs 2','profactor_2 1 vs 2','profactor_3 1 vs 4',  
'profactor_3 2 vs 4','profactor_3 3 vs 4') THEN DELETE;  
RUN;
```

SAS Code 3-5

```
DATA power1(keep=probchisq contrast waldchisq);  
SET testllogreg;/*importing the contrastestimate table from the above macro*/  
RUN;
```

Code 3-4 was used to take the parameters lowercl – which is the lower confidence limit of the predicted odds ratios and uppercl-which is the upper limit of the odds ratio estimates from the odds ratio output and code 3-5 was used to take the parameters probchisq (probabilities of chi-square), contrast (variable names of the two treatment groups-reference point) and waldchisq (Wald Chi-Square) from the contrast estimate output. Power was calculated by taking the number of times the null hypothesis was rejected over the total number of replications made.

$$\text{Power} = \frac{\text{Number of times } H_0 \text{ rejected}}{\text{Total number of replications}}$$

The hypothesis was tested using three different tests/statistics.

i. Probabilities of Chi-Square / p-values

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These were obtained from the contrast estimate output. Thus the CONTRAST statement computed the test statistic for $H_o : \beta_1 = \beta_2$, that is the hypothesis of equal slope for the two treatment groups. For each probability of chi-square value of the resultant contrast between treatment 1 and treatment 2 the null hypothesis was rejected when probability of chi-square $< \alpha(0.05)$ where α is the significance level

ii. Wald Chi-square tests

A Wald test is a statistic that takes the form of the squared value ratio for the estimate to its standard error. It follows an approximate chi-square distribution when the sample size is sufficiently large. The Wald chi-square value was used to test for the hypothesis $H_o : \beta_1 = \beta_2$ by rejecting the null hypothesis when Wald chi-square > 3.8415 at 5% significance level.

Under the null hypothesis Wald Chi-Square follows a Chi-Square distribution with 1 degree of freedom. The hypothesis of equal effect rates for groups β_1 and β_2 is rejected if Wald Chi-Square $> \chi^2_{1,\alpha}$, where $\chi^2_{1,\alpha}$ is the 100 α percentage point of the Chi-Square distribution with 1 degree of freedom. In this case $\chi^2_{1,\alpha} = \chi^2_{1,0.05} = 3.8415$ which is obtainable from the χ^2 statistical tables.

iii. 95% Wald Confidence limits (Odds Ratios)

The hypothesis of interest was;

$$H_o : OR = 1 \text{ versus } H_1 : OR \neq 1$$

that is rejected when $1 \notin OR$

The hypothesis was rejected when the value 1 was not an element of the confidence interval meaning that there is a significant difference between treatment 1 and treatment 2.

PROC MEANS was used to generate the needed power for the three different tests by taking the number of times the null hypothesis was rejected in each test and dividing it by the total number of replications.

3.11 CONCLUSION

This chapter has presented the different statistical tests and methodologies that were implemented in the data analysis. Previous literature has mentioned quite a number of procedures that were used in this study, the analysis of the results and their reporting will be presented in the next chapter. It also highlighted how the obtained results shall be interpreted comparative to the research objectives.

CHAPTER FOUR (4)

DATA ANALYSIS AND RESULTS

4.1 INTRODUCTION

This chapter recapitulates the methods and applications mentioned in the previous chapter. It forms the linchpin of the entire research work with detailed discussions of the reporting and interpretation of the outcomes. Computations of the various statistics produced in the outputs are illustrated in order to give a clear explanation of these statistics and their use in interpretation of the outcomes. With this at hand, ordinal logistic regression output variables shall be discussed as well as graphical presentation of findings will be done in order to have a clear and detailed reporting of results. The next section will discuss how each simulated dataset was analyzed.

4.2 INTERPRETATION OF PROC LOGISTIC OUTPUT

The LOGISTIC procedure is used to model cumulative logits by performing ordinal logistic regression using the proportional odds model. It fits the proportional odds model whenever the response variable has more than two levels. Thus, there is a need to ensure that one indeed, has an ordinal response variable otherwise PROC LOGISTIC will assume that one does. It is of great importance to ensure that the ordering of the response variables is correct when one is using ordinal data. The procedure still performs an analysis if the variables are incorrectly ordered, but the results will be erroneous. It is somehow a burden for the user to specify the correct order and then to check the results.

The “Response Profile” table in Output 4-1 shows that the responses are ordered correctly in terms of increasing response. For these data, ordering is not a problem since the total row counts are reasonably large.

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SAS Output 4-1

Response Profile		
Ordered Value	response1	Total Frequency
1	0	10
2	1	18
3	2	13
4	3	17
5	4	13
6	5	29

Probabilities modeled are cumulated over the lower Ordered Values.

The procedure next prints the “Class Level Information” table, which shows how parameterization takes in the form of incremental effects for the three prognostic factors and the treatment groups.

SAS Output 4-2

Class Level Information				
Class	Value	Design Variables		
profactor_1	1	1		
	2	-1		
profactor_2	1	1		
	2	-1		
profactor_3	1	1	0	0
	2	0	1	0
	3	0	0	1
	4	-1	-1	-1

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Class Level Information				
Class	Value	Design Variables		
COL1	0	1		
	1	-1		

For the appropriateness of the proportional odds assumption the PROC LOGISTIC prints out a table for the proportional odds test. The performed test is a score that determines whether, if one fits a different set of explanatory parameters β_k (in this case the parameters are profactor_1, profactor_2, profactor_3 and col&i, where col&i is the composition of the two treatment groups) for each logit function. The sets of these parameters are considered to be equal; hence the assumed model is as follows;

$$\log it(\theta_{hik}) = \alpha_k + X'_{hi}\beta_k$$

The tested hypothesis is that there is a common parameter vector β instead of distinct β_k , that is;

$$H_0 : \beta_k = \beta \text{ for all } k$$

Thus if the null hypothesis is rejected, then it implies that the assumption of proportional odds is also rejected, and consider a different approach, such as modeling generalized logits. If the null hypothesis is not rejected, then the test supports the assumption of the proportional odds. This test has $t \times (r-2)$ degrees of freedom, where t are the parameters to be compared for the t explanatory variables across $(r-2)$ logits and in this case $t=4$ and r is the number of response levels which in this case is 6.

Sample size requirements for this test are relatively demanding, thus approximately five observations are required at each outcome of each main effect. This condition was met since the initial sample size was far greater than five. Caution must be practiced in the interpretation of any resulting significance in samples that are small since they may make the statistic large, and

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in this regard non-significant results are always informative. When the proportionality assumption does not hold for all explanatory variables, but having proportionality for some then the partial proportional odds model is an alternative model that can be fit. However when there appears that there is no proportionality, then the most appropriate alternative approach may be to treat the data as nominal and fit a generalized linear model. The output below displays this score test;

SAS Output 4-3

Score Test for the Proportional Odds Assumption		
Chi-Square	DF	Pr > ChiSq
119.1398	24	<.0001

Chi-Square takes the value 119.1398 with 24 degrees of freedom. This shows that it is clearly significant, and so the assumptions of proportional odds hold for these data.

The tests for assessing model fit through explanatory capability are also supportive in relation to the logistic mode. The likelihood ratio test has a value of 43.9676 with 6 degrees of freedom and the score has a value of 35.9457 with 6 degrees of freedom as reflected in the output below.

SAS Output 4-4

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	43.9676	6	<.0001
Score	35.9457	6	<.0001
Wald	36.9890	6	<.0001

Output 4-5 below contains the “Type 3 Analysis of Effects” table profactor_1, profactor_3 together with the treatment groups represented by ‘col47’ are all influential effects. For those

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effects with 1 degree of freedom each, the tests are the same as printed for the parameter estimates listed in the output below (**Analysis of Maximum Likelihood Estimates**).

SAS Output 4-5

Type 3 Analysis of Effects			
Effect	DF	Wald Chi-Square	Pr > ChiSq
profactor_1	1	11.3773	0.0007
profactor_2	1	0.0778	0.7803
profactor_3	3	26.0993	<.0001
COL47	1	4.4974	0.0339

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	0	1	-2.9959	0.3913	58.6301	<.0001
Intercept	1	1	-1.9191	0.3175	36.5368	<.0001
Intercept	2	1	-1.2424	0.2877	18.6467	<.0001
Intercept	3	1	-0.1168	0.2636	0.1965	0.6576
Intercept	4	1	0.7726	0.2747	7.9114	0.0049
profactor_1	1	1	0.7390	0.2191	11.3773	0.0007
profactor_2	1	1	-0.0522	0.1872	0.0778	0.7803
profactor_3	1	1	1.6846	0.3393	24.6492	<.0001
profactor_3	2	1	0.1780	0.3224	0.3046	0.5810
profactor_3	3	1	-0.2875	0.3195	0.8100	0.3681
COL47	0	1	0.4008	0.1890	4.4974	0.0339

Another output of importance is the odds ratio estimates. Model fitting is most easily interpreted by considering the odds ratios corresponding to the parameters, for the output below:

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- 0.4008 in the output above is the increment to log odds of a better effect for treatment 1; the odds ratio 2.229 in the output below indicates that treatment 1 is 2.229 times more likely to achieve a better outcome than the placebo group.
- 1.6846 in the output above is the increment to log odds for level 1 and 4 of profactor_3; the odds ratio 26.042 in the output below indicates that level 1 of profactor_3 is nearly 26 times more likely to achieve a better outcome than level 4.

SAS Output 4-6

Odds Ratio Estimates			
Effect	Point Estimate	95% Wald Confidence Limits	
profactor_1 1 vs 2	4.384	1.857	10.348
profactor_2 1 vs 2	0.901	0.432	1.877
profactor_3 1 vs 4	26.042	6.553	103.499
profactor_3 2 vs 4	5.772	1.521	21.900
profactor_3 3 vs 4	3.624	0.980	13.400
COL47 0 vs 1	2.229	1.063	4.676

The CONTRAST statement provides a mechanism for obtaining modified hypothesis tests. It is similar to the CONTRAST statement in PROC GLM and PROC CATMOD, depending on the coding systems used with any classification variables concerned. The CONTRAST statement enables you to specify a matrix, \mathbf{L} , for testing the hypothesis $L\beta = 0$. Optionally, the CONTRAST statement enables one to estimate each row, $l'_j\beta$, of $L\beta$ and test the hypothesis $l'_j\beta = 0$. The computed statistics are based on the asymptotic chi-square distribution of the Wald statistic. Output 4-7 below shows that treatment 1 and treatment 2 are different because Wald chi-square $(4.3152) > 3.8415$ and to further support this Probability of chi-square $(0.0378) < \alpha(0.05)$ where α is the significance level. This actually tells us that there is a treatment effect that is significant between these two treatments and in this case the null hypothesis is being rejected in favor of the alternative hypothesis.

SAS Output 4-7

Contrast Test Results			
Contrast	DF	Wald Chi-Square	Pr > ChiSq
col&i =1 vs col&i =0	1	4.3152	0.0378

Contrast Rows Estimation and Testing Results									
Contrast	Type	Row	Estimate	Standard Error	Alpha	Confidence Limits		Wald Chi-Square	Pr > ChiSq
col&i =1 vs col&i =0	EXP	1	1.4715	0.2737	0.05	1.022 1	2.118 7	4.3152	0.0378

4.3 POWER ANALYSIS

In the previous section we have seen how each and every simulated dataset was analyzed using the logistic regression approach. This section will present and report on the outcomes of power analysis and all the findings drawn from this analysis. The analysis is comprised of a graphical exploratory presentation using the STATISTICA package accompanied by a confirmatory significance test.

The parameters that were tested include the sample size, the probability of allocation and the probability of allocation given that the treatment groups are equally balanced. For each parameter under investigation, the effect on treatment balance for each respective parameter was also investigated to ensure that any effect on power is due to the parameter itself not imbalances within the treatment groups. The simulated results are presented in Appendix A.

4.3.1 Sample Size Considerations

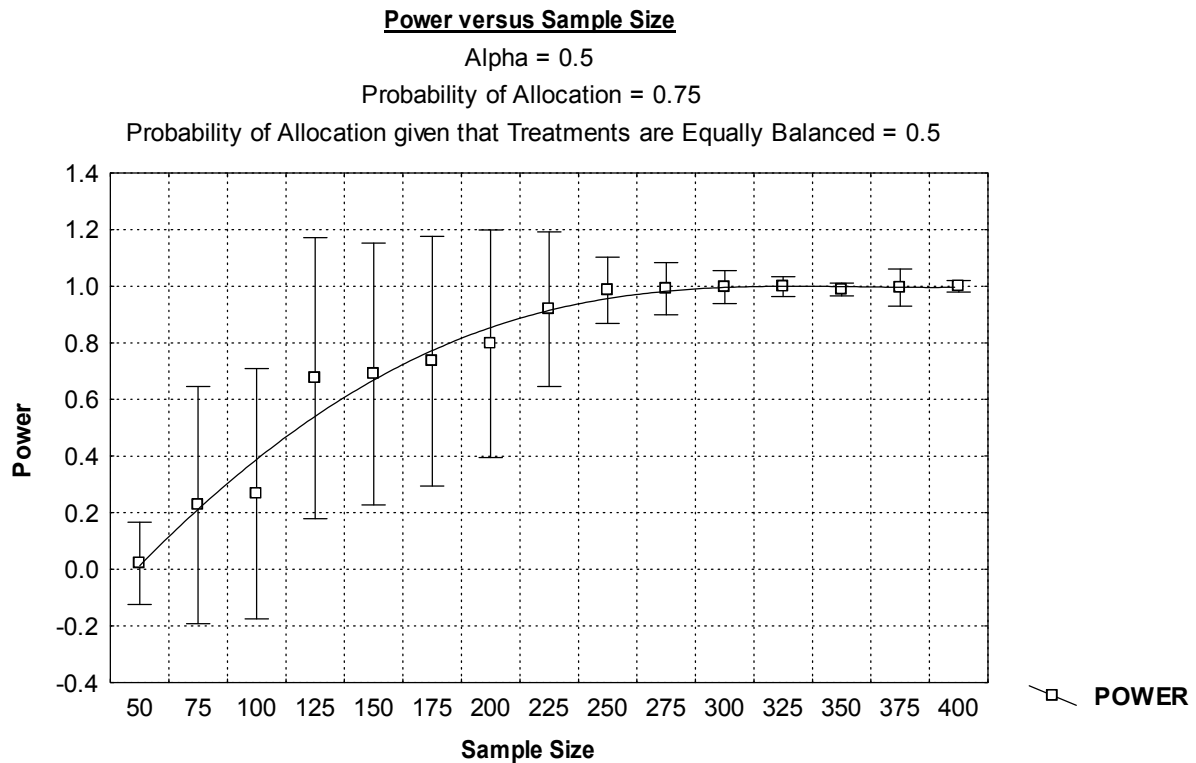


FIGURE 4-1 : POWER VS SAMPLE SIZE

There was an increase in power as the sample size increased. A steep increase in power was seen from a sample size of 50 to 225, and then as the sample size further increased from 250 to 400 there was no difference in power. From the plots above it can be seen that maximum power is attained with a minimum sample size of 300.

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In terms of treatment balance, sample size has no effect to the method of minimization. The minimization technique achieves tight balance within treatment groups despite any change in sample size. This result can be justified by the graph below where the graph is constant at all simulations.

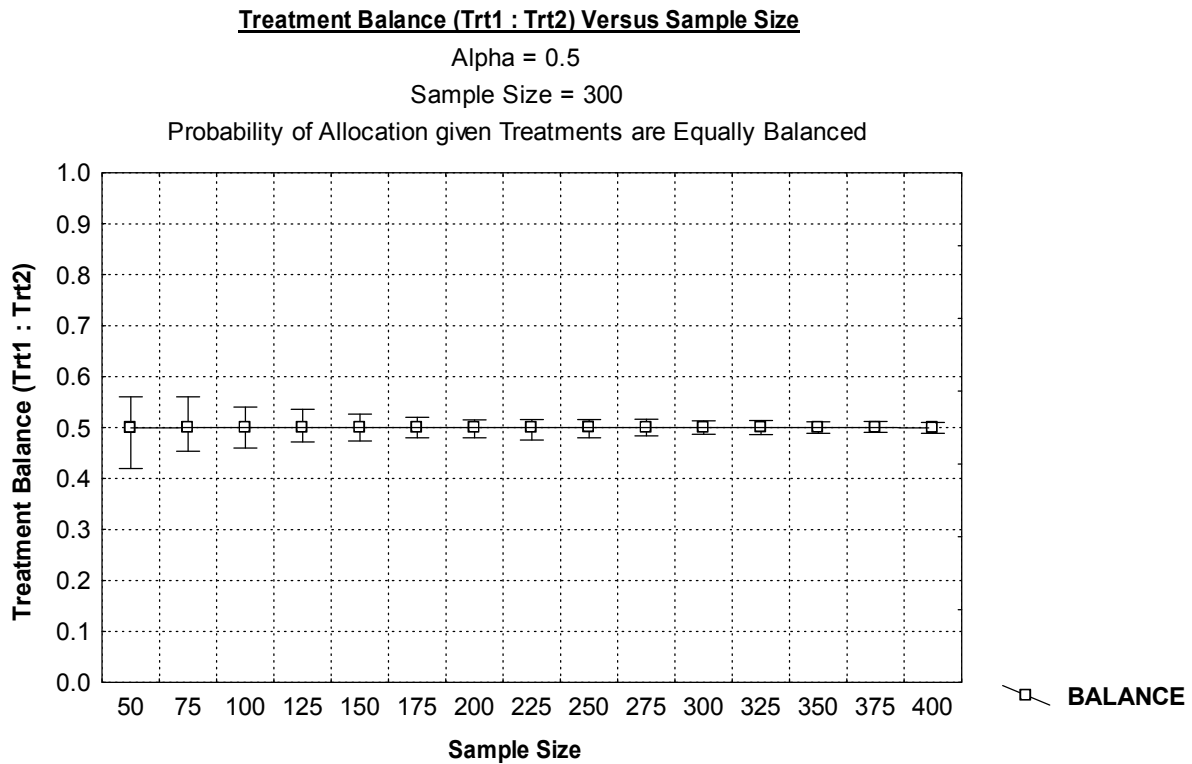


FIGURE 4-2 : TREATMENT BALANCE VS SAMPLE SIZE

4.3.2 Probability of Allocation $\{P_k\}$

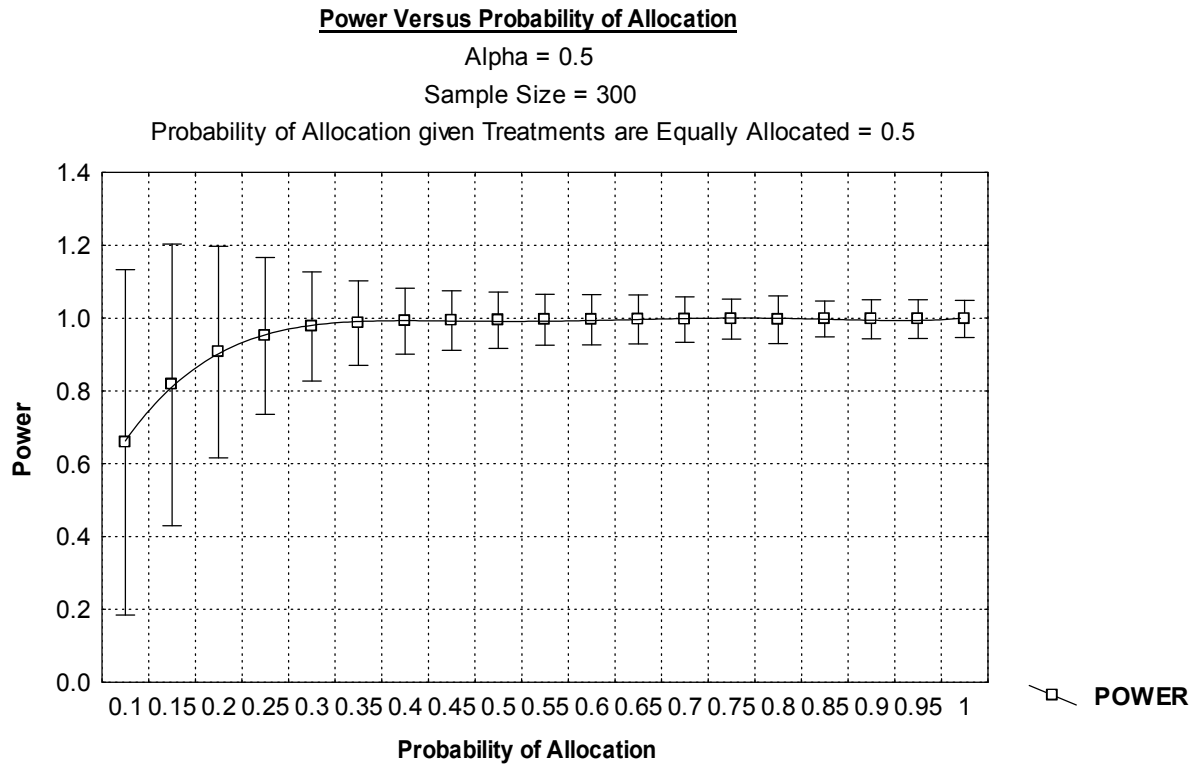


FIGURE 4-3 : POWER VS PROBABILITY OF ALLOCATION

The probability of allocation $\{P_k\}$ has small effect on power as compared to sample size. As $\{P_k\}$ increased, there was a gradual increase in power from 0.1 to 0.25. The plots above show that maximum power can be attained by a value of $\{P_k\}$ between 0.35 and 1 with a sample size of 300 at 5% significance level. $\{P_k\}$ has an effect on the balancing of treatment groups (graph given below in figure 4-4). Imbalances can be noticed for all values of $\{P_k\}$ between 0.1 and 0.5.

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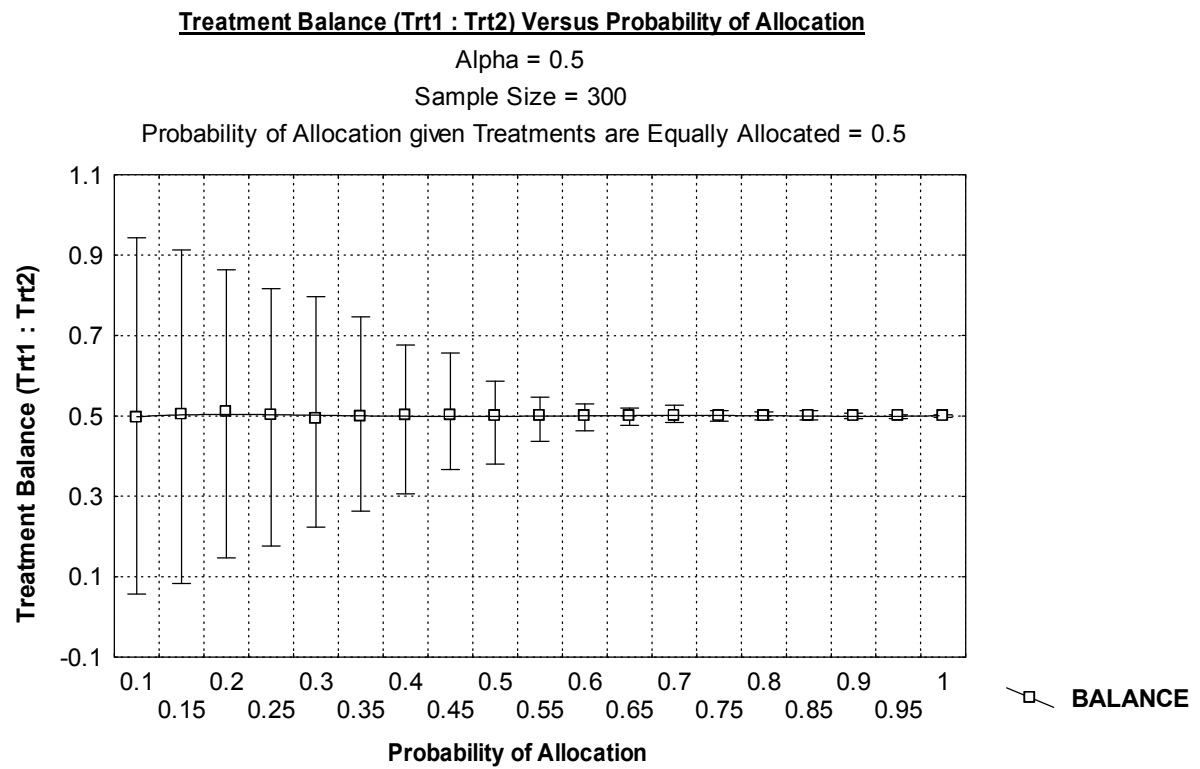


FIGURE 4-4 : TREATMENT BALANCE VS SAMPLE SIZE

4.3.3 Probability of Allocation when Treatment Groups are equally Balanced $\{P_k\}$

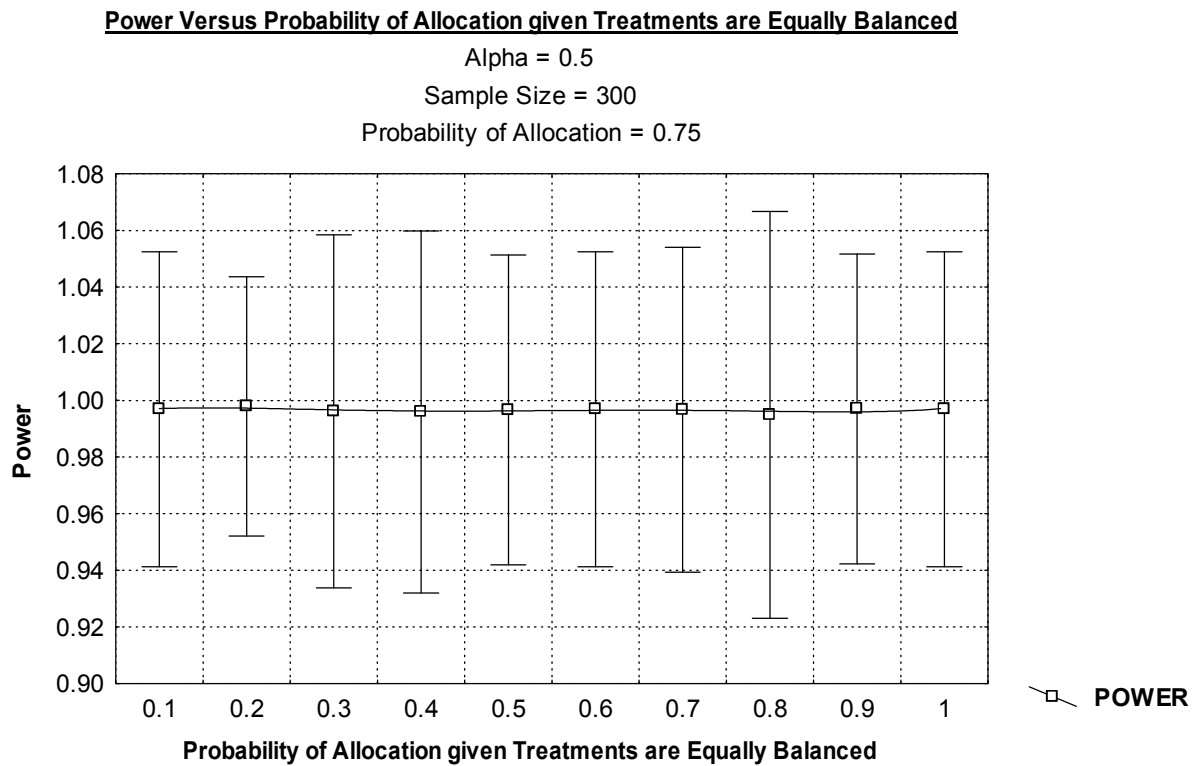


FIGURE 4-5 : POWER VS PROBABILITY OF ALLOCATION WHEN TREATMENT GROUPS ARE EQUALLY BALANCED

The value of $\{P_k\}$ (the probability of treatment allocation) for treatment allocation when treatment 1 and treatment 2 are equally allocated has no effect on power for $\{P_k\}$ greater than 0.1. Hence all values of $\{P_k\}$ give the same power for a sample size of 300. Below is the plot of probability of allocation when treatment groups are equally balanced versus treatment balance, and the same results as those for sample size and power are noticed. The graph is constant at the value 0.5 for treatment balance.

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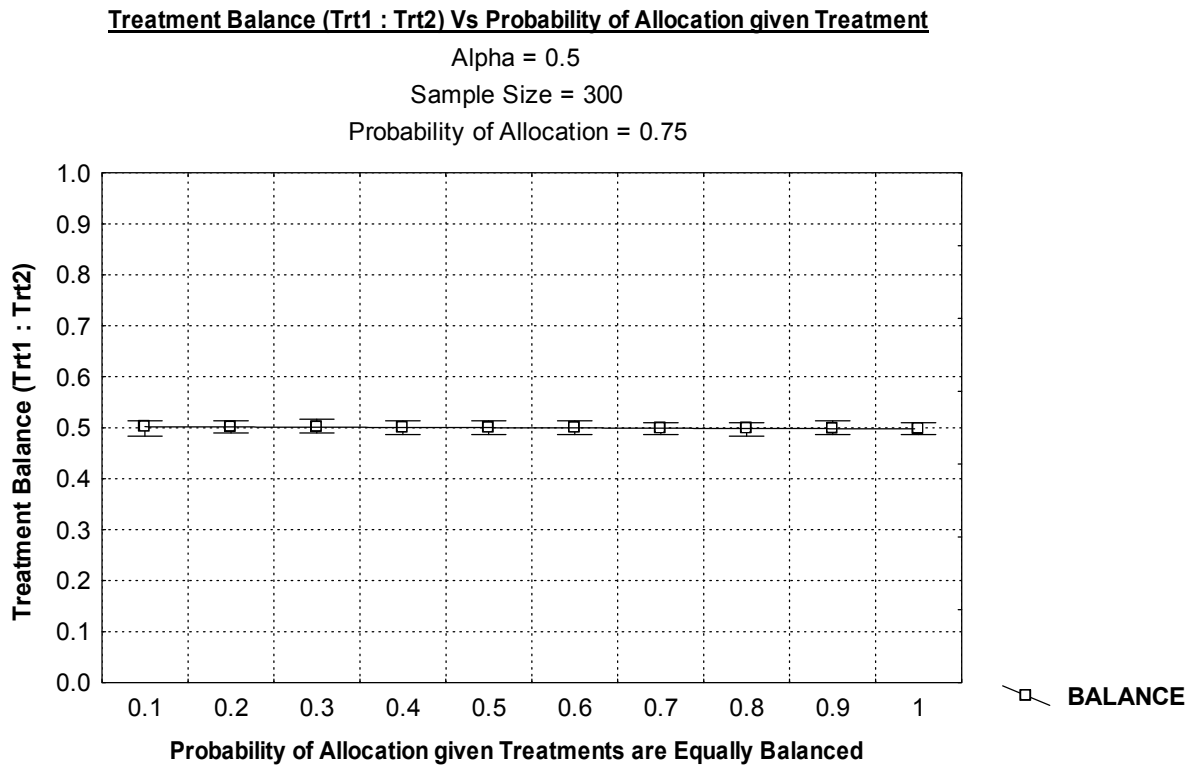


FIGURE 4-6 : TREATMENT BALANCE VS PROBABILITY OF ALLOCATION WHEN TREATMENT GROUPS ARE EQUALLY BALANCED

The primary aim of this study was to test the null hypothesis that there is no difference in treatment effect against the alternative hypothesis that the effect of treatment 1 (new drug) is better than the effect of treatment 2 (placebo). Three tests which include odds ratios, wald chi-square and chi-square probabilities were used to test for this hypothesis and the results are summarized in table 4-1 below.

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Table 4-1

POWER VS VARIABLE	INVESTIGATE D VARIABLE	TESTS		
		P-VALUES	ODD RATIOS	WALD-CHISQUARE
Power vs Sample Size	Sample Size $p_k = 0.75$ $p_{kr} = 0.5$	<i>rejected for</i> $n \geq 200$	<i>rejected for</i> $n \geq 125$	<i>rejected for</i> $n \geq 125$
Power vs Probability of Allocation	Probability of Allocation $n=300$ $p_{kr} = 0.5$	<i>rejected for</i> $p \geq 0.15$	<i>rejected for</i> $\forall p_k$	<i>rejected for</i> $\forall p_k$
Power vs Probability of Allocation/ Trts are Balanced	Probability of Allocation/ Trts are Balanced $n=300$ $p_k = 0.5$	<i>rejected for</i> $\forall p_{kr}$	<i>rejected for</i> $\forall p_{kr}$	<i>rejected for</i> $\forall p_{kr}$

To establish if there was a significant difference between the independent variables, normal probability plots were used to see whether the data were normal or not. The data satisfy the assumption of normality hence ANOVA was appropriate to use for testing difference of means. From the results of the ANOVA tests, of the three variables that were under investigation, sample size and probability of allocation had the most significant effect on power whilst the probability of allocation when treatment groups are equally balanced had no significant effect. Turkey's studentised range (HSD) test was further used to determine were the difference in

power existed in all the three variables. Sample size and probability of allocation showed some significant difference in power whilst the probability of allocation when treatment groups are equally balanced had no significant difference meaning that the powers were significantly equal for all the simulated scenarios.

4.4 CONCLUSION

This chapter has in brief presented all the analysis and reporting of results. Sample size is seen to have a greater significant effect on power, which is also the case in previous studies. The minimization technique achieves tight balance within treatment groups regardless of any change in sample size. The probability of allocation $\{P_k\}$ has a small effect on power as compared to sample size. Imbalances can be noticed for all values of $\{P_k\}$ between 0.1 and 0.5, hence $\{P_k\}$ has significant effect on balance. The value of $\{P_k\}$ for treatment allocation when treatment 1 and treatment 2 are equally allocated has no significant effect to power and balance. The next chapter will give the overall conclusion and discussions for this study mainly basing on the outcomes given in this chapter.

CHAPTER FIVE (5)

CONCLUSIONS AND DISCUSSIONS

5.1 INTRODUCTION

The main aim of this study was to investigate the maximization of power in clinical trials where minimization randomization technique is used as a method of treatment allocation. This chapter sums up the work undertaken in this study and articulates the extent to which the research meets the research goals. And finally, it makes suggestions for future research work. The conclusions drawn from this study are presented below.

5.2 DISCUSSIONS AND CONCLUSIONS

In this article, some common treatment trial scenarios were simulated and compared the results in terms of the distribution of balance between treatment groups and power. Whilst only a few selections of potential scenarios can be shown, this study has illustrated how prior investigation helps quantify the sensitivity of minimization to the choice of input parameters such as the probability of allocation and sample size. Other parameters such as, weighting of prognostic factors, number and type of factors was not investigated in this study.

The use of minimization as a means of treatment allocation is seen to be increasing. Decisions must to be made concerning the precise form of implementation. Choice of input parameters may influence the extent to which the process is successful in ensuring equality of patients between treatment groups and the resultant power for that particular trial. Improving the balance on treatment groups also potentially increases the statistical power attained in a trial. This study has shown how a simple minimization algorithm can be used to allow researchers to investigate the effects of varying the input parameters prior to study commencement. The advent of the wide availability of computing technology makes minimization a more realistic choice for many researchers, therefore it is vital that they make use of the technique most effectively.

This article has reviewed specific aspects on power of minimization techniques and also a review of literature in the use and applications regarding the minimization technique. The results from the reviewed papers provided that there is fairly conclusive evidence on the advantages and disadvantages of the minimization method within randomized controlled trials. From the reviews it can be concluded that minimization is an effective method for allocating participants to treatment groups within a randomized controlled trial. In the majority of cases, minimization has

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been shown to outperform simple randomization (when $\{p_k\}$ is set at 0.5) in achieving balanced treatment groups. This greater performance is particularly noticeable when trial sample sizes are small.

A number of trials have displayed significant treatment imbalance between groups unnecessarily. Since this technique minimizes imbalances between treatment groups many authors agreed that it yields tight balance as compared to other treatment allocation techniques. This was also noticed in this study, the technique exhibited tight balance between treatment groups for most of the simulated scenarios. Few studies have investigated the effect of the probability of allocation $\{p_k\}$ and furthermore other investigators argued to keep it between 1 and 0.75, this study also agrees to the issue of keeping $\{p_k\}$ between 1 and 0.75 but considering other statistical properties such as bias it is rather wiser to set $\{p_k\}$ at 0.75.

Though the statistical analysis is complex and not yet clearly worked out (Halpern J and Brown BW, 1986; Lachin JM et al, 1988), in this regard this study has used the necessary assumptions and computations concerning the analysis of categorical data from clinical trials which use minimization as a method of treatment allocation. Nevertheless minimization has a potential of selection bias and it is advised to be implemented in small trials in which a few factors are known to have an effect on outcome, hence according to the simulated scenarios the most advisable sample size should be 300 in order to achieve maximum power levels. However a sample size of 200 can also be considered as adequate since one can achieve 80% power, which is considered to be the moderately acceptable level even though quite a number of investigators need much higher levels of power for a study.

Quite a number of researchers have investigated the power of minimization compared to other randomization schemes using simulation studies. Sample size was seen to be the most significant factor affecting statistical power. This was also the case in this study where a significant increase in power was noticed when the sample size was increased as compared to other parameters. Though few studies have focused on investigating the power of minimization and some researchers highlighted that more research needs to be done into the efficiency of minimization, this study is somehow a stepping-stone in venturing more into this latter aspect. In summary, therefore, from the results presented in the previous chapter and the evidence from previous

researches, it is safe to suggest that minimization is a highly effective method for treatment allocation, and can advocate wider adoption of the technique within the clinical trial field.

5.3 RECOMMENDATIONS

Not many authors made unqualified recommendations as to whether minimization must be used in practice in preference to other techniques. Although considering minimization as valid and as efficient as any other allocation method, this study recommends the use of minimization because of its high ability to balance between treatment groups and availability of software that can handle the computations. Lachin et al. recommend complete, permuted block or urn randomization over covariate adaptive methods like minimization because of the implications for the analysis and because allocation sequences cannot be pre-generated (Lachin et al., 1988)

This paper has investigated some of the issues that arise in the practical application of the minimization allocation technique, which has risen sharply in recent years. Simulations have been performed using the most common scenario of two treatment groups. Datasets have been simulated under different minimization criteria to show how outcomes may vary as the input parameters are changed and suggest that this sort of approach should become standard practice in most clinical trials. Therefore it can be recommended that:

- i. Simulations can be usefully employed prior to study commencement to determine the best parameters to use.
- ii. Different statistics for calculating the desired power should be used to avoid taking too big or too small a sample to achieve the desired power.
- iii. A balanced allocation of subjects between treatment groups should be used to obtain the highest power for a test. If unequal allocation has to be carried out, it has to be taken into consideration when carrying out sample size considerations.
- iv. It is important that researchers justify the choices they make with regards to the procedure for allocating patients in a real life situation.
- v. Various tests should be used in the analysis of results so as to get correct and reliable report of the outcomes.

5.4 FUTURE AREAS OF RESEARCH

In some cases it might be of greater interest to incorporate existing data for investigations using the minimization method. This study has aimed at showing how a relatively simple minimization algorithm, generated using the SAS package, can be used to assist clinicians when they have decided to utilize minimization and need to determine the optimal parameters to achieve reliable results in clinical trials. The package simplifies the feasibility of the procedure and hence may make this the preferred allocation technique even when there are a small number of prognostic factors that have to be taken into account.

Vast amount of research still needs to be done on this adaptive method in the industrial world, recent guidelines for the pharmaceutical industry recommend that a random element should be incorporated into deterministic dynamic allocation procedures like minimization. In choosing the allocation method consideration should also be given to the organizational setup involved, for example the availability of computing facilities and whether trials require enrolment outside business hours. Further research into the efficiency of minimization in more complex designs such as in cluster randomized trials and cross-over trials, has also been suggested since research on minimization has been somewhat limited to simpler designs (Scott N.W et al, 2002). Pocock SJ believes that having a relatively straightforward randomization scheme may be more important than attempting theoretical optimality with more complex designs (Pocock SJ, 1975).

A potential area for further research in minimization is in methods for analyzing data, as this is currently debated but in this study ordinal logistic regression was used since the data was categorical. McEntegart also notes that the effect of sample size on the choice of minimization functions has not been studied (McEntegart DJ, 2003). Additional education for clinicians and investigators on technicalities concerning the minimization treatment allocation method and instructions on its smooth integration into clinical studies might be advantageous.

5.5 CONCLUDING REMARKS

The primary aim for using minimization is the desire to achieve balanced groups with respect to both the members in each treatment arm and the characteristics of each group. This study has shown how variation of parameters using simulations can be a useful tool in assessing balance and statistical power characteristics of the minimization allocation algorithm. Maximum power can be achieved with a sample of size 300 but a relatively small sample size of 200 can be adequate to have the minimum required power of 80%. The probability of allocation should be fixed at 0.75 and set to 0.5 if the treatment groups are equally allocated. The number of individuals in each treatment arm is almost the same using these parameters, thus minimization yields tight balance, which is always the case in previous studies.

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APPENDIX A

$\{p_k\}$ = probability of allocation to treatment k (trt1_placebo or trt2_drug)

$\{p_{kr}\}$ = probability of allocation to treatment k given trt1_placebo = trt2_drug

α = significance level

LOWERCL = mean for the wald odds ratio lower confidence limits

UPPERCL = mean for the wald odds ratio upper confidence limits

PROCHISQ = p-value for the contrastestimates output (mean)

WALDCHISQ = mean for the wald chisq values

POWER_PC = generated power using PROCHISQ

POWER_WC = generated power using WALDCHISQ

POWER_CL = generated power using wald odds ratio confidence limits

MINIMUM = minimum value/percentage for treatment balance

MAXIMUM = maximum value/percentage for treatment balance

MEAN = overall measure of balance between treatment groups(mean of min and max)

STDV = standard deviation of mean

Power and Sample size

$$\{p_k\} = 0.75, \{p_{kr}\} = 0.5, \alpha = 0.05$$

SAMPLE SIZE	LOWERCL	UPPERCL	PROCHISQ	WALDCHISQ	POWER_PC	POWER_WC	POWER_CL	STDV
50	0.4582315	4.2084516	0.5419675	0.7573912	0.0216000	0.0216000	0.0213000	0.1453807
	0.4557906	4.1912045	0.5465505	0.7304822	0.0210000	0.0210000	0.0210000	0.1413713
	0.4556066	4.1865055	0.5464727	0.7333802	0.0204000	0.0204000	0.0204000	0.1416158
	0.4564008	4.1955163	0.5454048	0.7372095	0.0207000	0.0207000	0.0207000	0.1423737
	0.4541034	4.1684066	0.5483638	0.7276468	0.0211000	0.0211000	0.0211000	0.1403494
75	0.8265419	4.8560352	0.2424451	2.5063071	0.2273000	0.2273000	0.2273000	0.4191089
	0.8293328	4.8782894	0.2356100	2.5223161	0.2245000	0.2245000	0.2245000	0.4172735
	0.8269196	4.8621079	0.2390416	2.5053674	0.2238000	0.2238000	0.2238000	0.4168028
	0.8286351	4.8727259	0.2373188	2.5183139	0.2252000	0.2252000	0.2252000	0.4177324
	0.8228665	4.8365229	0.2435153	2.4752843	0.2210000	0.2210000	0.2210000	0.4149412
100	0.8824023	3.8485921	0.2092848	2.8318108	0.2669000	0.2669000	0.2669000	0.4423618
	0.8871219	3.8715640	0.2050804	2.8717982	0.2781000	0.2781000	0.2781000	0.4480853

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	0.8861303	3.8659906	0.2052745	2.8606489	0.2756000	0.2756000	0.2756000	0.4468279
	0.8859420	3.8658210	0.2061315	2.8618014	0.2753000	0.2753000	0.2753000	0.4466544
	0.8860727	3.8640664	0.2038096	2.8541147	0.2752000	0.2752000	0.2752000	0.4466373
125	1.1303697	3.7161979	0.0620331	5.6975847	0.6754000	0.6754000	0.6754000	0.4959890
	1.0945630	3.9004530	0.0779850	5.1394910	0.6088000	0.6088000	0.6088000	0.4948470
	1.0766591	3.9925808	0.0859613	4.8604441	0.5756000	0.5756000	0.5756000	0.4942763
	1.1017240	3.8636020	0.0747950	5.2511100	0.6221000	0.6221000	0.6221000	0.4950760
	1.1010080	3.8672870	0.0751140	5.2399480	0.6208000	0.6208000	0.6208000	0.4950530
150	1.1351826	3.7336743	0.0601300	5.7609414	0.6901000	0.6901000	0.6901000	0.4624753
	1.1349843	3.7326656	0.0604825	5.7594275	0.6794000	0.6794000	0.6794000	0.4667306
	1.1350670	3.7330860	0.0603360	5.7600580	0.6838000	0.6838000	0.6838000	0.4649580
	1.1350339	3.7329178	0.0603944	5.7598060	0.6820000	0.6820000	0.6820000	0.4656668
	1.1350280	3.7328900	0.0604040	5.7597640	0.6817000	0.6817000	0.6817000	0.4657850
175	1.1592502	3.4951390	0.0505382	6.3000910	0.7358000	0.7358000	0.7358000	0.4409283
	1.1406328	3.6000947	0.0668521	5.9514886	0.6750000	0.6750000	0.6750000	0.4684217
	1.1495012	3.6296282	0.0645716	6.0724937	0.6926000	0.6926000	0.6926000	0.4614627
	1.1638398	3.5098815	0.0596164	6.3673092	0.7337000	0.7337000	0.7337000	0.4420430
	1.1640100	3.5104280	0.0505827	6.3697997	0.7336000	0.7336000	0.7336000	0.4420840
200	1.1891946	3.3329314	0.0363778	6.9833354	0.7972000	0.7972000	0.7972000	0.4021049
	1.1912855	3.3394409	0.0370123	7.0213981	0.7994000	0.7994000	0.7994000	0.4004693
	1.1904140	3.3367290	0.0367480	7.0055390	0.7984000	0.7984000	0.7984000	0.4011510
	1.1907628	3.3378135	0.0368537	7.0118824	0.7988000	0.7988000	0.7988000	0.4008782
	1.1908210	3.3379940	0.0368710	7.0129400	0.7989000	0.7989000	0.7989000	0.4008330
225	1.2983138	3.4520970	0.0159462	9.1265338	0.9188000	0.9188000	0.9188000	0.2731557
	1.3003260	3.4575170	0.0158670	9.1640080	0.9185000	0.9185000	0.9185000	0.2735840
	1.2993591	3.4545342	0.0163280	9.1493618	0.9156000	0.9156000	0.9156000	0.2780007
	1.3033053	3.4659203	0.0153257	9.2161288	0.9211000	0.9211000	0.9211000	0.2695961
	1.3009970	3.4593240	0.0158400	9.1765000	0.9184000	0.9184000	0.9184000	0.2737270
250	1.4303236	3.6219274	0.0046391	12.0825793	0.9861000	0.9861000	0.9861000	0.1170819
	1.4315897	3.6256746	0.0050102	12.1096850	0.9823000	0.9823000	0.9823000	0.1318653

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	1.4310620	3.6241130	0.0048560	12.0983900	0.9838000	0.9838000	0.9838000	0.1257060
	1.4312732	3.6247378	0.0049174	12.1029086	0.9852000	0.9852000	0.9852000	0.1281695
	1.4313080	3.6248420	0.0049280	12.1036600	0.9831000	0.9831000	0.9831000	0.1285800
275	1.4795417	3.5898864	0.0027602	13.6711128	0.9915000	0.9915000	0.9915000	0.0918074
	1.4744463	3.5769816	0.0028682	13.5619222	0.9924000	0.9924000	0.9924000	0.0868504
	1.4765690	3.5823590	0.0028230	13.6074200	0.9920000	0.9920000	0.9920000	0.0889160
	1.4757202	3.5802078	0.0028412	13.5892199	0.9921000	0.9921000	0.9921000	0.0880897
	1.4755790	3.5798490	0.0028440	13.5861900	0.9922000	0.9922000	0.9922000	0.0879520
300	1.5168079	3.5413727	0.0015955	15.1354860	0.9970000	0.9970000	0.9970000	0.0582132
	1.5235493	3.5583772	0.0016033	15.2858446	0.9971000	0.9971000	0.9971000	0.0537762
	1.5207400	3.5512920	0.0016000	15.2232000	0.9970000	0.9970000	0.9970000	0.0556250
	1.5218640	3.5541261	0.0016014	15.2482550	0.9974000	0.9974000	0.9974000	0.0548855
	1.5220510	3.5545980	0.0016020	15.2524300	0.9972000	0.9972000	0.9972000	0.0547620
325	1.5487364	3.4982424	0.000964152	16.5505251	0.9988000	0.9988000	0.9988000	0.0346220
	1.5504540	3.5023740	0.0010240	16.5924800	0.9982000	0.9982000	0.9982000	0.0419820
	1.5500653	3.5013184	0.0010790	16.5846547	0.9976000	0.9976000	0.9976000	0.0489334
	1.5525599	3.5075611	0.0010298	16.6422562	0.9982000	0.9982000	0.9982000	0.0423903
	1.5505680	3.5026490	0.0010280	16.5952800	0.9981000	0.9981000	0.9981000	0.0424730
350	1.5270686	3.3407412	0.000928443	16.6934704	0.9883000	0.9883000	0.9883000	0.0458734
	1.5339733	3.3562378	0.0011065	16.8796134	0.9978000	0.9978000	0.9978000	0.0459476
	1.5240665	3.3339543	0.0010891	16.6174056	0.9973000	0.9973000	0.9973000	0.0518939
	1.5283690	3.3436440	0.0010410	16.7301600	0.9944000	0.9944000	0.9944000	0.0479050
	1.5284560	3.3438380	0.0010490	16.7326100	0.9949000	0.9949000	0.9949000	0.0480400
375	1.4451616	3.0669420	0.0017938	15.1325775	0.9957000	0.9957000	0.9957000	0.0654365
	1.4433320	3.0631024	0.0018139	15.0807698	0.9958000	0.9958000	0.9958000	0.0669343
	1.4440940	3.0647020	0.0018060	15.1023600	0.9955000	0.9955000	0.9955000	0.0663100
	1.4437894	3.0640623	0.0018089	15.0937217	0.9965000	0.9965000	0.9965000	0.0665599
	1.4440230	3.0645530	0.0018060	15.1003400	0.9972000	0.9972000	0.9972000	0.0663680
400	1.5180968	3.1465356	0.0006282	17.7510756	0.9996000	0.9996000	0.9996000	0.0199970
	1.5173303	3.1449191	0.000667485	17.7287560	0.9990000	0.9990000	0.9990000	0.0264496

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1.5164408	3.1430027	0.000629508	17.7017764	0.9991000	0.9991000	0.9991000	0.0299880
1.5175219	3.1453232	0.0006577	17.7343359	0.9997000	0.9997000	0.9997000	0.0248365
1.5171600	3.1445480	0.0006500	17.7234600	0.9992000	0.9992000	0.9992000	0.0266480

Power and Probability of Allocation to Treatment k when Treatments are Balanced

$$\{p_k\} = 0.75, \alpha = 0.05, n = 300$$

$\{P_{kr}\}$	LOWERCL	UPPERCL	PROCHISQ	WALDCHISQ	POWER_PC	POWER_WC	POWER_CL
0.1	1.5166434	3.5399216	0.0016448	15.1366884	0.9969000	0.9969000	0.9969000
	1.5182351	3.5449791	0.0016677	15.1678728	0.9962000	0.9962000	0.9962000
	1.5192986	3.5451616	0.0016639	15.1691253	0.9968000	0.9968000	0.9968000
	1.5182169	3.5449464	0.0016745	15.1674553	0.9961000	0.9961000	0.9961000
	1.5178973	3.5441608	0.0016853	15.1603195	0.9960000	0.9960000	0.9960000
0.2	1.5181888	3.5440452	0.0014754	15.1684759	0.9979000	0.9979000	0.9979000
	1.5165606	3.5433215	0.0016533	15.1523484	0.9964000	0.9964000	0.9964000
	1.5165811	3.5433408	0.0016432	15.1528554	0.9966000	0.9966000	0.9966000
	1.5178717	3.5440190	0.0016484	15.1597296	0.9965000	0.9965000	0.9965000
	1.5157823	3.5438091	0.0016443	15.1575681	0.9964000	0.9964000	0.9964000
0.3	1.5157880	3.5384479	0.0017540	15.1156921	0.9961000	0.9961000	0.9961000
	1.5182434	3.5449376	0.0016371	15.1679931	0.9964000	0.9964000	0.9964000
	1.5172473	3.5449357	0.0016410	15.1682947	0.9969000	0.9969000	0.9969000
	1.5194358	3.5453934	0.0016328	15.1723809	0.9964000	0.9964000	0.9964000
	1.5187574	3.5463149	0.0016369	15.1791138	0.9963000	0.9963000	0.9963000
0.4	1.5174106	3.5426059	0.0017166	15.1515860	0.9959000	0.9959000	0.9959000
	1.5179544	3.5442581	0.0016736	15.1617017	0.9962000	0.9962000	0.9962000
	1.5196935	3.5436882	0.0016610	15.1552407	0.9963000	0.9963000	0.9963000
	1.5168515	3.5440521	0.0016551	15.1588804	0.9971000	0.9971000	0.9971000
	1.5179228	3.5442456	0.0016608	15.1604894	0.9962000	0.9962000	0.9962000
0.5	1.5181834	3.5449649	0.0015795	15.1634864	0.9966000	0.9966000	0.9966000

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	1.5178371	3.5439786	0.0016451	15.1586486	0.9970000	0.9970000	0.9970000
	1.5197972	3.5438820	0.0016456	15.1577314	0.9962000	0.9962000	0.9962000
	1.5178471	3.5439696	0.0016456	15.1590576	0.9964000	0.9964000	0.9964000
	1.5208688	3.5440364	0.0016431	15.1594510	0.9967000	0.9967000	0.9967000
0.6	1.5193936	3.5479416	0.0016212	15.1948106	0.9969000	0.9969000	0.9969000
	1.5212732	3.5426559	0.0016369	15.1453858	0.9965000	0.9965000	0.9965000
	1.5162732	3.5426559	0.0016369	15.1453858	0.9969000	0.9969000	0.9969000
	1.5171771	3.5424339	0.0016358	15.1431148	0.9965000	0.9965000	0.9965000
	1.5187160	3.5437142	0.0016506	15.1557817	0.9964000	0.9964000	0.9964000
0.7	1.5220518	3.5543729	0.0015453	15.2530862	0.9967000	0.9967000	0.9967000
	1.5193184	3.5450532	0.0016453	15.1701245	0.9964000	0.9964000	0.9964000
	1.5183369	3.5451972	0.0016696	15.1703595	0.9962000	0.9962000	0.9962000
	1.5201375	3.5446533	0.0016461	15.1658243	0.9964000	0.9964000	0.9964000
	1.5181638	3.5447071	0.0016503	15.1666291	0.9959000	0.9959000	0.9959000
0.8	1.5172124	3.5429940	0.0018252	15.1437330	0.9948000	0.9948000	0.9948000
	1.5185406	3.5431314	0.0016381	15.1523301	0.9965000	0.9965000	0.9965000
	1.5175682	3.5433865	0.0016555	15.1522742	0.9963000	0.9963000	0.9963000
	1.5137660	3.5439353	0.0016445	15.1563388	0.9964000	0.9964000	0.9964000
	1.5147660	3.5439353	0.0016445	15.1563388	0.9957000	0.9957000	0.9957000
0.9	1.5196384	3.5486881	0.0015332	15.1966509	0.9970000	0.9970000	0.9970000
	1.5178016	3.5440682	0.0016373	15.1568141	0.9964000	0.9964000	0.9964000
	1.5185823	3.5435382	0.0016455	15.1518509	0.9960000	0.9960000	0.9960000
	1.5150856	3.5423343	0.0016566	15.1406026	0.9963000	0.9963000	0.9963000
	1.5167507	3.5414576	0.0016510	15.1332052	0.9964000	0.9964000	0.9964000
1	1.5108953	3.5273320	0.0016860	14.9990921	0.9969000	0.9969000	0.9969000
	1.5175148	3.5431723	0.0016419	15.1512809	0.9965000	0.9965000	0.9965000
	1.5185264	3.5433121	0.0016515	15.1511278	0.9964000	0.9964000	0.9964000
	1.5174663	3.5435628	0.0016455	15.1513269	0.9959000	0.9959000	0.9959000
	1.5155159	3.5431856	0.0016428	15.1512663	0.9965000	0.9965000	0.9965000

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

Power and Probability of Allocation to Treatment k

$$n = 300, \{p_{kr}\} = 0.5, \alpha = 0.05$$

$\{p_k\}$	LOWERCL	UPPERCL	PROCHISQ	WALDCHISQ	POWER_PC	POWER_WC	POWER_CL
0.10	1.1965878	4.8792735	0.0849362	6.2273265	0.6586000	0.6586000	0.6586000
	1.1980043	4.8922196	0.0849262	6.2311371	0.6542000	0.6542000	0.6542000
	1.2002443	4.8801284	0.0873339	6.2705581	0.6569000	0.6569000	0.6569000
	1.1982788	4.8838738	0.0857321	6.2430072	0.6565000	0.6565000	0.6565000
	1.1988425	4.8854073	0.0859974	6.2482341	0.6558000	0.6558000	0.6558000
0.15	1.3130748	4.2886037	0.0393668	8.3306163	0.8170000	0.8170000	0.8170000
	1.3153460	4.3019209	0.0398553	8.3586495	0.8182000	0.8182000	0.8182000
	1.3152104	4.2952623	0.0396111	8.3446329	0.8196000	0.8196000	0.8196000
	1.3139265	4.2335977	0.0385500	8.3611288	0.8164000	0.8164000	0.8164000
	1.3141394	4.3148461	0.0395958	8.3437569	0.8175000	0.8175000	0.8175000
0.20	1.3867418	4.0050477	0.0192633	10.1420379	0.9068000	0.9068000	0.9068000
	1.3848575	4.0016034	0.0192711	10.1114180	0.9079000	0.9079000	0.9079000
	1.3857997	4.0033256	0.0192672	10.1267280	0.9073000	0.9073000	0.9073000
	1.3853286	4.0024645	0.0192692	10.1190730	0.9076000	0.9076000	0.9076000
	1.3856819	4.0031103	0.0192677	10.1248142	0.9074000	0.9074000	0.9074000
0.25	1.4293061	3.8203553	0.0109286	11.5411255	0.9513000	0.9513000	0.9513000
	1.4158607	3.7850963	0.0103511	11.2819937	0.9540000	0.9540000	0.9540000
	1.4301759	3.8181476	0.0077912	11.5501783	0.9690000	0.9690000	0.9690000
	1.4201295	3.7921004	0.0105345	11.3750586	0.9520000	0.9520000	0.9520000
	1.4252679	3.8181136	0.0101294	11.4530274	0.9510000	0.9510000	0.9510000
0.30	1.4615107	3.7092703	0.0057331	12.7211847	0.9770000	0.9770000	0.9770000
	1.4836488	3.7632920	0.0052486	12.7740997	0.9800000	0.9800000	0.9800000
	1.4673809	3.7230872	0.0056770	12.8332361	0.9740000	0.9740000	0.9740000
	1.4680720	3.7291142	0.0055366	12.8449679	0.9770000	0.9770000	0.9770000

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

	1.4612777	3.7090782	0.0061701	12.7150313	0.9670000	0.9670000	0.9670000
0.35	1.4940599	3.6643517	0.0037414	13.8473449	0.9863000	0.9863000	0.9863000
	1.4769980	3.6183663	0.0040835	13.4968639	0.9870000	0.9870000	0.9870000
	1.4934179	3.6611793	0.0045833	13.8463608	0.9870000	0.9870000	0.9870000
	1.4833860	3.6385321	0.0042665	13.6181144	0.9840000	0.9840000	0.9840000
	1.4828679	3.6355563	0.0045030	13.6196113	0.9840000	0.9840000	0.9840000
0.40	1.5039849	3.6082699	0.0026763	14.3924255	0.9917000	0.9917000	0.9917000
	1.5268327	3.6638437	0.0027925	14.9016318	0.9930000	0.9930000	0.9930000
	1.5047588	3.6114628	0.0026621	14.4065662	0.9940000	0.9940000	0.9940000
	1.5001712	3.6022176	0.0028515	14.3004720	0.9910000	0.9910000	0.9910000
	1.5041023	3.6095848	0.0028130	14.3923871	0.9870000	0.9870000	0.9870000
0.45	1.5096224	3.5764369	0.0022648	14.7226946	0.9933000	0.9933000	0.9933000
	1.4998233	3.5528434	0.0025123	14.5072361	0.9930000	0.9930000	0.9930000
	1.5120372	3.5826389	0.0030572	14.7792947	0.9940000	0.9940000	0.9940000
	1.5102720	3.5771593	0.0023014	14.7438447	0.9920000	0.9920000	0.9920000
	1.5019704	3.5558141	0.0026045	14.5665111	0.9880000	0.9880000	0.9880000
0.50	1.5101645	3.5532672	0.0022059	14.8503118	0.9940000	0.9940000	0.9940000
	1.5113454	3.5563285	0.0023556	14.8792935	0.9930000	0.9930000	0.9930000
	1.5170653	3.5707880	0.0021976	14.9039062	0.9890000	0.9890000	0.9890000
	1.5274831	3.5949101	0.0017005	14.8414336	0.9970000	0.9970000	0.9970000
	1.5015605	3.5319592	0.0020622	14.6537562	0.9950000	0.9950000	0.9950000
0.55	1.5125232	3.5453805	0.0019267	14.9686677	0.9951000	0.9951000	0.9951000
	1.5147784	3.5510224	0.0017362	15.0199583	0.9970000	0.9970000	0.9970000
	1.5139216	3.5509001	0.0024115	14.9922616	0.9910000	0.9910000	0.9910000
	1.5241157	3.5741564	0.0022258	14.9360158	0.9930000	0.9930000	0.9930000
	1.5137670	3.5481645	0.0017911	14.9982200	0.9970000	0.9970000	0.9970000
0.60	1.5187506	3.5532902	0.0018294	15.1461123	0.9952000	0.9952000	0.9952000
	1.5305748	3.5827188	0.0018111	15.4130874	0.9950000	0.9950000	0.9950000
	1.5172569	3.5492179	0.0018021	15.1122568	0.9970000	0.9970000	0.9970000
	1.5214708	3.5608520	0.0020051	15.2048767	0.9940000	0.9940000	0.9940000

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

	1.5060318	3.5228218	0.0022213	15.0536141	0.9920000	0.9920000	0.9920000
0.65	1.5156903	3.5423327	0.0017477	15.0922643	0.9964000	0.9964000	0.9964000
	1.5266028	3.5679205	0.0021700	15.3523169	0.9920000	0.9920000	0.9920000
	1.5200920	3.5526630	0.0016187	15.1973056	0.9970000	0.9970000	0.9970000
	1.5132398	3.5362241	0.0018492	15.0372478	0.9970000	0.9970000	0.9970000
	1.5200328	3.5530208	0.0017162	15.1920428	0.9960000	0.9960000	0.9960000
0.70	1.5199596	3.5507400	0.0017664	15.2012284	0.9961000	0.9961000	0.9961000
	1.5219070	3.5559078	0.0020552	15.2479341	0.9940000	0.9940000	0.9940000
	1.5104633	3.5269847	0.0017328	15.0883177	0.9970000	0.9970000	0.9970000
	1.5193894	3.5489168	0.0016176	15.1883284	0.9960000	0.9960000	0.9960000
	1.5177223	3.5448909	0.0017262	15.1490885	0.9940000	0.9940000	0.9940000
0.75	1.5168079	3.5413727	0.0015955	15.1354860	0.9970000	0.9970000	0.9970000
	1.5181834	3.5449649	0.0015795	15.1634864	0.9966000	0.9966000	0.9966000
	1.5178371	3.5439786	0.0016451	15.1586486	0.9970000	0.9970000	0.9970000
	1.5197972	3.5438820	0.0016456	15.1577314	0.9962000	0.9962000	0.9962000
	1.5178471	3.5439696	0.0016456	15.1590576	0.9964000	0.9964000	0.9964000
0.80	1.5172745	3.5419549	0.0016345	15.1481574	0.9967000	0.9967000	0.9967000
	1.5167371	3.5426713	0.0016531	15.1444289	0.9971000	0.9971000	0.9971000
	1.5177257	3.5437199	0.0016418	15.1553171	0.9962000	0.9962000	0.9962000
	1.5177525	3.5437789	0.0016466	15.1563874	0.9966000	0.9966000	0.9966000
	1.5171728	3.5430825	0.0016524	15.1487865	0.9970000	0.9970000	0.9970000
0.85	1.5173931	3.5416351	0.0014653	15.1521740	0.9976000	0.9976000	0.9976000
	1.5169154	3.5442150	0.0012709	15.1734845	0.9967000	0.9967000	0.9967000
	1.5164030	3.5390238	0.0013500	15.1297504	0.9966000	0.9966000	0.9966000
	1.5200259	3.5487947	0.0018061	15.2118898	0.9970000	0.9970000	0.9970000
	1.5075786	3.5482622	0.0016789	15.1270776	0.9975000	0.9975000	0.9975000
0.90	1.5186146	3.5443160	0.0014619	15.1818238	0.9971000	0.9971000	0.9971000
	1.5171975	3.5410743	0.0018614	15.1539871	0.9970000	0.9970000	0.9970000
	1.5131428	3.5304111	0.0013921	15.0581857	0.9970000	0.9970000	0.9970000
	1.5095247	3.5219872	0.0014778	15.0749538	0.9970000	0.9970000	0.9970000

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

	1.5115831	3.5264821	0.0013546	15.0225606	0.9980000	0.9980000	0.9980000
0.95	1.5153765	3.5359381	0.0014857	15.1133844	0.9972000	0.9972000	0.9972000
	1.5065920	3.5438897	0.0016380	15.1177390	0.9960000	0.9960000	0.9960000
	1.5105892	3.5238136	0.0017432	15.0112003	0.9965000	0.9965000	0.9965000
	1.5152889	3.5357080	0.0014125	15.1103967	0.9960000	0.9960000	0.9960000
	1.5101238	3.5232433	0.0014418	15.0922841	0.9972000	0.9972000	0.9972000
1.00	1.5173509	3.5401066	0.0015052	15.1670454	0.9974000	0.9974000	0.9974000
	1.5133189	3.5306700	0.0017429	15.0814661	0.9970000	0.9970000	0.9970000
	1.5211241	3.5493599	0.0017184	15.1595829	0.9975000	0.9975000	0.9975000
	1.5187782	3.5442118	0.0017355	15.2012879	0.9980000	0.9980000	0.9980000
	1.5255204	3.5590808	0.0015101	15.3587473	0.9970000	0.9970000	0.9970000

Treatment Balance and Sample size

$$\{p_k\} = 0.75, \{p_{kr}\} = 0.5, \alpha = 0.05$$

SAMPLE SIZE	MINIMUM	MAXIMUM	MEAN	STDV
50	0.4200000	0.5600000	0.4993000	0.0206963
	0.4000000	0.5800000	0.5003960	0.0209257
	0.4028125	0.5834375	0.5001706	0.0208681
	0.4050000	0.5750000	0.5001220	0.0208684
	0.4000000	0.6000000	0.5001680	0.0208445
75	0.4533333	0.5600000	0.4998133	0.0139771
	0.3866667	0.5600000	0.4999920	0.0141277
	0.4266667	0.5733333	0.4999973	0.0140963
	0.4033334	0.5600000	0.4999473	0.0140901
	0.4085417	0.5641667	0.4999685	0.0140967
100	0.4600000	0.5400000	0.4999600	0.0106448
	0.4600000	0.5500000	0.5000770	0.0104716

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

	0.4568750	0.5485938	0.5000312	0.0104955
	0.4600000	0.5475000	0.5000478	0.0105149
	0.4500000	0.5500000	0.4999830	0.0104700
125	0.4720000	0.5360000	0.5000643	0.0084456
	0.4640000	0.5360000	0.4999920	0.0084280
	0.4560000	0.5360000	0.4999464	0.0084863
	0.4640000	0.5360000	0.4999648	0.0083534
	0.4620000	0.5360000	0.4999740	0.0084240
150	0.4733333	0.5266667	0.4999333	0.0067558
	0.4666667	0.5333333	0.4999860	0.0070364
	0.4700000	0.5300000	0.4999597	0.0068961
	0.4683334	0.5316667	0.4999728	0.0069663
	0.4695833	0.5304166	0.4999629	0.0069136
175	0.4800000	0.5200000	0.5000457	0.0058582
	0.4742857	0.5314286	0.4999463	0.0061200
	0.4771428	0.5257143	0.4999960	0.0059891
	0.4757143	0.5285715	0.4999712	0.0060546
	0.4767857	0.5264286	0.4999898	0.0060054
200	0.4800000	0.5150000	0.4999950	0.0054868
	0.4750000	0.5250000	0.5000545	0.0054007
	0.4775000	0.5200000	0.5000247	0.0054437
	0.4762500	0.5225000	0.5000396	0.0054222
	0.4771875	0.5206250	0.5000284	0.0054383
225	0.4755556	0.5155556	0.4995911	0.0047343
	0.4770370	0.5200000	0.4997980	0.0047490
	0.4755556	0.5244444	0.4999018	0.0047450
	0.4800000	0.5200000	0.4998996	0.0047678
	0.4777778	0.5222222	0.4999007	0.0047564
250	0.4800000	0.5160000	0.5001000	0.0041713
	0.4800000	0.5200000	0.4999508	0.0042510

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

	0.4800000	0.5180000	0.5000254	0.0042111
	0.4800000	0.5190000	0.4999881	0.0042311
	0.4800000	0.5182500	0.5000160	0.0042161
275	0.4836364	0.5163636	0.5000764	0.0040604
	0.4800000	0.5200000	0.5000349	0.0039904
	0.4818182	0.5181818	0.5000556	0.0040254
	0.4809091	0.5190909	0.5000453	0.0040079
	0.4815909	0.5184090	0.5000530	0.0040210
300	0.4866667	0.5133333	0.5000767	0.0035789
	0.4833333	0.5166667	0.4999477	0.0035323
	0.4850000	0.5150000	0.5000122	0.0035556
	0.4841667	0.5158334	0.4999800	0.0035440
	0.4847916	0.5152083	0.5000041	0.0035527
325	0.4861538	0.5138462	0.5001617	0.0035319
	0.4845510	0.5154490	0.5000120	0.0030810
	0.4830769	0.5169231	0.5000111	0.0033104
	0.4830769	0.5169231	0.5000037	0.0033482
	0.4875000	0.5125000	0.5000222	0.0025852
350	0.4885714	0.5114286	0.4999257	0.0030026
	0.4857143	0.5171429	0.5000166	0.0030866
	0.4871428	0.5142857	0.4999711	0.0030446
	0.4864286	0.5157143	0.4999939	0.0030656
	0.4869642	0.5146428	0.4999768	0.0030498
375	0.4906667	0.5120000	0.5000160	0.0029128
	0.4853333	0.5146667	0.5000320	0.0028191
	0.4880000	0.5133333	0.5000240	0.0028659
	0.4866667	0.5140000	0.5000280	0.0028425
	0.4866667	0.5140000	0.5000250	0.0028600
400	0.4890000	0.5100000	0.4994600	0.0027398
	0.4875000	0.5125000	0.4999677	0.0026144

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

0.4875000	0.5125000	0.5000130	0.0026345
0.4878750	0.5118750	0.4998408	0.0026458
0.4882500	0.5112500	0.5000130	0.0026345

Treatment Balance and Probability of Allocation to Treatment k when Treatments are Balanced

$$\{p_k\} = 0.75, \alpha = 0.05, n = 300$$

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

$\{P_{kr}\}$	MINIMUM	MAXIMUM	MEAN	STDV
0.1	0.4833333	0.5133333	0.5019733	0.0032188
	0.4866667	0.5133333	0.5016933	0.0033115
	0.4933333	0.5166667	0.5019500	0.0032621
	0.4900000	0.5133333	0.5020733	0.0034322
	0.4933333	0.5166667	0.5020433	0.0032527
0.2	0.4900000	0.5133333	0.5013376	0.0034347
	0.4900000	0.5166667	0.5016267	0.0034398
	0.4900000	0.5133333	0.5013600	0.0032906
	0.4900000	0.5100000	0.5014367	0.0033103
	0.4866667	0.5166667	0.5015333	0.0033055
0.3	0.4900000	0.5166667	0.5011067	0.0034267
	0.4900000	0.5133333	0.5008233	0.0032744
	0.4900000	0.5166667	0.5008400	0.0035741
	0.4900000	0.5166667	0.5009467	0.0034260
	0.4866667	0.5133333	0.5010467	0.0034423
0.4	0.4866667	0.5133333	0.5005167	0.0035183
	0.4833333	0.5166667	0.5003333	0.0036104
	0.4833333	0.5166667	0.5004367	0.0035543
	0.4866667	0.5133333	0.5004300	0.0036264
	0.4866667	0.5133333	0.5006167	0.0035149
0.5	0.4866667	0.5133333	0.5000767	0.0035789
	0.4833333	0.5133333	0.5000033	0.0034610
	0.4866667	0.5100000	0.4999100	0.0035861
	0.4866667	0.5166667	0.4998433	0.0037268
	0.4866667	0.5133333	0.4999667	0.0035356
0.6	0.4866667	0.5133333	0.4996951	0.0034530
	0.4866667	0.5133333	0.4996033	0.0035994
	0.4900000	0.5133333	0.4995700	0.0035426
	0.4866667	0.5133333	0.4994733	0.0036274

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

	0.4833333	0.5133333	0.4993500	0.0035247
0.7	0.4866667	0.5100000	0.4990114	0.0033653
	0.4866667	0.5100000	0.4990633	0.0034109
	0.4866667	0.5100000	0.4988800	0.0035469
	0.4833333	0.5100000	0.4991467	0.0033690
	0.4900000	0.5100000	0.4990100	0.0035181
0.8	0.4866667	0.5100000	0.4986200	0.0033159
	0.4766667	0.5133333	0.4984833	0.0034722
	0.4833333	0.5166667	0.4986133	0.0035841
	0.4866667	0.5100000	0.4985233	0.0036116
	0.4866667	0.5133333	0.4984133	0.0036463
0.9	0.4866667	0.5100000	0.4982098	0.0034823
	0.4866667	0.5100000	0.4981067	0.0033239
	0.4833333	0.5100000	0.4982300	0.0032180
	0.4833333	0.5100000	0.4980600	0.0032800
	0.4866667	0.5100000	0.4979367	0.0034204
1	0.4866667	0.5100000	0.4977444	0.0031629
	0.4833333	0.5100000	0.4979033	0.0033105
	0.4866667	0.5166667	0.4978900	0.0033720
	0.4833333	0.5100000	0.4975133	0.0032291
	0.4833333	0.5100000	0.4975133	0.0033673

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

Treatment Balance and Probability of Allocation to Treatment K

$$n = 300, \{p_{kr}\} = 0.5, \alpha = 0.05$$

$\{p_k\}$	MINIMUM	MAXIMUM	MEAN	STDV
0.10	0.0566667	0.9433333	0.4958700	0.3849012
	0.0600000	0.9400000	0.4855000	0.3867404
	0.0500000	0.9400000	0.5034333	0.3875621
	0.0500000	0.9500000	0.4927067	0.3841906
	0.0500000	0.9500000	0.4949667	0.3851182
0.15	0.0833333	0.9133333	0.5038767	0.3390351
	0.0933333	0.9033333	0.5304233	0.3347048
	0.0900000	0.9033333	0.5186900	0.3378706
	0.0866667	0.9000000	0.4915233	0.3385000
	0.0900000	0.9066667	0.5049000	0.3386087
0.20	0.1466667	0.8633333	0.5100433	0.2906893
	0.1266667	0.8566667	0.5032767	0.2901321
	0.1266667	0.8633333	0.4985100	0.2885636
	0.1433333	0.8600000	0.4971967	0.2884522
	0.1333333	0.8500000	0.4978467	0.2889940
0.25	0.1766667	0.8166667	0.5024173	0.2408541
	0.1633333	0.8266667	0.5123167	0.2408001
	0.1766667	0.8300000	0.4916800	0.2424776
	0.1933333	0.8300000	0.5029900	0.2421489
	0.1566667	0.8266667	0.4969867	0.2416612
0.30	0.2233333	0.7966667	0.4935738	0.1914325
	0.2266667	0.7800000	0.5024400	0.1935088
	0.2133333	0.7866667	0.5088567	0.1933849
	0.2300000	0.7866667	0.5013500	0.1914303
	0.2366667	0.7833333	0.4862733	0.1916220
0.35	0.2633333	0.7466667	0.4982333	0.1442508

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

	0.2766667	0.7233333	0.4998267	0.1445906
	0.2833333	0.7466667	0.5059833	0.1465971
	0.2600000	0.7333333	0.4968667	0.1438473
	0.2700000	0.7233333	0.5003033	0.1435579
0.40	0.3066667	0.6766667	0.5020167	0.0978883
	0.3300000	0.6833333	0.4956733	0.0984949
	0.3233333	0.6900000	0.5011567	0.0993617
	0.3100000	0.6866667	0.4980933	0.0979071
	0.3166667	0.7033333	0.5028833	0.0999360
0.45	0.3666667	0.6566667	0.5018533	0.0585238
	0.3633333	0.6366667	0.5022033	0.0576932
	0.3600000	0.6566667	0.5034533	0.0580337
	0.3600000	0.6500000	0.4993233	0.0591688
	0.3666667	0.6500000	0.4983367	0.0585165
0.50	0.3800000	0.5866667	0.4999267	0.0302894
	0.4166667	0.5833333	0.5000000	0.0291354
	0.3933333	0.6066667	0.5003567	0.0301300
	0.4133333	0.5933333	0.5005100	0.0285865
	0.4066667	0.6033333	0.5001333	0.0296099
0.55	0.4366667	0.5466667	0.5007284	0.0144878
	0.4400000	0.5566667	0.5002767	0.0149920
	0.4433333	0.5533333	0.4998133	0.0150692
	0.4333333	0.5766667	0.5004633	0.0152266
	0.4466667	0.5466667	0.5001267	0.0145647
0.60	0.4633333	0.5300000	0.4997727	0.0089718
	0.4666667	0.5333333	0.4999167	0.0084622
	0.4633333	0.5333333	0.5001367	0.0089545
	0.4666667	0.5333333	0.4997767	0.0088830
	0.4566667	0.5300000	0.5000133	0.0088575
0.65	0.4766667	0.5200000	0.5000967	0.0062126

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

	0.4766667	0.5200000	0.4999567	0.0058916
	0.4766667	0.5200000	0.5001167	0.0059600
	0.4733333	0.5266667	0.4998500	0.0059816
	0.4800000	0.5266667	0.5000333	0.0059489
0.70	0.4833333	0.5266667	0.5002300	0.0047238
	0.4733333	0.5166667	0.4999933	0.0046211
	0.4833333	0.5166667	0.4998933	0.0044507
	0.4833333	0.5233333	0.4999600	0.0044040
	0.4833333	0.5166667	0.4998133	0.0045322
0.75	0.4866667	0.5133333	0.5000767	0.0035789
	0.4866667	0.5166667	0.5000733	0.0035756
	0.4833333	0.5133333	0.4999833	0.0035310
	0.4866667	0.5133333	0.5000367	0.0034253
	0.4800000	0.5133333	0.5000300	0.0035933
0.80	0.4900000	0.5100000	0.4999933	0.0030089
	0.4866667	0.5100000	0.4997467	0.0030241
	0.4900000	0.5100000	0.4999333	0.0028291
	0.4900000	0.5100000	0.5000267	0.0027861
	0.4900000	0.5100000	0.5001200	0.0028115
0.85	0.4900000	0.5133333	0.5001267	0.0024383
	0.4900000	0.5100000	0.4998800	0.0024614
	0.4866667	0.5100000	0.4998733	0.0023689
	0.4933333	0.5066667	0.4999333	0.0023854
	0.4933333	0.5066667	0.5000233	0.0023272
0.90	0.4933333	0.5066667	0.5000701	0.0020267
	0.4933333	0.5066667	0.5000433	0.0019182
	0.4933333	0.5066667	0.4999467	0.0020388
	0.4933333	0.5066667	0.5000000	0.0019954
	0.4933333	0.5066667	0.4999367	0.0019407
0.95	0.4933333	0.5033333	0.5001270	0.0015827

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

	0.4933333	0.5066667	0.5000633	0.0015379
	0.4933333	0.5066667	0.4999967	0.0016440
	0.4966667	0.5066667	0.5000467	0.0015918
	0.4933333	0.5066667	0.4999733	0.0016404
1.00	0.4966667	0.5033333	0.5000233	0.000983407
	0.4966667	0.5033333	0.5000333	0.0010328
	0.4966667	0.5033333	0.4999767	0.0010277
	0.4966667	0.5033333	0.4999900	0.000960752
	0.4966667	0.5033333	0.4999767	0.0011307

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

APPENDIX B

```
/*
-----
SAS SIMULATION CODE: MINIMIZATION TREATMENT ALLOCATION
-----

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MSc Biostatistics and Epidermiology
Department of Statistics
FortHare University
South Africa

-----
*****
Generation of n Subjects, Prognostic Factors and Response Values
*****
-----
*/
DATA code_1(keep=patient trt1_placebo trt2_drug profactor_1 profactor_2
profactor_3);
DO n=1 TO 50;
patient=n;
/*Two binary categorical prognostic factors 1&2 both with two levels and one
with four levels, factor 3*/
profactor_1=rantbl(20,0.65,0.35);
profactor_2=rantbl(21,0.55,0.45);
profactor_3=rantbl(22,0.30,0.31,0.26,0.13);
/*Two ordinal response variables both with six levels, trt1_placebo and
trt2_drug*/
slope=-0.9259*profactor_1-0.4746*profactor_2-0.9819*profactor_3;
func_1=1.5434+slope; p1=exp(func_1)/(1+exp(func_1));
func_2=3.0177+slope; p2=exp(func_2)/(1+exp(func_2));
func_3=3.66417+slope; p3=exp(func_3)/(1+exp(func_3));
func_4=4.4565+slope; p4=exp(func_4)/(1+exp(func_4));
func_5=5.5567+slope; p5=exp(func_5)/(1+exp(func_5));
trt1_placebo=rantbl(23,p1,p2-p1,p3-p2,p4-p3,p5-p4,1-p5)-1;
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);
trt2_drug=rantbl(24,a1,a2-a1,a3-a2,a4-a3,a5-a4,1-a5)-1;;
OUTPUT;
END;
RUN;
ODS RTF FILE='output111';
PROC PRINT DATA=code_1;
RUN;
PROC FREQ DATA=code_1;
RUN;
ODS RTF CLOSE;
/*
-----
*****
Creating Dummy Variables
*****
-----
*/
```

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

```

*****
-----
*/
DATA code_2;
SET code_1;
KEEP patient trt1_placebo trt2_drug 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
profactor_1 profactor_2 profactor_3;
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 profactor_1=1 THEN a1=1;
IF profactor_1=2 THEN a2=1;
IF profactor_2=1 THEN b1=1;
IF profactor_2=2 THEN b2=1;
IF profactor_3=1 THEN c1=1;
IF profactor_3=2 THEN c2=1;
IF profactor_3=3 THEN c3=1;
IF profactor_3=4 THEN c4=1;
a_bal=0; b_bal=0;
PROC SORT;
BY patient;
RUN;
/*PROC PRINT DATA=code_2;
RUN;
*/
-----
*****
Allocating Subjects to Treatments, trt1_placebo & trt2_drug
*****
-----
*/
OPTIONS nonotes nosource nonumber nodate;
%MACRO alloc;
PROC iml;
A=shape(0,50,10000);
B=shape(0,10000,34);
do k=1 to 10000;
use code_2;
read all var {patient profactor_1 profactor_2 profactor_3
trt1_placebo trt2_drug p trt
a1 a1_a a1_b
a2 a2_a a2_b

```

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

```

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 50;
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;
/*allocation of patients to either treatment1 or treatment2 using the
probability of allocation{Pk}*/
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; /*random assignment if treatments are balanced*/
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<50 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=50 then do;
do j=1 to 34;
B[k,j]=m[50,j];
end;
end;
end;
end;
CREATE A FROM A;
APPEND FROM A;
CREATE B FROM B;
APPEND FROM B;
quit;
run;
run;
%MEND;
%alloc;
/*
-----
*****
Creating The Dataset
*****

```

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

```
-----
*/
DATA dataset_1;
MERGE code_1 A;
ARRAY col{10000} col1-col10000;
ARRAY response{10000} response1-response10000;
DO i=1 to 10000;
IF col{i}=0 THEN response{i}=trt1_placebo;
ELSE
IF col{i}=1 THEN response{i}=trt2_drug;
END;
RUN;
/*PROC PRINT DATA=dataset_1;
RUN;*/
/*
-----
*****
Estimating Balance of Treatment Groups Using 10000 Replications
*****
-----
*/
ODS LISTING CLOSE;
%MACRO balla (dp);
%DO i=1 %TO 10000;
PROC MEANS DATA=dataset_1 n mean std;
VAR col&i;
output out=balance mean=means std=deviaton ;
RUN;
data &dp;
set &dp balance;
ip=&i;
RUN;
%END;
%MEND;
DATA testballa;
SET _null_;
RUN;
%balla(testballa);
DATA balance1(keep=means);
SET testballa;
run;
ODS LISTING;
PROC MEANS DATA=balance1;
VAR means;
RUN;
/*
-----
*****
Ordinary Logistic Regression Approach Using 10000 Replications
*****
-----
*/
/*ODS RTF FILE='output1';*/
ODS LISTING CLOSE;
%MACRO logreg (dt);
%DO i=1 %TO 10000;
proc logistic data=dataset_1;
```

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

```

TITLE2 'Logistic Regression Model with Polytomous Ordinal Response Variable';
class profactor_1 profactor_2 profactor_3 col&i;
model response&i=profactor_1 profactor_2 profactor_3 col&i/*selection=forward
expb */ ;
Ods output oddsratios=ore;
RUN;
/*creating the dataset for the odds ratio output*/
DATA &dt;
SET &dt ore;
it=&i;
RUN;
%END;
%MEND;
DATA testlogreg;
SET _null_;
RUN;
%logreg(testlogreg);

%MACRO llogreg (ds);
%DO i=1 %TO 10000;
/*ods graphics on;*/
/*PROC LOGISTIC PROCEDURE for modeling the categorical variables*/
proc logistic data= dataset_1 /*plots(only)=(effect(polybar)
oddsratio(range=clip))*/;
    class profactor_1 profactor_2 profactor_3 col&i /*param=ref*/;
    model response&i = profactor_1 profactor_2 profactor_3 col&i /;
    oddsratio col&i;
    oddsratio profactor_1;
    oddsratio profactor_2;
    oddsratio profactor_3;
    /*using the CONTRAST STATEMENT to compare treatment effect*/
    contrast ' col&i =1 vs col&i =0' col&i 1 -1/ estimate=exp;
    ods noresults;
    ods output contrastestimate=contrast;
RUN;
/*creating the dataset for the contrast estimates output*/
DATA &ds;
SET &ds contrast;
is=&i;
RUN;
/*ods graphics off;*/
%END;
%MEND;
DATA testllogreg;
SET _null_;
RUN;
%llogreg(testllogreg);
/*ODS RTF CLOSE;*/
/*
-----
*****
Power Simulation Using 10000 Replications
*****
-----
*/
DATA power1(keep=probchisq contrast waldchisq);
SET testllogreg;/*importing the contrastestimate table from the above macro*/

```

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

```

RUN;
DATA power1(keep=lowercl uppercl);
SET testlogreg;
/*removing other variables(taking odds confidence limits for treatments)*/
IF variable in (' profactor_1',' profactor_1',' profactor_1') or
effect in ('profactor_1 1 vs 2','profactor_2 1 vs 2','profactor_3 1 vs 4',
'profactor_3 2 vs 4','profactor_3 3 vs 4') THEN DELETE;
RUN;
DATA power2;
SET power1;
SET power1;
DO i=1 TO 10000;
/*setting the power parameters to zero(initiation of parameters)*/
power_pc = 0;
power_cl = 0;
power_wc = 0;
/*testing the null hypothesis that there is no treatment difference against
the alternative hypothesis that there exist a treatment effect*/
IF probchisq < 0.05 THEN power_pc = power_pc + 1;
ELSE power_pc = power_pc; /*reject H0 if probchisq < alpha(0.05)*/
IF lowercl > 1 THEN power_cl = power_cl + 1;
ELSE power_cl = power_cl; /*reject H0 if 1 is not an element of CL*/
IF waldchisq > 3.8415 THEN power_wc = power_wc + 1;
ELSE IF probchisq < 0.05 THEN power_wc = power_wc + 1;
ELSE power_wc = power_wc; /*reject H0 if waldchisq > 3.8415*/
END;
RUN;
PROC PRINT DATA=power2;
RUN;
ODS LISTING;
PROC MEANS DATA=power2;
VAR power_pc power_cl power_wc Lowercl Uppercl probchisq waldchisq;
RUN; /*power=(number of times in which H0 was rejected)/(total number of
replications)*/

/*****END*****/

```

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

APPENDIX C

- Distribution of variables. Output produced from Code_1;

Obs	patient	profactor_1	profactor_2	profactor_3	trt1_placebo	trt2_drug
1	1	2	1	4	4	5
2	2	1	2	3	5	4
3	3	1	1	1	1	0
4	4	2	1	3	4	5
5	5	2	1	1	3	3
6	6	2	2	3	5	5
7	7	1	1	3	4	5
8	8	2	2	2	4	4
9	9	1	1	4	5	0
10	10	1	2	3	2	5
11	11	1	1	1	1	0
12	12	2	1	3	5	5
13	13	1	2	2	1	5
14	14	2	2	1	0	4
15	15	1	1	2	2	1
16	16	1	2	4	4	5
17	17	1	1	3	5	3
18	18	1	2	1	1	4
19	19	1	2	2	3	3
20	20	1	1	3	3	4
21	21	1	2	2	2	1
22	22	2	2	2	5	3
23	23	1	2	2	5	1
24	24	1	1	1	5	2
25	25	1	1	2	0	1

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

Obs	patient	profactor_1	profactor_2	profactor_3	trt1_placebo	trt2_drug
26	26	1	1	1	1	2
27	27	2	1	3	4	5
28	28	2	2	3	4	5
29	29	2	2	2	5	5
30	30	1	2	3	5	5
31	31	2	1	2	5	4
32	32	2	1	3	5	3
33	33	1	1	3	1	5
34	34	1	1	3	5	3
35	35	2	2	3	3	5
36	36	2	1	4	5	5
37	37	1	1	2	3	4
38	38	1	1	4	2	0
39	39	1	2	4	4	5
40	40	1	2	4	2	4
41	41	1	2	3	4	3
42	42	1	1	3	3	2
43	43	1	2	1	1	1
44	44	2	1	4	4	5
45	45	1	1	1	0	1
46	46	1	2	1	1	0
47	47	2	2	4	5	5
48	48	1	1	1	0	0
49	49	2	2	3	5	5
50	50	1	1	1	1	0

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

profactor_1	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	32	64.00	32	64.00
2	18	36.00	50	100.00

profactor_2	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	27	54.00	27	54.00
2	23	46.00	50	100.00

profactor_3	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1	12	24.00	12	24.00
2	11	22.00	23	46.00
3	18	36.00	41	82.00
4	9	18.00	50	100.00

trt1_placebo	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	4	8.00	4	8.00
1	9	18.00	13	26.00
2	5	10.00	18	36.00
3	6	12.00	24	48.00
4	10	20.00	34	68.00
5	16	32.00	50	100.00

Maximization of Power in Randomized Clinical Trials using the Minimization Treatment Allocation Technique

trt2_drug	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	7	14.00	7	14.00
1	6	12.00	13	26.00
2	3	6.00	16	32.00
3	7	14.00	23	46.00
4	8	16.00	31	62.00
5	19	38.00	50	100.00