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ANALYSIS OF REPEATED MEASUREMENTS DESIGNS (RMDS) STRONGLY BALANCED FOR RESIDUAL EFFECTS IN CLINICAL TRIALS

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Article Info

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Abstract

Statistics has been an important part of research in clinical trials. Good knowledge of statistical concepts and experimentations layout improves the reliability and quality of clinical studies. It has been observed that in many clinical studies, scientists and experimenters mostly use t-tests and simple analysis of variance technique for comparing treatments means and their performance. But there are many situations in which the experimental subjects are exposed more than once to the treatments and in different periods. In such situations, one-way ANOVA or simple experimental designs are not suitable. In such a situation RMDs are recommended in which the experimental subjects are exposed more than once to the treatments. The present article illustrates an example using RMDs and analysis in SPSS which is showing better results as compared to simple statistical designs.

Keywords
RMDs, Strongly Balanced Designs, Block Designs, Optimal Designs

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1. Introduction

Clinical studies help different therapies resulting in the optimal combinations of treatment. Before the advancement of such clinical experimentations, the main response was obtained from the patients or from their medical history to draw conclusions. In 20th century, the concepts of statistics were applied to medical research and experimentations. Statistics is basically science of the inferential process

particularly the plan and analysis of surveys, experiments and observational studies (Piantadosi, 2005). The correct utilization of statistical concepts in biomedical and clinical research plays an important role in improving the quality of research studies and observing research ethics. However the misuse of statistical concepts is unethical and can have damaging clinical results in medical outcomes. The experimental structure which allows us to use present experimental resources more efficiently is to measure each experimental subject under different treatments in different periods is RMDs (RMDs) (see Jones & Kenward, 1989). These designs are also famous with the names of cross-over designs, time-series designs, before after designs, switch-over trials, designs involving sequences of treatments *etc*. Such designs have been used extensively and advantageously in different fields of research studies preferably in nutrition experiments with dairy cattle, clinical trials in medical research, psychological experiments and bio-assays. Longitudinal studies are the kind of such designs because in these studies we record observations on same subjects in different time periods (Keselman *et. al*.,1999; Keselman *et. al*, 2001; Ellis,1999; van Der Leeden,1998). An example of a repeated measurement data in a longitudinal study can be the measurement of blood pressure of patients after every ten days in which patients are followed at an interval of 2 weeks for 2 months. The main advantage of using such experimental designs is that each treatment serves as its own control. These designs have been studied by several research workers; (Williams, 1949; Patterson, 1952; Patterson & Lucas, 1962; Berenblut, 1964; Saha, 1970; Sharma, 1981) etc are a few among them.

The present study brings the attention of clinical scientists and experimenters towards the latest developments in the construction and analysis of RMDs. The construction procedure to develop RMDs strongly balanced for carryover effects with v = 15 with the sets of shifts [1,2,3,9]+[8,6,7,4]+[11,12,13,14] has been constructed through the Method of Cyclic Shifts (Rule I). This rule of construction has been discussed in detail in (Iqbal & Jones 1994, Iqbal & Tahir 2009, Iqbal *et al*. 2010, Bashir *et al*. 2018 and Rasheed *et al*.2018). Considering the parameters of the proposed designs, this study demonstrates the use of RMDs with the help of SPSS by using the data of 45 patients whose Hemoglobin (Hb) (g/dl) were examined at 5 different time periods i.e. 0 days, 10^{th} day, 20^{th}-day 40^{th} day and 60^{th} day from a clinical study by giving fifteen different kinds of treatments/medicines.

2. Basic Assumptions and Uses of RMDs

RMDs is a design in which experimental subjects are examined over two more periods/time. The experimental subjects are given treatments repeatedly over different periods rather different subjects are given different treatments.

The use of RMDs can be justified in the following ways.

- When the budget is limited, the experimenter is bound to use each experimental subject for several tests.
- There are many experiments in which treatment has not such a devastating effect on the experimental subject. In such situations, experimental subjects can be used more times than once.
- One of the purposes of the experiment is to look for the significance of several effects like a direct, period or carryover effects, etc. Such designs are recommended in these situations.
- Sometimes experimental units are few in amount, so they have to be used repeatedly.
- When there are carryover effects in the model. The carry-over or residual effect is the effect of a previous treatment level on the observed behavior in a preceding period of the same treatment condition.

The carryover effect in the model should be balanced out to avoid bias in the study. It means that each treatment should be followed every other treatment in the level or period the equal number of times which introduces the term of balancing in these designs.

Main assumptions of such designs are as follow;

- The dependent variable is continuous and is examined on an interval or ratio scale.
- The sample will be selected randomly from the population.
- The dependent variable has normal distribution.
- The population variances for test occasions are equal.

Following figures show the verification of the assumptions for carrying out the analysis through the repeated measurements model.

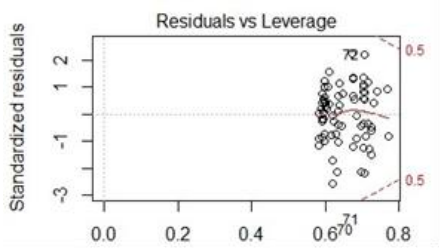

Figure 1: Residual Vs Leverage

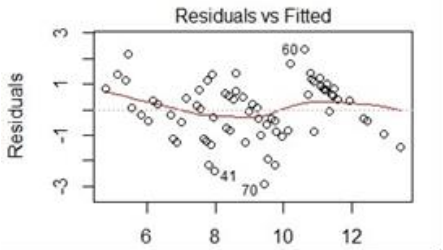

Figure 2: Residual Vs Fitted

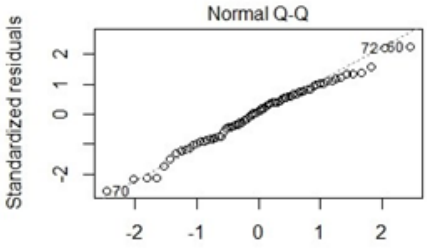

Figure 3: Q-Q plot

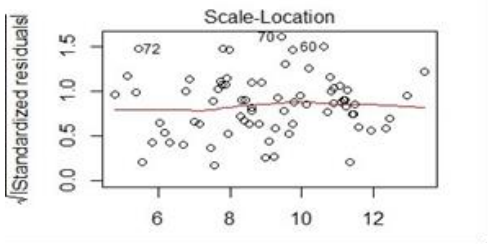

Figure 4: Location-Scale

Figure 1 does not show any influential cases as all of the cases are within the dashed Cook's distance line. If there is any point outside of Cook's distance line we would further evaluate those data points. The plot of residuals vs. fitted plot should be random and there should be no clear pattern in it The graph of our study shows good fit. The normal Q-Q plot in figure 3 helps determine if data points of Hb (g/dl) is normally distributed by plotting quantiles (i.e. percentiles) from our distribution against a theoretical distribution. Since Hb (g/dl) is normally distributed as it is plotted on the straight line on the QQ-plot. Plot looks relatively fine indicating normal distribution with straight line. The Scale-Location plot in figure shows whether residuals are spread equally along with the predictor range, i.e. Homoscedastic. The line on this plot is horizontal showing it Hetroscedastic.

4. Analysis of RMDs in SPSS And Results

The layout of the design which will be used for the analysis of hemoglobin is discussed in [Table 1]. We have the first shift = [1,2,3,9], second shift = [8,6,7,4] and third shift is [11,12,13,14]. The layout will be constructed using the first shift in [Table 1]. Write the first fifteen experimental subjects from 0 to 14. Add the first element of the first shift in the first row which will generate the first row of the design. Since the design is cyclic, the treatment 15 will be replaced by 0 and 16 by 1, and so on.

Table 1: Layout of the Treatments on Experimental Subjects

								Patients							
Periods (days)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
0	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
10	1	2	3	4	5	6	7	8	9	10	11	12	13	14	0
20	3	4	5	6	7	8	9	10	11	12	13	14	0	1	2
40	6	7	8	9	10	11	12	13	14	0	1	2	3	4	5
60	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
								Patients							
Periods	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
0	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
10	8	9	10	11	12	13	14	0	1	2	3	4	5	6	7
20	14	0	1	2	3	4	5	6	7	8	9	10	11	12	13
40	6	7	8	9	10	11	12	13	14	0	1	2	3	4	5
60	5	6	7	8	9	10	11	12	13	14	0	1	2	3	4
								Patients							
Periods	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**

0-day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
10-day	11	12	13	14	0	1	2	3	4	5	6	7	8	9	10
20-day	8	9	10	11	12	13	14	0	1	2	3	4	5	6	7
40-day	6	7	8	9	10	11	12	13	14	0	1	2	3	4	5
60-day	7	8	9	10	11	12	13	14	0	1	2	3	4	5	6

One way RMDs in SPSS can be performed with the procedure "Analyze" menu > "General Linear Model" > "Univariate".

For analyzing RMDs the data in SPSS is different from other ANOVA models as it includes direct effect, carryover or residual effect and period effect. [Table 2] shows the few entries data that would be added in SPSS data editor.

The syntax of SPSS used for the analysis is ;

UNIANOVA Hemoglobin BY patients period treatment carryover

/METHOD=SSTYPE (3)

/INTERCEPT=INCLUDE

/CRITERIA=ALPHA(0.05)

/DESIGN=patients period carryover treatment.

Table 2: Data in SPSS

Patients	**Periods**	**Treatments**	**Carryover**	**Hb (g/dl)**
1	1	0	0	12.0
1	2	1	0	9.3
1	3	3	1	6.5
1	4	6	3	5.6
1	5	0	6	8.9
2	1	1	1	7.6
2	2	2	1	12.3
2	3	4	2	8.0
2	4	7	4	12.2
2	5	1	7	12.0
3	1	2	2	9.3
3	2	3	2	6.5
3	3	5	3	5.6
3	4	8	5	8.9

3. Comparison of RMDs With Other Designs In The Literature

RMDs provide efficient results as compared to other designs present in the literature since they include direct, period, and carryover effects in the model. In completely randomized designs (CRD), the treatments will be compared with each other without considering other extraneous factors. In randomized complete design (RCBD) in which periods (0 days, 10^{th} day, 20^{th} day 40^{th} day, and 60^{th} day) will be treated as blocks. Models for CRD, RCBD, and RMD are as follow respectively with mean square error (MSE) ;

Total Sum of Squares = Treatments Sum of Squares + Error Sum of Squares (MSE = 4.111)

Total Sum of Squares = Treatments Sum of Squares + Blocks Sum of Squares + Error Sum of Squares (MSE = 4.187)

Total Sum of Squares = Treatment Sum of Squares + Period Sum of Squares + Direct Sum of Squares + Carryover Sum of Squares + Error Sum of Squares (MSE = 3.480)

The procedure for comparing the performance of design used in the literature is well known as relative efficiency. Relative Efficiency = $\frac{MSE_{CRD}}{MSE_{RMD}}$ = 4.111/3.480 = 1.18 x 100 = 118 %

and $\frac{MSE_{RCBD}}{MSE_{RMD}}$ = 4.187/3.480 = 1.20 x 100 = 120% which means that RMD is 118% more efficient than CRD and 120 % efficient than RCBD. In both situations, whether is one-way ANOVA or two-way ANOVA, proposed RMDs are far better procedure than both as they consider carry-over effects and period effects at the same which improve the efficiency of the study. The SPSS will produce variou tables as output but for the interpretation purpose ANOVA table will be discussed. In baseline time period (0 day), the average hemoglobin is 9.727 (SE = 0.3405), on the 10th day the average is improved to 9.638 (SE = 0.3459). In the third period (20th day), the average hemoglobin is 9.9664 (SE = 0.3039), on the 40th day the average was 9.671 (SE = 0.2962), and in the 60th day the average hemoglobin was observed 9.807 (SE = 0.2707). The ANOVA table [Table 3] is telling us a good story about the significance between the difference of treatments means applied on 45 patients. The treatments is showing a significant result (p = 0.031**). There is overall significance between the treatment means and also carry-over effects of treatments is playing its significant role in (p = 0.010***).

Table 3: Analysis of Variance for Hb (g/dl)

Source	SS	Degree of freedom	MSE	F	p-value
Corrected Model	408.03	76	5.369	1.543	0.013**
Intercept	21186.111	1	21186.114	6088.120	0.000***
Period	0.919	4	.230	0.066	0.992
Treatment	92.518	14	6.608	1.899	0.031**
Patients	302.07	44	6.865	1.973	0.001***
Carryover	107.70	14	7.693	2.211	0.010**
Error	515.02	148	3.480		
Total	22099.12	225			
Corrected Total	923.05	224			

****significant**
*****highly significant**

4. Discussion

Presently, The RMDs strongly balanced for carryover effects have attained immense importance in clinical studies for the reason of their estimability property of treatment and carry-over effects independently. In this layout of the design, extra period/strongly circular balanced has been used in which treatments in the first period are the same as in the fifth period. In RMDs each experimental subject i.e. patient is considered as a block. There is always a desire for an experimenter to have independent estimates of direct and carry-over effects. Different arrangements of treatments have been used in clinical research but the pattern used by this method gives the estimation of direct and carry-over effects independently as both carryover effects and direct effects are repeated same number of times. This procedure can be extended to several numbers of treatments and period sizes. They allow the comparison of treatments on a within-patients as well as within-period effect. In our proposed structure of design

which are strongly circular balanced carryover effect is replicated with the same number of times as direct effect and therefore share equal efficiency. The researchers before choosing the design of their interest should consider the carryover effect and other factors in their mind before applying statistical designs and getting their response.

5. Conflict of Interest

There is no conflict of interest.

6. References

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