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MAXIMIZATION OF POWER IN RANDOMIZED CLINICAL TRIALS USING THE MINIMIZATION TREATMENT ALLOCATION TECHNIQUE: A SIMULATION STUDY*

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ABSTRACT

One of the key aims in randomized clinical trials is to make comparisons among two or more treatments. Hence forth, appropriate treatment allocation procedures are required. Of these methods, the use of minimization has been seldom reported mainly because of the controversy surrounding the statistical efficiency in detecting treatment effect and its complexity in implementation. A simulation study using the ideas of Pocock and Simon for two different treatment groups was designed using SAS version 9.1. Categorical prognostic factors together with multi-level response variables were used. Power simulation was then carried out using ordinal logistic regression models. Several scenarios were simulated and within these scenarios, increasing the sample size significantly increased the power of detecting the treatment effect. Maximum power can be achieved with a sample of size 250 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 as proposed by Pocock and Simon.

KEY WORDS

Minimization, Randomization, Sample Size, Power, Logistic regression

1. INTRODUCTION

In randomized clinical trials subjects should be assigned to treatment groups on the basis of a random process that is unpredictable. In such studies, several methods of randomization are available to create comparable intervention groups, for example; blocking, stratification, or minimization. The main purpose behind this is to attain a better balance of known prognostic factors within the various treatment groups and this potentially increases the statistical power attained in a trial (Weir CJ and Lees KR, 2003;

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Rosenberger WF, 2002). Ignorance of this balance at the design stage may lead to loss of statistical efficiency, especially in small trials (J. Ciolino, et al. 2011). This makes the design stage to be the greatest determinant of power in a study (Treasure T, MacRae KD., 1998).

Despite notable advantages and recommendations by many statistical and clinical investigators, minimization remains infrequently used due to lack of easily accessible tools (Cai HW, et al. 2010). However, as computing facilities are becoming more widely available, minimization can become a more feasible option for many researchers, hence more research needs to be done to ensure that there are solid results in regard to its statistical efficiency. A general and moderately simple way to achieve this is the use of simulation which is a well-known component of modern statistical studies. Previous studies conducted by Tu et al. (2000) together with Weir and Lees (2003) have investigated the statistical power of minimization using simulations but results have differed and McEntegart (2003) states that more research is needed before drawing conclusions regarding statistical efficiency of minimization.

This article focuses on investigating the minimization algorithm described by Pocock and Simon (1975). A simulation study for two different treatment groups is designed using SAS version 9.1. Categorical prognostic factors together with multi-level response variables are used and power simulation is carried out using ordinal logistic regression models. Several scenarios are simulated and within these scenarios, the effect of sample size and probability of allocation on treatment balance and statistical power will be investigated.

2. METHODS

A simulation study was designed using SAS version 9.1. The program was implemented and developed from the ideas of Pocock and Simon. The number of prognostic factors used in this minimization algorithm was primarily limited by statistical concerns since it is recommended that all covariates minimized should be included in statistical analysis (Taves DR, 2010). Initially two ordinal categorical response variables with six levels each were simulated together with three categorical prognostic factors. The simulation trial was meant to initially distribute the prognostic factors as shown in table 1 in the Appendix.

Dummy variables were used to differentiate between the two treatment groups. The probability of allocation to either treatments was set to range from 0.1 to 1 and the minimization treatment allocation algorithm 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 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. The algorithm is summarized in Figure 1 provided in the Appendix.

2.1 Simulation Options

From previous studies by Angie Wade et al. (2006), highlighted that increasing the number of simulations to 2500 or 5000 would increase precision to ± 0.06 and 0.04 standard deviations respectively. Further doubling of the number of simulations to 10000 would only further increase precision by less than 0.01 standard deviations. For further accuracy of results, 10000 simulations were performed.

2.2 Treatment Allocation, Algorithm

PROC IML was used to generate the algorithm for treatment allocation technique. A total of 10000 replications were used in allocating patients to the two treatment groups. The minimization algorithm took into account the technique described by Pocock and Simon. This was done using the following algorithm.

Step 1: 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 i.e. the difference between the highest and lowest value.

Step 2: 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 were assigned to that patient was used. G_k was 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 $\left|N_{ri1} - N_{ri2}\right|$. The overall amount of imbalance was measured as the summation of all $\left|N_{ri1} - N_{ri2}\right|$.

Step 3: 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 RANUNI was used to generate random numbers between 0 and 1 which have a uniform distribution.

2.3 Investigating Balance of Treatment Groups

It is of interest to investigate the effect of varying parameters within the minimization algorithm on treatment balance. Macros were 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.

3. ANALYSES 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), however conventional tests are normally 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.

3.1 Power Calculation using the Logistic Regression Approach

Power analysis is essential to the health and behavioral sciences, and its use is progressively growing wherever simulation 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. However, Hosmer and Lemeshow (2000) proposed that their modification may be too conservative. 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 is the one which was used in this study. The hypothesis was tested using three different tests/statistics at 5% significance level. These include the probabilities of Chi-Square, the Wald Chi-square tests and the 95% Wald Confidence limits (Odds Ratios).

3.1.1 Probabilities of Chi-Square (p-values)

These were obtained from the contrast estimate output. Thus the CONTRAST statement computed the test statistic for;

$$H_o : \beta_1 = \beta_2 ,$$

where β_1 is the effect due to treatment 1 and β_2 is the effect due to treatment 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;

$$P\text{-}value < 0.05$$

3.1.2 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;

$$H_o : \beta_1 = \beta_2$$

The null hypothesis was rejected when Wald Chi-square > 3.8415 at 5% significance level. Under the null hypothesis Wald Chi-Square followed a Chi-Square distribution with 1 degree of freedom. The hypothesis of equal effect rates for groups β_1 and β_2 was rejected if;

$$\text{Wald Chi-Square} > \chi^2_{1,\alpha},$$

where $\chi^2_{1,\alpha}$ is the 100α 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 Chi-square statistical tables.

3.1.3 95% Wald Confidence limits (Odds Ratios)

The hypothesis of interest was;

$$H_o : OR = 1 \text{ versus } H_1 : OR \neq 1 \text{ that is rejected when } 1 \notin \text{OR}$$

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 then 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.

4. RESULTS

The simulation program generated the intended covariates as proposed. 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 was investigated to ensure that any effect on power is due to the parameter itself not imbalances within the treatment groups. A suitable sample size that will achieve maximum power was firstly established by setting all the other parameters to values proposed by Pocock and Simon. We then went on to determine a probability of allocation that will also give maximum power and lastly the probability of allocation given that the treatment groups are equally balanced was also investigated. The analysis is comprised of a graphical exploratory presentation using the STATISTICA package accompanied by a confirmatory significance testing using SAS version 9.1. ANOVA was used for comparisons in power and treatment balance.

4.1 The Effect of Sample Size on Power and Treatment Balance

The initial task was to find a minimum sample size that will give us maximum power under the conditions proposed by Pocock and Simon. Therefore sample size was to vary

from 50 to 400 in lags of 50 per simulation. There was a significant increase in power as the sample size increased. The minimum power (0.020) was achieved at a sample size of 50 whilst a maximum power of 0.999 was achieved at a sample size of 400. A post hoc analysis using the Duncan's Waller groupings revealed an upward steep significant difference in power from a sample size of 50 to 225, and then as the sample size further increased from 250 to 400 there was no significant difference in power. From Table 2 and Figure 2 (in Appendix), maximum power is attained with a minimum sample size of 250.

In terms of treatment balance, Table 2 in the Appendix shows that there exist some imbalances on small sample sizes; however the allocation technique achieves tight balance within treatment groups at a sample size of 325. There exists no further significant change in treatment balance from a sample size of 325 to 400 and this result can be justified by Figure 3 in the Appendix where there is no significant difference on the standard deviation (SD) of the confidence limits for the respective sample sizes.

4.2 The Effect of Probability of Allocation on Power and Treatment Balance

Sample size was now set at 250 since it is the minimum sample size that attained maximum power in our initial simulation. As the probability of allocation increased, there was a gradual increase in power from 0.1 to 0.25. The plots in Figure 4 show that power was constant between 0.35 and 1. Table 3 in the Appendix shows that there is no significant difference in power from a probability of allocation of 0.75 to 1. Thus a probability of allocation of 0.75 would give a maximum power for the simulated scenario.

The probability of allocation also shows an effect on treatment balance. Figure 5 in the Appendix shows some huge imbalances for all values of the probability of allocation between 0.1 and 0.5. However Table 3 shows that tight balance can be achieved with probability of allocations between 0.75 and 1. These results show a strong positive relationship between treatment balance and power.

4.3 The Effect of Probability of Allocation given Treatment Groups are Balanced on Power and Treatment Balance

The value of the probability of treatment allocation when treatment 1 and treatment 2 are equally allocated has no effect on power for all probabilities. All values of the probability of treatment allocation gave the same power for a sample size of 250 (see Figure 6 in Appendix). There were no significant differences in power for all the simulated scenarios (see Table 4 in Appendix).

Figure 7 shows the plot of probability of allocation when treatment groups are equally balanced versus treatment balance, the plot shows that there is tight balance for all the simulated cases. The graph is constant at the value 0.5 for treatment balance. Table 4 also shows that there exists tight balance for all the different probabilities having the SD for the achieved treatment balance being significantly the same.

5. 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 be made concerning the precise form of implementation. Choice of input parameters may influence the extent to which the process is successful in ensuring the number of patients between treatment groups and the resultant power for that particular 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. Of these, improving the balance on treatment groups also potentially increases the statistical power attained in a trial. 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 through simulations.

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 250 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.

Since this technique minimizes imbalances between treatment groups many authors agreed that it yields tight balance as compared to other treatment allocation techniques (J.M. Lachin, 1988). In this study, the technique exhibited tight balance between treatment groups for most of the simulated scenarios. 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. From the results of this study, minimization can be seen as a highly effective method for treatment allocation, and hence advocate for wider adoption of the technique within the clinical trial field.

Maximum power can be achieved with a sample of size 250 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.

6. 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. Therefore it can be recommended that,

i) Simulations can be usefully employed prior to study commencement to determine the best parameters to use.

ii) 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.

iii) It is important that researchers justify the choices they make with regards to the procedure for allocating patients in a real life situation.

iv) If pre-adjustment methods (such as minimization) are employed, post-adjustment procedures should be used in the analysis stage.

7. 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 version 9.1 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. 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.

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APPENDIX

Table 1
Distribution of Prognostic Factor

Prognostic Factor	Factor Level	Number of Patients	% Distribution
Factor 1	1	32	64
	2	18	36
Factor 2	1	27	54
	2	23	46
Factor 3	1	12	24
	2	11	22
	3	18	36
	4	9	18

Prognostic factors used in the simulation study.

Table 2
Overall Mean Power and Treatment Balance for Various Sample Sizes, Alpha fixed at 0.5, Probability of Allocation fixed at 0.75 and Probability of Allocation given Treatments are Equally Balance is fixed at 0.5 for all scenarios

Sample Size	Power						Duncan's Groupings	Treatment Balance	
	95% CI	[a]Power	Wald	[b]Power	P-Value	[c]Power		SD	Overall Mean Balance
50	(0.456, 4.190)	0.020	0.737	0.020	0.545	0.020	I	0.020	0.500
75	(0.826, 4.861)	0.224	2.505	0.224	0.239	0.224	H	0.014	0.500
100	(0.885, 3.863)	0.274	2.856	0.274	0.205	0.274	G	0.010	0.500
125	(1.100, 3.868)	0.620	5.237	0.620	0.075	0.620	F	0.008	0.500
150	(1.135, 3.733)	0.683	5.759	0.683	0.060	0.683	E	0.007	0.500
175	(1.155, 3.549)	0.714	6.212	0.714	0.058	0.714	D	0.006	0.500
200	(1.190, 3.336)	0.798	7.007	0.798	0.036	0.798	C	0.005	0.500
225	(1.300, 3.457)	0.918	9.166	0.918	0.015	0.918	B	0.005	0.500
250	(1.431, 3.624)	0.984	12.099	0.984	0.004	0.984	A	0.004*	0.500
275	(1.476, 3.581)	0.992	13.603	0.992	0.003	0.992	A	0.004*	0.500
300	(1.521, 3.551)	0.997	15.229	0.997	0.002	0.997	A	0.004*	0.500
325	(1.550, 3.502)	0.998	16.593	0.998	0.001	0.998	A	0.003*	0.500
350	(1.528, 3.343)	0.995	16.730	0.995	0.001	0.995	A	0.003*	0.500
375	(1.444, 3.064)	0.996	15.101	0.996	0.002	0.996	A	0.002*	0.500
400	(1.517, 3.144)	0.999	17.727	0.999	0.0006	0.999	A	0.002*	0.500

[a]Power = Power generated from Wald's 95% Odds Ratio Confidence Limits;
[b]Power = Power generated from the Wald Chi-Square value;
[c]Power = Power generated from the contrast estimates p-values.
Duncan's Groupings - Means with the same letter are not significantly different.
(*) No significant difference in SD of the overall treatment balance Overall Mean Balance = Average mean balance from 5 different simulations using 10 000 replications.

Table 3
Overall Mean Power and Treatment Balance for Various Sample Sizes, Alpha fixed at 0.5, Sample Size fixed at 250 and Probability of Allocation given Treatments are Equally Balance is fixed at 0.5 for all scenarios

Probability of Allocation	Power						Duncan's Groupings	Treatment Balance	
	95% CI	[a]Power	Wald	[b]Power	P-Value	[c]Power		SD	Overall Mean Balance
0.10	(1.198, 4.884)	0.656	6.244	0.656	0.085	0.656	I	0.385	0.494
0.15	(1.314, 4.286)	0.818	8.347	0.818	0.039	0.818	H	0.337	0.510
0.20	(1.385, 4.003)	0.907	10.124	0.907	0.019	0.907	G	0.289	0.501
0.25	(1.424, 3.806)	0.955	11.440	0.955	0.010	0.955	F	0.241	0.501
0.30	(1.468, 3.726)	0.975	12.777	0.975	0.006	0.975	E	0.192	0.498
0.35	(1.486, 3.643)	0.986	13.685	0.986	0.004	0.986	D	0.144	0.500
0.40	(1.507, 3.619)	0.991	14.478	0.991	0.003	0.991	C	0.099	0.500
0.45	(1.507, 3.568)	0.992	14.663	0.992	0.003	0.992	B C	0.058	0.501
0.50	(1.513, 3.561)	0.994	14.825	0.994	0.002	0.994	A B C	0.030	0.500
0.55	(1.515, 3.553)	0.995	14.983	0.995	0.002	0.995	A B C	0.015	0.500
0.60	(1.518, 3.553)	0.995	15.185	0.995	0.002	0.995	A B C	0.009	0.500
0.65	(1.519, 3.550)	0.996	15.174	0.996	0.002	0.996	A B	0.006	0.500
0.70	(1.517, 3.545)	0.995	15.174	0.995	0.002	0.995	A B	0.005	0.500
0.75	(1.518, 3.543)	0.996	15.154	0.996	0.002	0.996	A	0.004*	0.500
0.80	(1.517, 3.543)	0.997	15.151	0.997	0.002	0.997	A	0.003*	0.500
0.85	(1.515, 3.544)	0.997	15.159	0.997	0.002	0.997	A	0.002*	0.500
0.90	(1.514, 3.532)	0.997	15.098	0.997	0.002	0.997	A	0.002*	0.500
0.95	(1.511, 3.532)	0.997	15.089	0.997	0.002	0.997	A	0.002*	0.500
1.00	(1.519, 3.544)	0.997	15.193	0.997	0.002	0.997	A	0.002*	0.500

[a]Power = Power generated from Wald's 95% Odds Ratio Confidence Limits;
[b]Power = Power generated from the Wald Chi-Square value;
[c]Power = Power generated from the contrast estimates p-values.
Duncan's Groupings - Means with the same letter are not significantly different.
(*) No significant difference in SD of the overall treatment balance Overall Mean Balance = Average mean balance from 5 different simulations using 10 000 replications.

Table 4
Overall Mean Power and Treatment Balance for Various Sample Sizes, Alpha fixed at 0.5, Sample Size fixed at 250 and Probability of Allocation is fixed at 0.75 for all scenarios

Probability of Allocation When Groups are Balanced	Power						Duncan's Groupings	Treatment Balance	
	95% CI	[a]Power	Wald	[b]Power	P-Value	[c]Power		SD	Overall Mean Balance
0.1	(1.518, 3.544)	0.996	15.160	0.996	0.002	0.996	A B	0.003*	0.502
0.2	(1.517, 3.544)	0.997	15.158	0.997	0.002	0.997	A	0.003*	0.501
0.3	(1.518, 3.544)	0.996	15.161	0.996	0.002	0.996	A B	0.003*	0.501
0.4	(1.518, 3.544)	0.996	15.158	0.996	0.002	0.996	A B	0.004*	0.500
0.5	(1.519, 3.544)	0.997	15.160	0.997	0.002	0.997	A	0.004*	0.500
0.6	(1.519, 3.544)	0.997	15.157	0.997	0.002	0.997	A	0.004*	0.500
0.7	(1.520, 3.547)	0.996	15.185	0.996	0.002	0.996	A B	0.003*	0.499
0.8	(1.516, 3.543)	0.996	15.152	0.996	0.002	0.996	AB	0.004*	0.499
0.9	(1.518, 3.544)	0.996	15.156	0.996	0.002	0.996	A B	0.003*	0.498
1.0	(1.516, 3.540)	0.996	15.121	0.996	0.002	0.996	A B	0.003*	0.498

[a]Power = Power generated from Wald's 95% Odds Ratio Confidence Limits;
[b]Power = Power generated from the Wald Chi-Square value;
[c]Power = Power generated from the contrast estimates p-values.
Duncan's Groupings - Means with the same letter are not significantly different.
(*) No significant difference in SD of the overall treatment balance
Overall Mean Balance = Average mean balance from 5 different simulations using 10 000 replications.

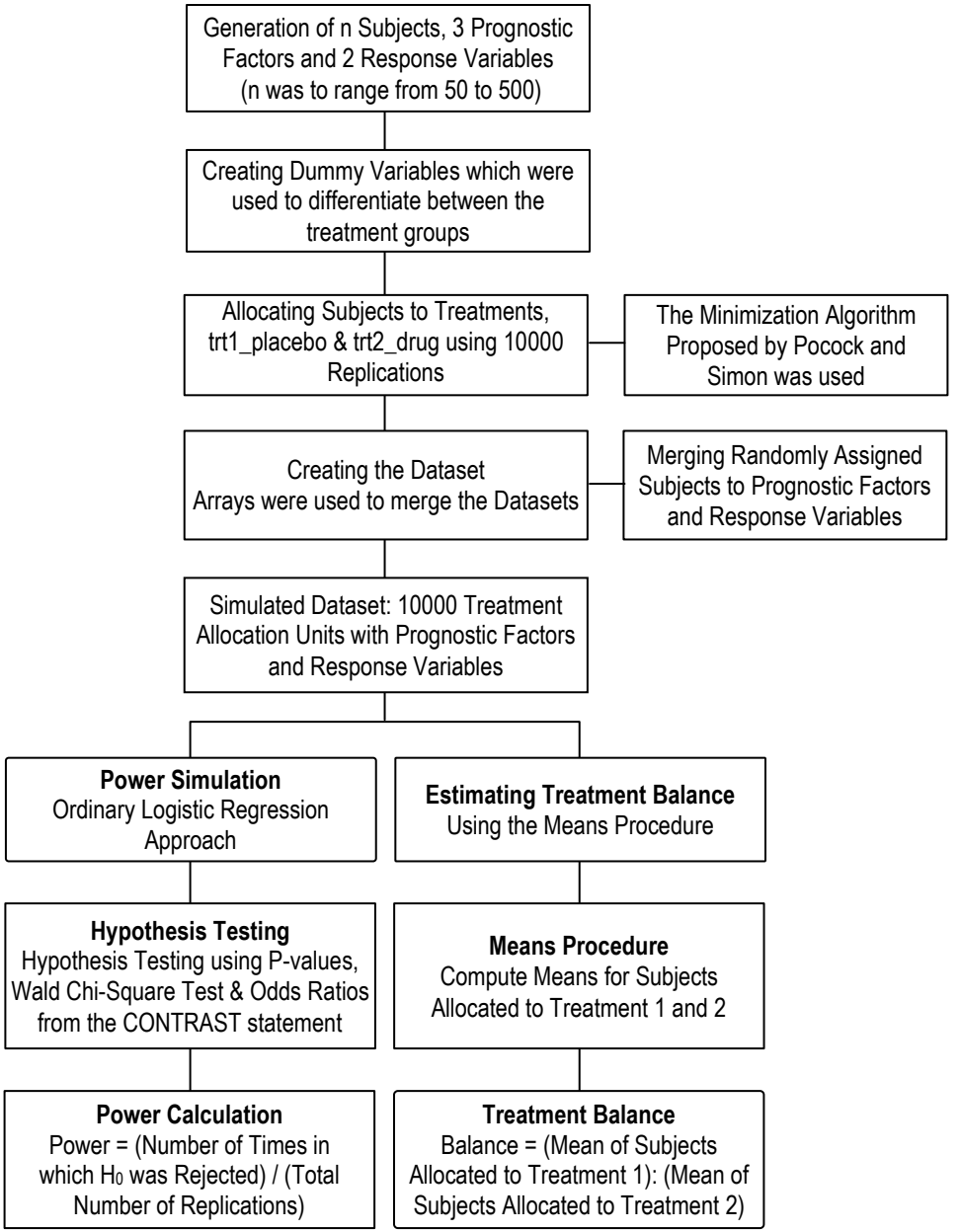

Figure 1: Flowchart for the algorithm used in this study for data simulation, treatment allocation using the minimization technique, treatment balance testing and power simulation using the ordinary logistic regression approach

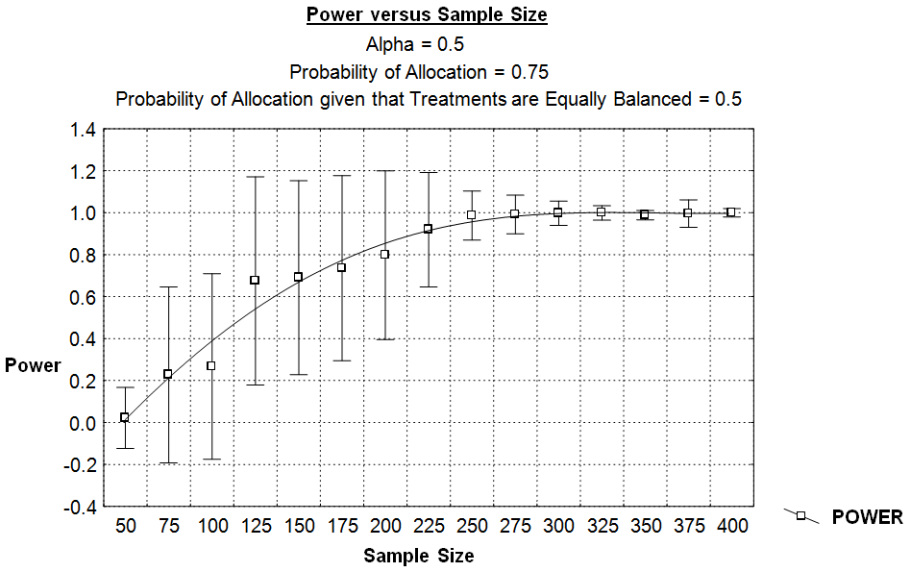

Figure 2: Power versus Sample Size whilst probability of allocation is set at 0.75 and probability of allocation given treatment groups are equally balanced is set at 0.5

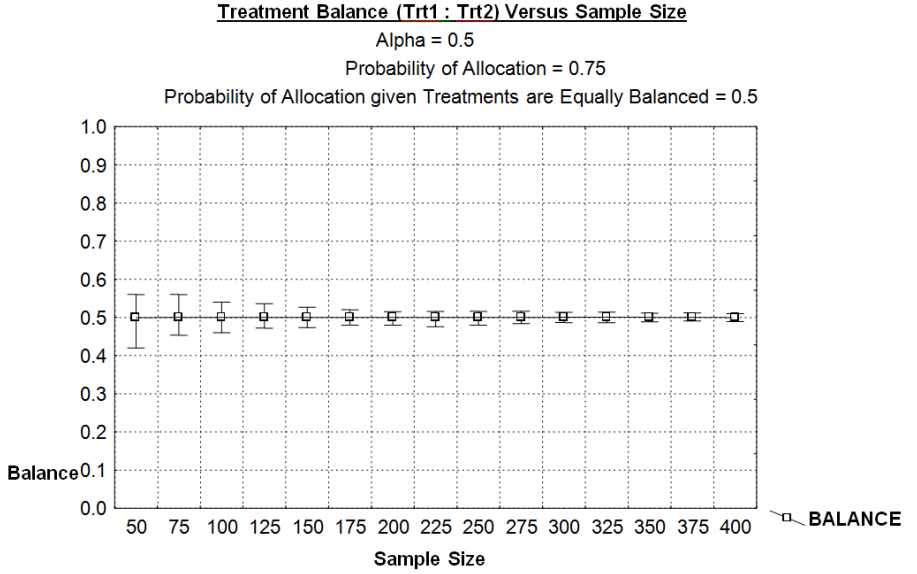

Figure 3: Treatment balance versus Sample Size whilst probability of allocation is set at 0.75 and probability of allocation given treatment groups are equally balanced is set at 0.5

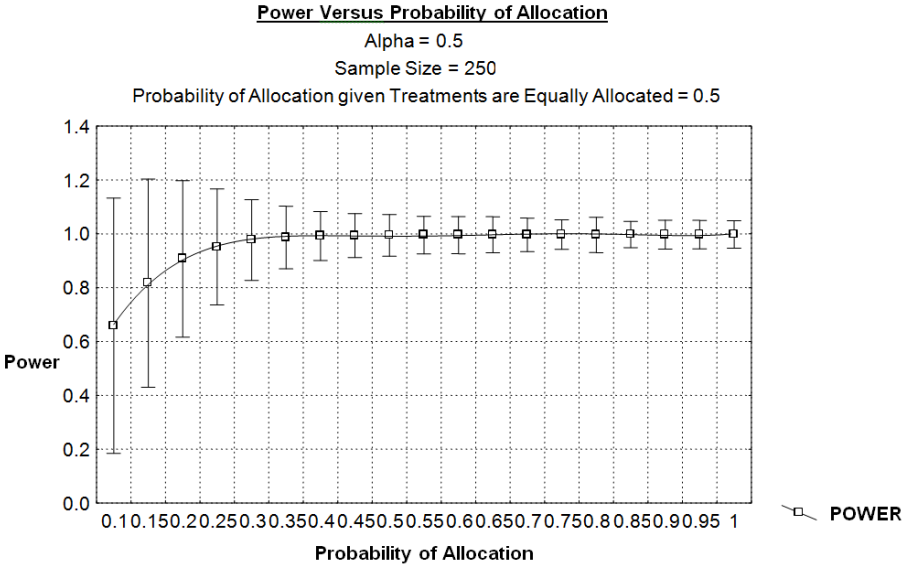

Figure 4: Power versus probability of allocation whilst sample size is set at 250 and probability of allocation given treatment groups are equally balanced is set at 0.5

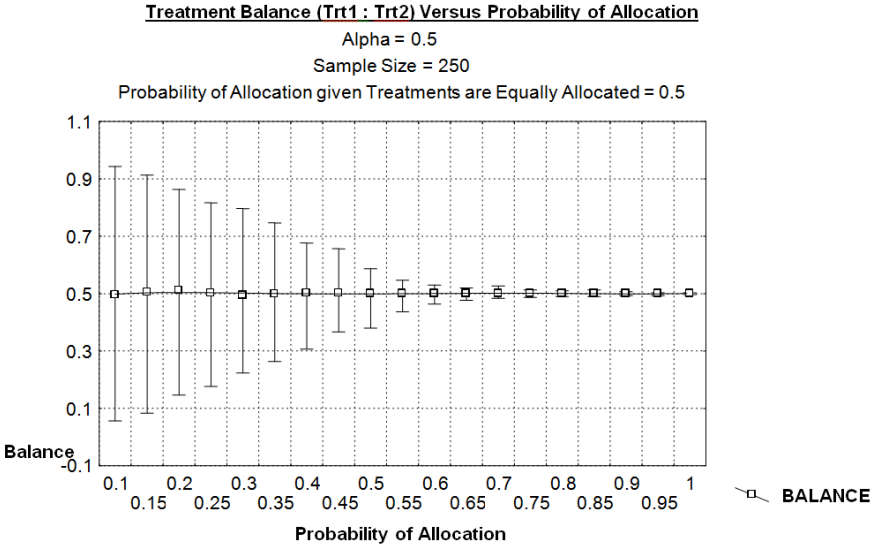

Figure 5: Treatment balance versus probability of allocation whilst sample size is set at 250 and probability of allocation given treatment groups are equally balanced is set at 0.5

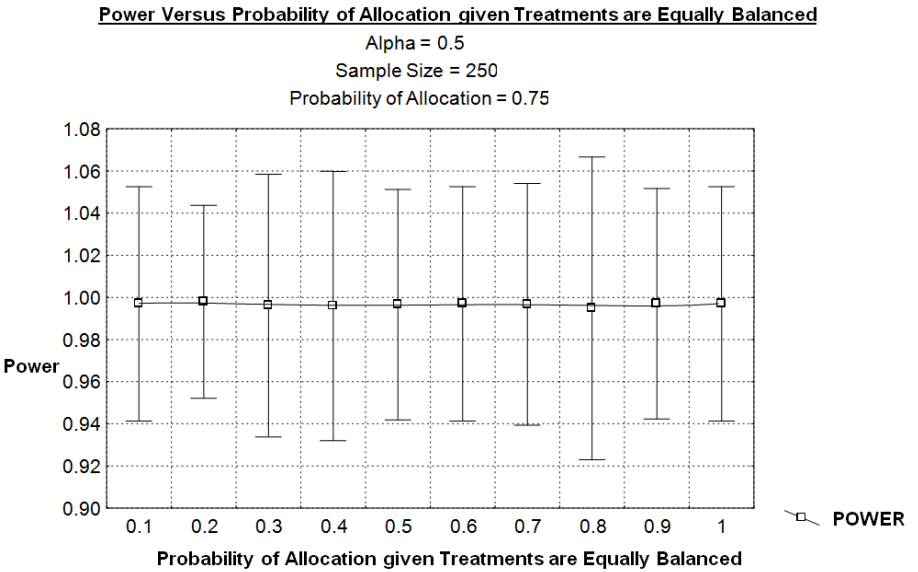

Figure 6: Power versus probability of allocation given treatment groups are equally balanced whilst sample size is set at 250 and probability of allocation is set at 0.75

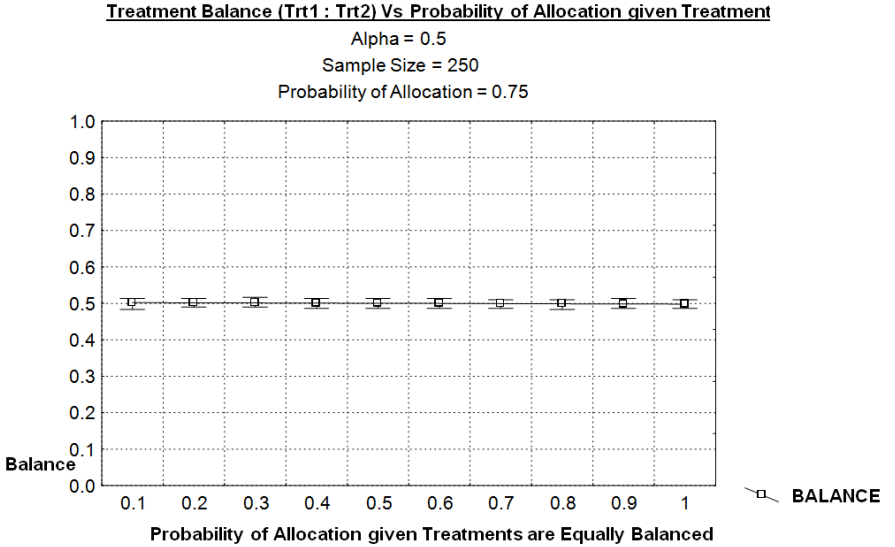

Figure 7: Treatment balance versus probability of allocation given treatment groups are equally balanced whilst sample size is set at 250 and probability of allocation is set at 0.75

SIMULATION CODE

```
/*
-------------------------------------------------------------------------
SAS SIMULATION CODE, MINIMIZATION TREATMENT ALLOCATION
-------------------------------------------------------------------------
2009 Copyright (c) by Marange C.S
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
*************************************************************************
-------------------------------------------------------------------------
*/
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
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
*************************************************************************
-------------------------------------------------------------------------
*/
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;
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*/
RUN;
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;
DATA power2;
```

```
SET power1;
SET powerr1;
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 exsist 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**************************/
```