CROSSOVER TRIAL IN MEDICAL STATISTICS

Norzaida Abas

Submitted in partial fulfillment of the
University of Wales
requirements for the degree of
Master of Science in Statistics.

1995

School of Mathematics
University of Wales College of Cardiff

DECLARATION

I hereby declare that this dissertation entitled "Crossover Trial in Medical Statistics" is entirely my own work, and that due reference and acknowledgement are made where necessary. It has not been, or currently being submitted in consideration for any other degree.

Candidate : .....

Director of Studies : .....

Date : 28/9/95

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Mr. Terence C. Iles whose guidance, suggestions and constructive criticisms I found most helpful in completing my dissertation. I also would like to extend my gratitude to Dr F.D.J.Dunstan for providing me with some of the required data.

To my parents , Abas and Mariam
for the love and encouragement

and husband ,Rashid
and sons,
Hadi and Hakim
for simply being wonderful.

SUMMARY

In clinical trials, crossover trials are experiments in which patients are allocated a series of treatments with the objective of comparing the different treatments or different doses of the same treatment. This design attracts clinicians because it eliminates between-subjects variability. However, there is the possibility of the existence of residual or carryover effects and this has lead different authors to develop different assumptions in order to interpret the outcome of the trial.

In this project some aspects of crossover trials are reviewed. The assumptions of the underlying models are critically described and each type of the design is complemented by a numerical example. Details of the calculations are described, and particular trials are interpreted. These analysis are included in the hope that they explain the theoretical aspects of crossover trials.

The topic of crossover trial is indeed very, very extensive, and with only limited time, this project covers only a fraction of this subject. The main types of crossover trials are the simple 2x2 design, the extensions of the two treatments design and the design with more than two treatments and more than two periods. This project concentrates on the statistical aspects of these designs and particularly on the simple 2x2 design. The 2x2 design is by far the most popular but unfortunately the most controversial due to carryover effects. Recent suggestions by some authors on this issue will also be discussed.

CONTENTS

CHAPTER

1

INTRODUCTION TO CROSSOVER TRIALS

In clinical trials to compare the effect of two treatments say treatment A and B one of the two following methods could be adopted:--

- patients are randomly divided to two groups, and each group would be randomly assigned to one treatment only. This procedure is called Parallel group trial.
- patients are randomly divided into two groups, and each would receive both treatments. However, the sequence of treatments received by the two groups is different, if the first group were to receive the treatments in the sequence of A then B, the second group would receive the treatments in the reverse order B then A. Such a procedure is known as Crossover trial.

Table 1.1

	Period 1	Period 2
GROUP 1	A	B
GROUP 2	B	A

This second procedure is quite appealing to clinicians based largely on the intuitive feeling that by observing the same patient for different treatments would give a more accurate result than would be given by observing different treatments on different patients. In other words the between patient's variability is being eliminated.

The striking feature of a crossover trial is that each patient receives more than one treatment. The two treatments in the two periods design that was described earlier is the simplest of the family of crossover trials. It is also known as 2x2 or AB/BA design. A more complicated design would involve two treatments in more than two periods designs, or more than two treatments in more than two periods design.

Table 1.2 Example of two treatments in more than two periods design.

	Period 1	Period 2	Period 3
GROUP 1	A	B	B
GROUP 2	B	A	A

Table 1.3 Example of 4 treatments in 4 periods design

	Period 1	Period 2	Period 3	Period 4
GROUP 1	A	B	C	D
GROUP 2	B	C	D	A
GROUP 3	C	D	A	B
GROUP 4	D	A	B	C

Although crossover trials are popular in clinical research such as pharmacology, not all types of conditions could apply crossover trials. Crossover trials are restricted to or suitable for only certain conditions such as chronic, relatively stable diseases and noncurative disease. In the issues of British Medical Journal for the period from Jan 1980-April 1988, more than 80 clinical trials adopted the crossover principle. Of this figure more than half were applied to conditions such as hypertension, diabetes, angina and asthma (Jones and Kenward (1989)). If this design is applied to conditions where the treatments are expected to affect a cure, by the time the patient is due to receive the second or later treatments it is

possible the patient may already have been cured. It is possible that clinicians are becoming more cautious in the use of crossover trials. A survey of the British Medical Journal between July 1989 and December 1994 showed only 18 articles describing crossover trials.

In crossover trials it is important to recognise the factors that might have influenced patients' response. The contributing factors are as follows:--

- ***Direct treatment effects***

This is the treatment's effects on the subjects during the period which the treatment is applied.

- ***Period effects***

Senn (1993) reffered to period effect as a trend affecting the experiment as a whole. Suppose subjects are given two identical treatments for both periods of the trial. It is possible that measurements in one period might be significantly larger or smaller than the other period , for example responses in period two may be larger than responses in period one. Bearing this in mind, a crossover trial is conducted such that two groups of patients receive treatments in different order.

- ***Carryover or Residual effects***

One of the drawbacks of this design is the possibility that the effects of a treatment given in one period might not be confined to that period alone, therefore the effects could be carried over into succeeding periods. This kind of effect is known as the carryover effect. There are a few types of carryover effects for example first-order carryover effects which stay one period beyond application. Second-order carryover effects stay two periods beyond application, and generally kth-order carryover effects stay for k periods beyond application.

To solve the problem of carryover effects,right after each treatment the patients are required to 'rest' for a specific time before receiving the next treatment. This period is called the washout period and its purpose is to let the body 'wash out' totally the effect of a treatment given previously.

- ***Period by treatment effects***

This is also known as Direct-treatment by period interaction. As the name suggests, different conditions may be present in different periods and this might have an effect on patients. For example certain diseases and conditions depend on the weather. Let say a trial is conducted from December to Febuary for period 1 and March to May for period two. If the trial is applied to patients with an asthmatic problem, it is possible that the patients under treatment are being affected by the weather conditions.

1.1 THE STRUCTURE OF THIS REPORT

The majority of this report is about the 2 x 2 crossover design. It is mentioned by various authors that the 2 x 2 design is more frequently used in clinical trials than trials with more than are two treatments in more than two periods. The statistical analysis and the intepretations of these analysis are covered in some detail in chapter two and three.

Chapter four will briefly review the complex designs for two treatments. These designs refer to the two treatment designs with either more than two periods or more than two sequence groups or both.

Chapter five discusses the higher order designs, those which involve designs with more than two treatments in more than two periods. The scope of these designs is indeed quite vast, although in this report the

discussion is restricted to designs with the number of periods equals to the number of treatments.

In this report there are four numerical examples. Three of these are about the 2x2 design while the fourth concerns with the design with more than two treatments and more than two periods. Although statistical packages are available, most of the calculations are done using the spreadsheet in EXCEL 5. Hence each step of the calculations can be easily understood.

Throughout this report patients will be refered to as 'subjects'.

In all of the trials described in this report the conventional assumption of normally distributed response variables is made. However, diagnostic checks to verify this assumption are made in the illustrative examples.

CHAPTER 2

SIMPLE AB/BA DESIGN

2.1 INTRODUCTION

This design consists of two treatments being assigned to subjects over two periods of time and it is used where there are only two alternative treatment sequences. Subjects in one group would receive treatment A first and after a washout period would receive treatment B. The other group would receive treatments in the reverse order treatment B first then treatment A, also with a washout period in between treatments.

Table 2.1

	Period 1	Period 2
GROUP 1	A	B
GROUP 2	B	A

THE MODEL

The basic approach of the two periods crossover design and its analysis was proposed by Grizzle (1965), and it later become widely used as a reference on the use of crossover trials in clinical trials. The model and notation used throughout this report will be based on his work.

For this design there are only two treatment sequences.

i) sequence 1: treatment A in the first period followed by treatment B in the second period.

ii) sequence 2: treatment B in the first period followed by treatment A in the second period.

Let i and k be the index for sequences and periods, respectively. Since subjects are randomly assigned to either treatment sequence, there exist two groups with n_i (i=1,2) subjects in each group. Let the observed response or outcome on the jth subject in the ith sequence during period k be denoted by Y_{ijk} . Table 2.2 shows the layout of responses from subjects.

Table 2.2

Group	Period 1	Period 2
1.AB Sequence	$Y_{111}, Y_{121}, \ldots\ldots Y_{1n11}$	$Y_{112}, Y_{122}, \ldots\ldots Y_{1n12}$
2.BA Sequence	$Y_{211}, Y_{221}, \ldots\ldots Y_{2n21}$	$Y_{212}, Y_{222}, \ldots\ldots Y_{2n22}$

The appropriate model for the response Y_{ijk} is:--

$$Y_{ijk} = \mu + \pi_k + \phi_\ell + \lambda_\ell + \xi_{ij} + \varepsilon_{ijk}$$

where

μ : overall mean
π_k : effect of the kth period, k= 1,2
ϕ_ℓ : direct effect of the given treatment , ℓ = A,B
λ_ℓ : carryover effect of the treatment l in the first period on the response of subjects in the second period. ℓ = A,B
ξ_{ij} : subject effect , i=1,2 , k=1,2
ε_{ijk} : random error , i=1,2, j= 1,2,...n_i , k=1,2

Both ξ_{ij} and ε_{ijk} are assumed to be random effects that are independent with variances σ_ξ^2 and σ_ε^2 , respectively.

The typical responses Y_{ijk} for each group in each period are as follows:--

Table 2.3

Group	Period 1	Period 2
1.AB Sequence	$\mu+\pi_1+\phi_A+\xi_{1j}+\varepsilon_{1j1}$	$\mu+\pi_1+\phi_B+\lambda_A+\xi_{1j}+\varepsilon_{1j2}$
2.BA Sequence	$\mu+\pi_1+\phi_B+\xi_{2j}+\varepsilon_{2j1}$	$\mu+\pi_2+\phi_A+\lambda_B+\xi_{2j}+\varepsilon_{2j2}$

The total responses and mean responses for each group in each period are presented in table 2.4 and 2.5 respectively.

Table 2.4

Group	Period 1	Period 2	Total
1.AB Sequence	$Y_{1.1}$	$Y_{1.2}$	$Y_{1..}$
2.BA Sequence	$Y_{2.1}$	$Y_{2.2}$	$Y_{2..}$
Total	$Y_{..1}$	$Y_{..2}$	$Y_{...}$

Table 2.5

Group	Period 1	Period 2	Mean
1.AB Sequence	$\bar{Y}_{1.1}$	$\bar{Y}_{1.2}$	$\bar{Y}_{1..}$
2.BA Sequence	$\bar{Y}_{2.1}$	$\bar{Y}_{2.2}$	$\bar{Y}_{2..}$
Mean	$\bar{Y}_{..1}$	$\bar{Y}_{..2}$	$\bar{Y}_{...}$

2.2 ESTIMATION AND TESTING

In this section, the following test will be carried out :--

- testing for carryover effects
- testing for treatment effects
- testing for period effects

Since ξ_{ij} and ε_{ijk} are assumed to be random, then the fixed effects model associated with each subjects are shown in the table below.

Table 2.6

Group	Period 1	Period 2
1.AB Sequence	$\mu+\pi_1+\phi_A$	$\mu+\pi_2+\phi_B+\lambda_A$
2.BA Sequence	$\mu+\pi_1+\phi_B$	$\mu+\pi_2+\phi_A+\lambda_B$

2.2.1 *Testing for carryover effects*

Over the years much has been said about the carryover effects and the validity of the statistical tests that are used to identify its presence.

However the popular view when it comes to testing for carry over effect is to assume that there is no direct treatment by period interaction. In a 2x2 crossover design, the carry over effect is said to be intrinsically aliased with the direct treatment by period interaction. Furthermore because of this aliasing, a test for non existence of carryover effects (i.e $\lambda_A = \lambda_B = 0$) can not be carried out. However we can test for $\lambda_A = \lambda_B$, i.e that the carryover effects are equal.

Hence,

$$\text{Ho}: \ \lambda_A = \lambda_B$$

Let T_{ij} denote the total of subjects' responses in period 1 and period 2.

Total responses for the jth subject in group 1 is

$$T_{1j} = Y_{1j1} + Y_{1j2}$$

and for the jth subject in group 2,

$$T_{2j} = Y_{2j1} + Y_{2j2}$$

The expected values of T_{1j} and T_{2j},

$$E[T_{1j}] = 2\mu + \pi_1 + \pi_2 + \phi_A + \phi_B + \lambda_A$$

$$E[T_{2j}] = 2\mu + \pi_1 + \pi_2 + \phi_A + \phi_B + \lambda_B$$

Now let $\delta_\lambda = \lambda_A - \lambda_B$ and its estimator is $d_\lambda = \overline{T}_{1.} - \overline{T}_{2.}$

with $E[d_\lambda] = \delta_\lambda$

$$Var[d_\lambda] = \sigma_\delta^2 \frac{(n_1+n_2)}{n_1 n_2} \qquad \text{where } \sigma_\delta^2 = 2(2\sigma_\xi^2+\sigma_\varepsilon^2)$$

σ_δ^2 is a pooled variance and is estimated by:

$$s_\delta^2 = \frac{\Sigma (T_{1j}-\overline{T}_{1.})^2 + \Sigma (T_{2j}-\overline{T}_{2.})^2}{(n_1 + n_2 - 2)}$$

The test statistic for carryover effects is :-

$$t_\lambda^* = \frac{d_\lambda}{s_\delta}\sqrt{\frac{n_1 n_2}{n_1 + n_2}}$$

The null hypothesis is rejected if $|t_\lambda^*| > t_{\alpha/2}(n_1+n_2-2)$

However in determining the critical region, Grizzle (1965) proposed to take a 10% two-sided level instead of the usual 5% two-sided level since testing for carryover must be done prior to testing for other effects, and the use of a 5% levelfor this preliminary test he felt was too conservative.

<u>When the Null hypothesis of $\lambda_A=\lambda_B$ is accepted</u>

If there is enough statistical evidence to support equal carryover effects then the analysis on treatment effects and period effects can be carried out.

<u>When the Null hypothesis of $\lambda_A=\lambda_B$ is rejected</u>

When the outcome of the test statistic is to reject the fact that $\lambda_A=\lambda_B$,we cannot proceed to test for treatment effects and period effects as shown later in section 2.2.2 and 2.2.3, respectively.

It must be noted that different authors have different intrepretations on this outcome. The views of these authors will be discussed in section 2.4.

For now we will assume that there is no evidence of differential carryover effects. Hence we can proceed to test for treatment effects and period effects.

2.2.2 *Testing for treatment effects*

It is important to note the assumption of equality of carryover effects (i.e $\lambda_A=\lambda_B$) prior to testing for treatment effects.

The null hypothesis is Ho : $\pi_A = \pi_B$

Let D_{ij} denote the difference between subjects' responses in period 1 and period 2. Hence,

For the jth subject in group 1,

$$D_{1j} = Y_{1j1} - Y_{1j2}$$

and for the jth subject in group 2,

$$D_{2j} = Y_{2j1} - Y_{2j2}$$

The expected values of D_{1j} and D_{2j} ,

$$E[D_{1j}] = \pi_1 - \pi_2 + \phi_A - \phi_B$$

$$E[D_{2J}] = \pi_1 - \pi_2 + \phi_B - \phi_A$$

Now let $\delta_\phi = \phi_A - \phi_B$. To test the null hypothesis, we evaluate the difference between D_{1j} and D_{2j} such that:-

$$E[\overline{D}_{1.}] - [\overline{D}_{2.}] = (\pi_1 - \pi_2 + \phi_A - \phi_B) - (\pi_1 - \pi_2 + \phi_B - \phi_A)$$

$$E[\overline{D}_{1.} - \overline{D}_{2.}] = 2(\phi_A - \phi_B)$$

Thus,

$$d_\phi = \frac{1}{2}[\overline{D}_{1.} - \overline{D}_{2.}]$$

with $E[d_\phi] = \delta_\phi$

$$\text{Var}[\,d_\phi\,] = \frac{\sigma_\phi^2}{4}\,\frac{(n_1+n_2)}{(n_1 n_2)} \qquad \text{where } \sigma_\phi^2 = 2\sigma_\varepsilon^2$$

σ_ϕ^2 is a pooled variance and is estimated by

$$s_\phi^2 = \frac{\Sigma(D_{1j} - \overline{D}_{1.})^2 + \Sigma(D_{2j} - \overline{D}_{2.})^2}{(n_1 + n_2 - 2)}$$

The appropriate 2-sample t test for testing for no difference in the treatment effects is :--

$$t_\phi^* = \frac{2\,d_\phi}{s_\phi}\sqrt{\frac{n_1 n_2}{n_1 + n_2}}$$

The critical region is :- $|t_\phi^*| > t_{\alpha/2}\,(n_1+n_2-2)$

2.2.3 *Testing for Period effects*

Here the test is to find out if the mean level of responses changed from period 1 to period 2.

$$\text{Ho} : \pi_1 = \pi_2$$

As before prior to testing for period effects, the assumption made is no difference of carry over effect (i.e $\lambda_A = \lambda_B$)

In testing for period effects, again we will make use of D_{ij}, difference of subjects responses in period 1 and period 2.

As defined earlier,

$$D_{1j} = Y_{1j1} - Y_{1j2}$$

$$D_{2j} = Y_{2j1} - Y_{2j2}$$

and the expected values

$$E[D_{1j}] = \pi_1 - \pi_2 + \phi_A - \phi_B$$

$$E[D_{2j}] = \pi_1 - \pi_2 + \phi_B - \phi_A$$

Now let $\delta_\pi = \pi_1 - \pi_2$

Then in order to test the null hypothesis, we need the sum of D_{1j} and D_{2j} such that

$$E[\bar{D}_{1.}] + E[\bar{D}_{2.}] = \pi_1 - \pi_2 + \phi_A - \phi_B + \pi_1 - \pi_2 + \phi_B - \phi_A$$

$$E[\bar{D}_{1.} + \bar{D}_{2.}] = 2(\pi_1 - \pi_2)$$

Hence the estimator for δ_π is $d_\pi = \frac{1}{2}(\bar{D}_{1.} + \bar{D}_{2.})$

The test statistics is given by

$$t_\pi^* = \frac{2d_\pi}{s_\pi}\sqrt{\frac{n_1 n_2}{n_1 + n_2}}$$

where s_π^2 is a pooled variance

$$s_\pi^2 = \frac{\Sigma(D_{1j} - \bar{D}_{1.})^2 + \Sigma(D_{2j} - \bar{D}_{2.})^2}{(n_1 + n_2 - 2)}$$

Reject the null hypothesis if $|t_\pi^*| > t_{\alpha/2}(n_1+n_2-2)$

2.2.4 THE ANALYSIS OF VARIANCE AND F-TESTS

The analysis of variance of the full model is presented in table 2.7.

Jones and Kenward (1989) reported that the first ANOVA table for 2x2 crossover design was given by Grizzle (1965), but was only applicable when the sample sizes in the two groups of subjects are equal (i.e $n_1=n_2$). Grizzle then made some amendments (Grizzle, 1974) which unfortunately did not improve the situation (Grieve, 1982). The correct ANOVA table as presented in the table 2.7 was given by Grieve (1982) though it was proposed earlier by Hills and Armitage (1979).

The Total corrected sum of squares (SS) is a decomposition of SS between-subjects and SS within-subjects. The SS between-subjects comprises of i) SS carryover and ii) SS between-subjects residual (SSR_{BS}). The SS within-subjects is made up of i) SS direct-treatments (adjusted for periods), ii) SS period (adjusted for direct-treatments) and iii) SS within-subjects residual (SSR_{WS}).

F-TESTS

Earlier in testing the hypothesis of interest, we made use of 2-sample t-tests. If we construct an ANOVA table, we could use the appropriate sum of squares for F-tests which are as effective as 2-sample t-tests in testing the hypothesis of interest (note that $t^2 = F$, where the numerator of F has 1 degree of freedom) .

- ***Testing for carryover effect***

Ho : $\lambda_A = \lambda_B$

$$\text{Let} \quad F_\lambda^* = \frac{\text{MS Carryover}}{MSR_{BS}}$$

Reject the null hypothesis if $|F_\lambda^*| > F_{\upsilon 1,\upsilon 2}$

As before, the following tests can only be carried out if this null hypothesis is accepted.

- ***Testing for Direct Treatment effect***

Ho : $\phi_A = \phi_B$ [assuming $\lambda_A = \lambda_B$]

$$\text{Let} \quad F_\phi^* = \frac{\text{MS Direct treatments}}{MSR_{WS}}$$

Reject the null hypothesis if $|F_\phi^*| > F_{\upsilon 1,\upsilon 2}$

- ***Testing for Period effects***

$$\text{Ho} : \pi_1 = \pi_2 \qquad [\text{ assuming } \lambda_A = \lambda_B \text{ }]$$

$$\text{Let} \quad F_\pi^* = \frac{\text{MS Periods}}{MSR_{WS}}$$

Reject the null hypothesis if $|F_\pi^*| > F_{\upsilon 1,\upsilon 2}$

TABLE 2.7 Analysis of Variance of the full model (Kenward and Jones(1989)

SOURCE	D.F	SUMS OF SQUARES
Between-subject	1	$\frac{2n_1n_2}{(n_1+n_2)}(\bar{Y}_{1..}-\bar{Y}_{2..})^2$
B-S Residual	n_1+n_2-2	$\sum_{i}^{2}\sum_{j}^{n_i} Y_{ij.}^2 - \sum \frac{Y_{i...}^2}{2n_i}$
W-SUBSECT: Direct treat. (adjusted for periods)	1	$\frac{n_1n_2}{2(n_1+n_2)}(\bar{Y}_{1.1}-\bar{Y}_{1.2}-\bar{Y}_{2.1}+\bar{Y}_{2.2})^2$
Periods (adjusted for treatment)	1	$\frac{n_1n_2}{2(n_1+n_2)}(\bar{Y}_{1.1}-\bar{Y}_{1.2}+\bar{Y}_{2.1}-\bar{Y}_{2.2})^2$
Within-subject Residual	n_1+n_2-2	$\sum_{i}^{2}\sum_{j}^{n_i}\sum_{k}^{2} Y_{ijk}^2 - \sum_{i}^{2}\sum_{j}^{n_i}\frac{Y_{ij.}^2}{2} - \sum_{i}^{2}\sum_{k}^{2}\frac{Y_{i.k}^2}{n_i} + \sum_{i}^{2}\frac{Y_{i...}^2}{2n_i}$
TOTAL	$2(n_1+n_2)-1$	$\sum\sum\sum Y_{ijk}^2 - \frac{Y_{...}^2}{2(n_1+n_2)}$

2.3 NUMERICAL ILLUSTRATION 1

The data from this example is taken from Fleiss (1986a). This study was about comparing the effects of 2 dose preparations of aspirins (say dose A and dose B) on gastric bleeding. Radioactive tagging was used to measure the amount of bleeding from patients. 16 patients took part in the study and each received a preparation for one week, and after a washout period of one week, they were given the other preparation. In the study patients were divided into eight pairs, in each pair patients would either be allocated to sequence 1 which is dose A followed by dose B, or sequence 2 which is dose B followed by dose A. These eight pairs of patients then formed a 2x2 Latin Square. An overview of the Latin Squares design is given in section 5.2 of Chapter 5.

Table 2.8

Square	Sequence	Patient no.	Period 1	Period 2
1	AB	1	1	2
	BA	2	5.1	3.8
2	AB	3	2.9	3.9
	BA	4	0.6	1.0
3	AB	5	4.8	3.1
	BA	6	4.0	5.8
4	AB	7	4.4	4.9
	BA	8	1.6	0.8
5	AB	9	2.3	1.3
	BA	10	4.1	4.7
6	AB	11	4.9	2.3
	BA	12	3.2	0.9
7	AB	13	6.8	4.5
	BA	14	2.3	4.0
8	AB	15	6.1	2.2
	BA	16	3.4	3.6

However instead of analysing the data as a Latin Square as Fleiss did, we divide patients into 2 groups with eight patients in each group. The first group consists of patients from each pair of the 2x2 Latin Square who were being allocated to sequence 1, and group 2 would then consists of the rest of the patients. Table 2.9 presents the new layout of the data. Notice that patients with odd numbers were refered to sequence 1 and those with even numbers to sequence 2.

Table 2.9

	Patient no.	Period 1	Period 2
AB	1	1	2
	3	2.9	3.9
	5	4.8	3.1
	7	4.4	4.9
	9	2.3	1.3
	11	4.9	2.3
	13	6.8	4.5
	15	6.1	2.2
BA	2	5.1	3.8
	4	0.6	1.0
	6	4.0	5.8
	8	1.6	0.8
	10	4.1	4.7
	12	3.2	0.9
	14	2.3	4.0
	16	3.4	3.6

The first part of this example is to test the various hypotheses using the t-tests. The final part is setting up of the analysis of variance table and consequently the F-tests for testing the same hypotheses. The calculations for this example is done using worksheet on 'EXCEL 5' and a copy of the worksheet is given in table 2.11

1)The first test that will be carried out is to test for differential carry over effects.

$$\text{Ho}: \lambda_A = \lambda_B$$

and $d_\lambda = \bar{T}_{1.} - \bar{T}_{2.} = 7.2625 - 6.1375 = 1.125$

$$s_\delta^2 = \frac{\Sigma (T_{1j} - \bar{T}_{1.})^2 + \Sigma (T_{2j} - \bar{T}_{2.})^2}{(n_1 + n_2 - 2)} = 8.209821$$

The test statistic for carryover effects is :-

$$t_\lambda^* = \frac{d_\lambda}{s_\delta}\sqrt{\frac{n_1 n_2}{n_1 + n_2}} = \frac{1.125 \quad (8 \times 8)^{1/2}}{2.865279\,(8+8)^{1/2}}$$

$$= 0.785$$

The p-value is 0.2223

and thus we accept the null hypothesis for no differential carryover effects.

2)Since carryover effects are not significant, we can proceed to test for treatments effects

The null hypothesis is Ho : $\phi_A = \phi_B$

$$d_\phi = \frac{1}{2}[\bar{D}_{1.} - \bar{D}_{2.}]$$

$$= 0.925$$

$$s_\phi^2 = \frac{\Sigma (D_{1j} - \bar{D}_{1.})^2 + \Sigma (D_{2j} - \bar{D}_{2.})^2}{(n_1 + n_2 - 2)}$$

$$= 2.033393$$