DESIGN AND ANALYSIS OF TWO TREATMENTS IN FIVE PERIODS CROSS-OVER DESIGNS

BY

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DECLARATION

Declaration by Candidate

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To my wife, children, parents, brothers, sisters, and friends without whose love and support this work would not have been possible.

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ABSTRACT

A crossover design is a repeated measurements design such that each experimental unit receives different treatments during the different time periods. A cross-over design with t treatments, p periods, and s sequences is denoted by C (t, p, s). In a majority of bioequivalence studies, design and analysis of lower order cross-over designs are normally associated with erroneous results. Higher order crossover designs are desirable in the analysis of crossover designs to eliminate carryover effects. The purpose of the study was to design and analyze two treatments in five periods crossover designs. The specific objectives of the study were to: Estimate treatments and residual effects of the designs; evaluate the design's optimality criteria; evaluate the design's robustness for missing data; and compare the Bayesian and the t- test analysis methods on treatments and carryover effects. The treatments and residual estimates were obtained using the Best Linear Unbiased Estimation (BLUE) method while the optimality criteria of the designs were determined by the variances of the treatments and carry-over effects, where the designs with minimum variance were considered to be optimum. In addition, the covariance of the two effects was used to evaluate the optimality of designs which estimate treatment effects in the presence of carry-over effects. Break down numbers were used to rank the designs according to their robustness against missing data. In the Bayesian method of analysis, the posterior quantities were obtained for the mean intervals of treatments and carry-over effects and the highest posterior density (HPD) graphs were plotted and interpreted using conditional probability statements. For validation purposes, the t-tests were performed and their results were compared with the Bayesian results. The C(2,5,2) in this study comprised of fifteen designs $(D_1 - D_{15})$ while the C(2,5,4) comprised of twelve designs$(D_{16} - D_{27})$. The findings of the study indicated that a majority of the designs considered gave estimates for treatments and carry-over effects . Additionally, two designs were optimal in estimating treatment effects for C $(2\times 5 \times 2)$ cross-over designs. Moreover, one design was found to be optimal and robust for missing data for C $(2\times 5 \times 4)$, and it was hence used in the analysis of a hypothetical example. From the Bayesian analysis, the probability of significant treatment difference in the presence of carryover effects was 1, while from the t-test, the calculated t −value of 11.73 was greater than the two sided tabulated value at 5% level of significance. The two analysis methods implied significant differences in the treatment effects. Finally, the mean subject profiles for a majority of periods and their respective sequences implied a direct treatment effect in favor of treatment B. In conclusion, it was established that variance-balance plays a major role in determining a suitable design. This is due to the fact that the optimal and robust for missing data in the study was more variance-balanced as compared to the other designs whose optimality and robustness for missing data were relatively lower. The study recommends that the optimal and robust for missing data design in this study be applied in bioequivalence experiments in assessment of efficacy of new treatments against standard ones. For further research the BLUE method should be used in estimation of effects for designs with more than two treatments.

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ABBREVIATIONS AND ACRONYMS

ANOVA: Analysis of Variance

ATE: Average treatment effects

BLUE: Best linear unbiased estimation

F.D.A: Food and Drug Authority

HPD: Highest posterior density

P.O.C: Proof of Concept

C (2,5): Two treatments five periods cross-over designs

C (2 ,5 ,2): Two treatments, five periods and two sequence cross-over design

D (2 ,5 ,4): Two treatments, five periods and four sequence cross-over design

D: Design

D_e: Eventual design.

∞ : Breakdown number of a perpetually connected design

DEFINITIONS OF TERMS

Break down Number: The maximum number of observations that can be lost before a design can be disconnected.

Carry-over effects: The effects of a treatment that persist after the end of the treatment period. Carry –over effects appear when the response to a current treatment is affected by the treatment that was applied in a previous period.

Cross-over design: This is a repeated measurements design such that each experimental unit receives different treatments during the different time periods.

Direct treatment effect: The effect of treatment at the time of its application. Often times abbreviated to treatment effect (when there is no possibility of confusion)

Eventual Design: The design containing the remaining subjects after drop out.

Period effect: A period is each one of the occasions in which a treatment is applied and thus period effects refers to those changes in the value of the response that are due to the response variable being measured at say, time t instead of $t+1$ or $t-1$.

Perpetually Connected Design: A planned design is perpetually connected if all subjects complete the first two periods and the eventual design is connected irrespective of subject dropout behavior in succeeding periods

Wash out Periods: A washout period is a gap in time between the applications of treatment levels such that any residual effect of a previous treatment level is removed and there is no detectable carry – over effects when assessing treatment effects.

CHAPTER ONE: INTRODUCTION

1.1 Introduction

This chapter covers the background to the study, statement of the problem, study objectives, significance of the study, justification and the scope of the study.

1.2 Background information

1.2.1 Cross-Over Designs

A cross over study is a longitudinal study in which subjects receive a sequence of different treatments. The designs are common in many scientific disciplines such as pharmacy, agriculture and engineering where treatments are normally assessed on their effectiveness.

A Crossover design which compares two treatments over two periods C(2,2,2), has held a dominant position in the application of crossover designs to the extent that in the majority of articles and texts, it is referred to as the cross-over design (Reed, 2012). Critiques of C (2, 2, 2) with sequence AB and BA are well known. The most serious of these is that the carryover effect is confounded with sequence by period effects leading to erroneous analyses (Reed, 2011). Statisticians have been critical of the use of crossover designs whose carryover effects are not equal for clinical trials because in such a case the estimate of the treatment difference is biased (Hills & Armitage, 1979). To overcome the problems experienced in lower order designs, higher order crossover designs may be used (Hills & Armitage, 1979). The first strategy is to extend the number of sequences such as Balaam's C (2, 2, 4) design (Balaam, 1968). Secondly, the classical C (2, 2, 2) design should be extended by adding a third period, fourth period or more and repeating the treatments in a particular order. Mathews (1987); Laska, Meisner, & Kushner, (1983) and Reed (2012) developed a method of obtaining unbiased estimates for treatment and carry-over effects using BLUE. This was an

alternative to the Ordinary Least Squares (OLS) method which occasionally gave biased estimates. In this study, unbiased estimates for C (2, 5) designs were obtained using BLUE method, the sequences and periods of the designs were increased to satisfy in part the two strategies outlined above.

1.2.1.1 Average treatment effects

The average treatment effects (ATE) is a measure used to compare treatments or interventions in randomized experiments, evaluation of policy interventions, and medical trials. The ATE measures the difference in mean outcomes between units assigned to the treatment and the units assigned to the control or standard treatment.

In a randomized trial, the average treatment effect can be estimated from a sample using a comparison in mean outcomes for treated and untreated units. Both observational studies and experimental study designs with random assignment may enable one to estimate an ATE in a variety of ways.

1.2.1.2 Washout period

A washout period is a period of time during a bioequivalence study when a participant is taken off a study drug or other medication in order to eliminate the effects of the treatment. It basically means a period of time a patient is not being actively treated while awaiting for a new treatment to begin.

1.2.1.3 Carry-over effect

The presence of the effect of one period at the start of the subsequent period is referred to as the carry-over effect. Carry-over effects normally affect the results obtained when assessing the treatment efficacy in bioequivalence studies. The presence of carry-over effects depends on; the design, the setting, the treatment and the response. Carry-over effects can arise in a number of ways: for example, pharmacological carry-over occurs

when the active ingredients of a drug given in one period are still present in the following period; psychological carry-over might occur if a drug produces an unpleasant response that might lead to a downgrading of the perceived response.

1.2.2 Optimality Criteria

The world is facing depletion of resources and search for optimal utilization measures are inevitable in all fields of human endeavor. Since the resources are scarce, we need to produce and perform maximally by utilizing optimum cross-over designs in bioequivalence studies and related experiments.

The alphabetical optimality criteria such as; A-criterion, D-criterion, T-criterion and E-criterion are normally applied in determining the optimality criteria for crossover designs. However, this is limited to cross-over designs with three or more treatments. For two treatments cross-over designs, the criterion usually adopted is that a crossover design is optimal if it provides minimum variance unbiased estimates of the treatments and carryover effects.

1.2.3 Robustness for Missing Data

In most crossover experiments where human behavior or animal responses are involved such as clinical trials, there is a strong possibility of recording missing values (Godolphin & Godolphin, 2019). Subjects may drop out of the study due to illness, drug toxicity, vacations and many other unpredictable events leading to missing data and significant difficulties in statistical analysis (Godolphin & Godolphin, 2015). Data may be missing due to random process independent of the experiment and its effects, a process dependent on the experiment or because the design is purposely incomplete (Mathews & Hernderson, 2013). In studies which use a crossover design, a specific pattern of dropout behavior can result in a disconnected design in which some and

occasionally all contrasts in treatment direct, treatment carryover and period effects will not be estimable (Godolphin & Godolphin, 2015). Such a situation has the potential to compromise the experiment severely, and could result in substantial loss of information about the aims of the study as well as incurring unwarranted excess monetary and time costs from a repeated experiment (Godolphin & Godolphin, 2019). The current study explores the methods used to limit the impact of missing data. And the methods are illustrated by assessing five period in two and four sequence cross-over designs.

1.2.3.1 Breakdown Numbers

A design is said to be disconnected if the experimenter is unable to estimate both the treatment effects and carryover effects due to missing data. Different designs can loose different number of observations before they become disconnected. A breakdown number is the maximum number of observations that can be lost before a design can be disconnected. Designs with higher breakdown numbers are regarded as more robust for missing data compared to designs with relatively lower breakdown numbers and are highly recommended for bioequivalence studies where missing data is expected.

1.2.3.2 Perpetually Connected Designs.

A perpetually connected design is designed in such a way that, provided that all subjects have completed the first two periods of study, the design will not be replaced by a disconnected eventual design due to missing data, irrespective of the type of drop-out behavior that may occur (Godolphin & Godolphin, 2019).

Perpetually connected designs are the most robust for missing data and are highly recommended for bioequivalence studies (Godolphin & Godolphin, 2015). In the event that more than one design is perpetually connected, the variances for treatments estimates can be used to determine the designs robustness for missing data.

1.2.4 Bayesian Method of Analysis

Crossover designs are mostly applied in clinical trials in assessment of the efficacy of new therapies as compared to standard therapies that are existing for the purpose of introducing them to the market. Phase three failure rates for investigational drugs are disappointingly high and costly. It is estimated that at least 50% of failures are attributable to some measure of efficacy (Hay et al, 2014). In early drug development, robust success criteria aid in making informed decisions on whether drug has sufficient efficacy and differentiation to other products to proceed to phase 3 development and to deliver benefit to patients. The phase two trial is typically the first time an investigational drug is tested in the target patient population to establish efficacy. In such settings, either a traditional approach using classical statistical methods or a Bayesian approach may be used to analyze the study. In a classical trial design, the null hypothesis may be rejected in favor of the alternative hypothesis once a pre-specified significance level is met. In contrast, Bayesian approaches focus on how the trial may change our opinion about the treatment effect using probability distributions (Spiegelhalter, Abrams, & Myles, 2004). First a prior belief about the treatment effect may be presented through a probability distribution. Then the trial is conducted, and based on the observed data; the prior belief is updated to represent the posterior belief and the updated probability distribution representing the final opinion of the treatment effect. Prior beliefs can be informative when based on results from previous studies, or non-informative when little prior knowledge exists and you wish to allow the current trial data to drive the posterior belief regarding the treatment effect. Bayesian approaches to the design and analysis of phase 2 trials are increasingly being advocated and implemented (Sambucin, 2020).This framework can facilitate more intuitive success criteria and can easily quantify probabilities of interest, such as the probability

of the drug being at least as efficacious as certain clinically relevant threshold. The Bayesian analysis can also naturally accommodate adaptive trial design such as interim analysis to stop the trial for futility and adding or dropping dose levels (Lin & Lee, 2020). This study applied the Bayesian approximation method to analyze the two treatment five period C (2, 5) crossover designs with the aim of assessing the efficacy of two treatments.

1.2.4.1 Posterior Probability Density

A posterior probability in Bayesian statistics is the revised or updated probability of an event occurring after taking into consideration new information. The posterior probability is calculated by updating the prior probability using the Bayes theorem.

1.3 Statement of the Problem

In a majority of bioequivalence studies, design and analysis of lower order cross-over designs are normally associated with erroneous analysis. Additionally, the drop-out behavior problem in cross-over designs results in disconnected designs in which some and occasionally all contrasts in treatment direct and treatment carry-over effects are not estimable resulting in; loss of parameter contrasts precision in effects of interest, and incurring unwarranted excess monetary and time costs from repeated experiments (Godolphin & Godolphin, 2019). Moreover, the classical hypothesis testing techniques are inappropriate for cross-over designs and have resulted in biased and erroneous conclusions (Fleiss, 1989). Higher order cross-over designs like the C (2, 5) designs in this study are desirable in the analysis of cross-over designs since they eliminate the effects of carry-over and periods by sequence interaction effects, and are optimal and robust for missing data. They are also relatively free from analysis errors when compared to lower order cross-over designs.

1.4 Justification

The Kenyan nation has identified; affordable health care, food security, and manufacturing as part of the fourth president's big four agenda for the nation. Cross-over trials are expected to play a central role in achieving this development goals where the newly developed treatments are compared with the standard existing treatments in the market in establishing their effectiveness and safety. Higher order cross-over designs like the C (2, 5) in this study will be applicable in industrial, pharmaceutical, and agricultural experiments where the assessment for effectiveness for two treatments in five periods is a requirement.

1.5 Objectives of the Study

1.5.1 General Objective

The general objective of this study was to design and analyze two-treatment five-period crossover designs.

1.5.2 Specific Objectives

The specific objectives are to;

1. Estimate treatments and residual effects of the designs using BLUE method
2. Compare the Optimality criteria for C $(2, 5)$ cross-over designs
3. Assess the Robustness for the C $(2, 5)$ cross-over designs against missing data
4. Compare the Bayesian test and t −test analysis methods on the treatments and carry-over effects.

1.6 Significance of the Study

The five period cross-over design will allow treatment effects to be estimated even in the presence of carry-over effects, provide unbiased estimates for intra subject variability and drawing inference on the carry-over effect. Additionally, the optimality

criteria will guide the experimenters on the right designs to apply in estimating particular contrasts effects. Moreover, the robustness for missing data will enable experimenters choose designs which are more robust thus avoiding loss of information about the aims of the study as well as incurring excess monetary and time costs from repeated experiment. The Bayesian analysis will enable treatment effects to be tested with or without the carry-over effects, unlike the classical methods where the presence of carry-over effects is tested first and if the carry-over effects are present, only the first period is considered with 10 % significance level. This is because the Bayesian methods has the potential to produce more efficient and informative statistical analyses than those based on traditional approaches.

1.7: Scope of the Study

The purpose of this study was to extend the work done by Mathews (1994) and Reed (2012) in three and four periods respectively, to five periods cross-over designs. The study specifically focused on the development of fifteen new $C(2,5,2)$ cross-over designs. Some pairs of $C(2,5,2)$ were combined to form $C(2,5,4)$ cross-over designs. The treatment effects and carry-over effects for all the designs were obtained using BLUE method and the variance of all the designs were evaluated. Further, the designs robustness against missing data was assessed and the most optimal and robust design was used in the analysis of a hypothetical example.

CHAPTER TWO: LITERATURE REVIEW

2.0 Introduction

The literature review of this study is divided into four components; cross-over designs with carry-over effects, optimality criteria for cross-over designs, robustness for Missing data and the analysis of cross-over designs.

2.1 Crossover Designs with Carry-Over Effects

Cross-over designs with carry-over effects were mainly developed to counter changes in design patterns. (Balaam, 1968). The general linear model presented by this classic paper was not explicitly analyzed but from the data analysis they performed, it led to a general liner model with error terms assumed to be identically and normally distributed with equal correlation. In order to address these critical assumptions, Grizzle in the year 1965 developed the concept of analysis of cross-over designs with residual effect. The analysis included the assumption of a mixed model in the analysis of two period, two treatment two sequence cross-over designs under which the subject effects and error terms are random effects (Grizzle, 1965).

Researchers frequently used designs that had two treatments and two periods in the analysis of cross-over experiments (Reed, 2011). It was later discovered that these designs lack the structure to test for carry-over effects and also produce biased direct treatment effects under the presence of carry-over effects (Hills & Armitage, 1979). In practice, these designs are not usually recommended despite the suggestions of possible solutions to it (Fleiss, 1989).

To overcome the problems in the C (2, 2, 2) design, higher order cross-over designs are recommended (Hills & Armitage, 1979). Two strategies have been recommended. The first one is the extension of the number of sequences such as Balaam's C (2, 2, 4)

design (Balaam, 1968). Secondly, the extension of the classic design through an addition of the third period, fourth period or more and the repetition of the treatments in a certain order. Lucas (1957) introduced the extra period design by repeating the treatment in the last period of the design, an idea that originated from Yates (1947). The extra period design allows the residual and the direct treatment effects to be orthogonal to sequences. In contrast, considering these designs, the subject effects and the direct treatment effects are not orthogonal to each other and the degree of non-orthogonality is not great (Lucas, 1957). In using these designs, much more attention is put on increasing efficiency when measuring cumulative and residual effects as compared to loosing efficiency on direct treatment effects. Lucas's work was extended by Patterson in the year 1959 to wide class of extra – period cross-over designs. Atkinson (1966) described and generalized the idea of tied-double change-over designs. The importance of designs is realized when the estimates of both direct and residual effects tend to give equal estimated variances for both effects when the number of periods increases. Kushner and Federer (1981) presented a class of two treatment cross-over designs and set up a general model for use with virtually any kind of cross-over designs. Additionally, they compared the efficiency and effect of complete random designs with extra period designs and demonstrated that complete random designs will be no better than the three or four period cross-over alternatives in the presence of residual effects or period by treatment interactions.

Alternatively, Reed (2011) introduced a two period design in place of a randomized two treatment design. Reed used the Grizzle (1965) approach to extend the classic AB/BA through the addition of a third period in which he realized that the method of adding an extra period was much less costly and that carry-over effects were measured with a higher precision. The three period designs are more efficient since they can be

conducted in the presence of carry-over effects and have much more statistical power as compared to the classic design (Reed, 2011). The food and drug authority (FDA) proposed a four period design with four sequences as the most suitable in Bioequivalence studies with two treatments if the carry-over effects are expected (F.D.A, 2001). In this regard, Reed (2012) considered four period cross-over designs in two and four sequences and estimated both the treatment and residual effects using the methods by Mathews (1987) and Kushner, (1997a). In order to realize efficiency in cost and statistical power, thorough investigation has been carried out to determine higher order two treatment designs (Godolphin & Godolphin, 2019). The current study endeavors to make a contribution by designing and analyzing new higher order for C (2,5) designs in two and four sequences.

2.2 Optimality Criteria for Cross-Over Designs

Research in the literature of cross-over designs was mainly concentrated in dealing with continuous response variables (Jankar, Mondal, & Yang, 2020). There has been an extensive study to determine the problems associated with optimal cross-over designs for continuous responses. For this reason, Bose and Dey in the year 2009 gave examples of practical cases where the responses are discrete in nature such as binary responses (Jones and Kenward, 2014 & Senn, 2001).

As all the effects are fixed for linear models, the fisher information matrix is independent of model parameters (Kim, 2020; Stufken, 1991). Various optimality criteria such as A-, D-, and E- optimality criterion depend on this information matrix (Pukeilsheim, 1993). The literature contains numerous results that rhymes with the optimality of cross-over designs for linear models. Hedeyat and Afsarinejad (1978), Cheng and Wu (1980) and Kurnest (1984) studied the optimality of balanced uniform designs (Lui, 2016). Cheng and Wu (1980) formulated theorems for optimality of

designs which are neither balanced nor strongly balanced. Dey *et al* (1983) were among the first ones to provide results for optimality of designs when $p \leq t$ considering arbitrary p and t with both $p \leq t$ and $p \geq t$. Kushner (1997) obtained conditions for universal optimality through approximate theory. The current study obtained the optimality criteria for the new C (2×5) Cross-over design using the variance of treatment and carry-over estimates as suggested by (Jones & Kenward, 2014).

2.3 Robustness for Missing Data

The problem of missing data is still a concern since it has not been fully addressed in the literature provided from the analysis of cross-over designs. The occurrence of missing data poses a challenge in the inter-subject analysis steps suggested by Balaam (1968) since the subject must be dropped out from the analysis even if only one observation from the subject is missing and the missing values might be replaced by estimates which are very difficult to obtain. Lucas (1957) and Balaam (1968) suggested that missing values can be estimated by the replacement method which minimizes the error sum of squares during analysis. A second approach is the use of a multivariate model used in the analysis of incomplete multivariate data. Traditionally, the case wise deletion method was used to solve the missing data problem in which if there was at least one missing data point, all data from the same subject was deleted. This was the case in the early days of multivariate analysis. The application of case-wise deletion to cross-over designs implies the deletion of all data from any subject for which any one observation is missing. Another method to deal with missing values was known as pairwise deletion introduced by Glasser (1964) by using all available data in the j^{th} variable to estimate its mean and variance. Further, he suggested that using all available data in the $j^{th} variable$ of the same subject must be dropped out from the analysis even if only one observation from the subject is missing and the missing values might be

replaced by estimates which are very difficult to obtain. There has been little literature information on how robust various cross-over designs are to data that becomes unavailable during the course of the experiment. In higher order cross-over studies, this issue is heightened further as the number of experimental and associated washout periods are increased which can lead to trials with lengthy follow-up studies (Godolphin & Godolphin, 2019). The most notable effects of the missing data in any experimental analysis conducted by a researcher is the loss of precision in the estimation of parameters related to both the direct treatment and residual effects and a disconnected design from which essential assumptions are difficult to visualize. (Godolphin & Godolphin, 2015). The consideration of robustness properties of cross-over designs with regard to subject dropout appears to be confined to the class of planned designs which are uniformly balanced repeated measurements, (Majumdar, Dean, & Lewis, 2008; Godolphin & Godolphin, 2015; Godolphin & Godolphin, 2019). The current study seeks to assess the two treatments, five periods' designs against missing data. In particular, some C $(2, 5, 4)$ cross-over designs are examined and ranked by breakdown numbers and minimum variance, thus enabling the identification of a good design which is robust against missing observations caused by subject dropout.

2.4. Analysis of Cross-over Designs

Box (1954a) considered the problem of the effects of inequality of variance and of correlation between errors in two way analysis of variance, he found the sum of squares for treatment effects is not stochastically independent of that error. Additionally, he noted that there were difficulties in testing hypothesis using dependent data. To test the treatment effects, he developed a conservative F-test used in the analysis of cross-over designs. Through his work, a univariate model was developed which was used as a theoretical basis for testing multivariate data in cross-over designs, although there is no

direct connection with cross-over design analysis his work gives the theoretical foundation of hypothesis testing in cross-over design analysis (Trawinski & Bargmann, 1964).

In order to address the problem encountered in the estimation of residual and direct effects in the two treatment designs, Grizzle (1965) developed a linear model to this effect. In his model, it is difficult to estimate period effects in the presence of residual effects. The residual effects are also completely confounded with sequence effects. In addition, if residual effects are simultaneously present in the model, there's loss of efficiency in the estimation of treatment effects since it is only based on first period data. For hypothesis testing, he found that the subjects – within sequence mean square is proper term for testing the inequality for residual effects. He also found that there is no appropriate error term to test the significance of treatments effects in the presence of residual effects. The early development by Grizzle (1965) took into consideration the use of first period data to estimate treatment effects. This was later corrected by (Grizzle, 1974), who noted that data from both periods should be used to estimate the treatment effects. In contrast, Balaam (1968) presented an interesting analysis procedure. He performed both intra and inter experimental subject analysis by using raw data and taking the sum difference of observations from the same subject respectively. From the experimental intra-subject analysis, he noted that the method is more efficient than the inter subject analysis since by performing sums and differences on the observations, it eliminates between subject variability. However, his model is different from Grizzle's by including period by treatment interaction effects and eliminating residual effects.

The analysis of variance for C $(2, 2, 2)$ cross-over design was given by Grizzle (1965), who proposed a preliminary test for the residual or carry-over effects from a drug

administration in the first period. The significance of the preliminary test-statistic at 0.05, 0.01 or 0.001 significance level is carried out in order to make a correct decision. A carry-over effect is ignored if the test statistic is not significant and the ANOVA test is used to test the hypothesis of no difference. The recommended method to be used in the analysis of cross-over designs is the confidence interval approach rather than the hypothesis testing approach (Westlake, 1972, 1973& Metzler, 1974). For this reason, the authors argue that more focus should be put on testing how significant the difference is rather than just testing the difference (Grizzle, 1974). A biologically meaningful measure of Bioequivalence is the posterior probability that the difference in information means is less than a specified fraction such as 20% of the standard (Grizzle, 1974). In support of this assumption, a proposed Bayesian Formulation was illustrated by taking data from three different drugs and their appropriate posterior probabilities determined to help in decision making on whether the carry-over effects are present or not. Taking evidence from the existing literature, little has been done on analysis of higher order cross-over designs using Bayesian approach. The current study weighs in by analyzing the most robust C (2, 5 ,4) using the Bayesian approximation method.

CHAPTER THREE: METHODOLOGY

3.0 Introduction

In this chapter, the methods used to achieve all the specific objectives are given; the methods include estimation of the direct treatments and treatments carry-over effects using BLUE method, Optimality criteria for the C$(2,5)$ Cross-over designs , Robustness of the designs against missing data and analysis of a hypothetical example based on Bayesian methods.

3.1 Estimation of the direct treatments and treatments carry-over effects for C $(2,5)$ cross-over designs using BLUE.

3.1.1 The Five period cross-over designs

In higher order five period cross-over designs with two treatments, thirty two possible treatments sequences can result; AAAAA, BAAAA, ABAAA, AABAA, AAABA, AAAAB, BBAAA, BABAA, BAABA, BAAAB, ABBAA, ABABA, ABAAB, AABBA, AABAB, AAABB and their duals.

For a cross-over trial, the number of treatments, periods and sequences will be denoted by, t, p, s respectively. So, for example, in a trial in which each subject received two treatments A and B, in one of the thirty two sequences ABABA: it is given by; $t = 2, p = 5$ & $s = 32$. In general, the response observed on the k^{th} subject in period j of sequence group i is denoted by $\mathbf{y_{ijk}}$.

To represent the sums of observations, the dot notation is useful, for example:

$$y_{ij.}=\sum_{k=1}^{n_i} y_{ijk},\ y_{i..}=\sum_{j=1}^{p} y_{ij.}\ ,\ y_{...}=\sum_{i=1}^{s} y_{i...} \tag{3.1.1}$$

In a similar way, the corresponding mean values will be denoted, respectively, as

$$\overline{y}_{ij.}=\frac{1}{n_i}\sum_{k=1}^{n_i} y_{ijk},\ \ \overline{y}_{i..}=\frac{1}{pn_i}\sum_{j=1}^{p} y_{ij.},\ \overline{y}_{...}=\frac{1}{p\sum n_i}\sum_{i=1}^{s} y_{i...} \tag{3.1.2}$$

To construct a statistical model, it is assumed that y_{ijk} is the observed value of a random variable. For a continuous outcome, the observed value of y_{ijk} can be represented by a linear model written as;

$$y_{ijk} = \mu + \pi_j + \tau_{d[i,j]} + \boldsymbol{\lambda_{d[i,j-1]}} + s_{ik} + e_{ijk}, \quad (3.1.3)$$

Where the terms in the model are,

$\boldsymbol{\mu}$, an intercept;

$\boldsymbol{\pi_j}$, an intercept associated with period $j, j = 1, \dots, p$;

$\boldsymbol{\tau_{d[i,j]}}$, a direct treatment effect associated with the treatment applied in period j of sequence $i, d[i, j] = 1, \dots, t$;

$\boldsymbol{s_{ik}}$, an effect associated with the k^{th} subject on sequence $i, i = 1, \dots, s, k = 1, \dots, n_i$;

$\boldsymbol{e_{ijk}}$, a random error term with zero mean and variance σ^2, and

$\boldsymbol{\lambda_{d[i,j-1]}}$ **,** a simple first order carry-over effect that is affecting the outcome in the subsequent period only.

Additional terms such as second order carry-over and direct treatment by –period interaction effects can be added to this model, but such terms are rarely of much interest in practice.

3.1.2 The Best Linear Unbiased Estimation Method (BLUE)

Consider the estimation of contrasts among direct and residual treatment effects under (3.1.3),

Let

$\hat{\mu}=(\tau_A-\tau_B)$, (3.1.4)

and

$\hat{\mu}_0=(\lambda_A-\lambda_B)$, (3.1.5)

The best linear unbiased estimators of μ and μ_0 can be written as linear combinations of cell means for example;

$\hat{\mu}=\sum\sum a_{ij}\bar{y}_{ij}$ (3.1.6)

and

$\hat{\mu}_0=\sum\sum b_{ij}\bar{y}_{ij}$. (3.1.7)

Note that estimability of μ and μ_0 ensures that;

$\sum_{i=1}^{p} a_{ij}=0$, (3.1.8)

and

$\sum_{i=1}^{p} b_{ij}=0$, for $j=1,\ldots,s$, (3.1.9)

Where p represents the number of periods and s represents the number of sequences. In order to obtain the unbiased estimates given in (3.14) and (3.15), the conditions given in (3.1.6), (3.1.7) (3.18) and (3.19) must be satisfied.

3.2 Optimality Criteria for C (2×5)Cross-Over Designs

According to (Laska, Meisner, & Kushner, 1983), the precision of a design is measured in terms of the covariance matrix, V_d, of the BLUEs of the parameters or contrasts of interest. When there are many parameters, a choice must be made as to a criterion for V i.e. some function of V. The well-known classical optimality criteria include; D-

optimality, A-optimality and T-optimality criteria. For two treatments, the criterion usually adopted in the literature is that a cross-over design is optimal if it provides minimum variance unbiased estimators of treatment effects and carry-over effects (Jones & Kenward, 2014, p. 106).

The variances of (3.1.6) and (3.1.7) can be written as;

$$\text{var}(\hat{\mu})=[\text{s}\sum\sum\frac{\text{a}_{\text{ij}}^2}{\text{N}}]\sigma^2, \tag{3.2.1}$$

and

$$\text{var}(\hat{\mu}_0)=[\text{s}\sum\sum\frac{\text{b}_{\text{ij}}^2}{\text{N}}]\sigma^2, \tag{3.2.2}$$

The variances given in (3.2.1) and (3.2.2) are used to obtain the efficiency in estimating both the direct treatment effects and the carryover effects respectively.

Consider the estimation of contrasts among direct and among carryover effects, the cumulative treatment effects are defined as the sum of the direct and the carry-over effects and can be given by;

$$(\tau_{\text{A}}-\tau_{\text{B}})_{\text{C}}=(\tau_{\text{A}}-\tau_{\text{B}})+(\lambda_{\text{A}}-\lambda_{\text{B}}). \tag{3.2.3}$$

Recall,

$$\text{var}(\text{a}+\text{b})=\text{var}(\text{a})+2\text{cov}(\text{ab})+\text{var}(\text{b}). \tag{3.2.4}$$

This implies that,

$$\text{cov}(\text{ab})=\frac{1}{2}\big(\text{var}(\text{a}+\text{b})\big)-(\text{var}(\text{a})+\text{var}(\text{b})) \tag{3.2.5}$$

Substituting $(\tau_{\text{A}}-\tau_{\text{B}})$ and $(\lambda_{\text{A}}-\lambda_{\text{B}})$ (3.2.3) to a and b (3.2.5) gives

$$\mathrm{cov}((\tau_A-\tau_B)(\lambda_A-\lambda_B)\ )=\frac{1}{2}[\mathrm{var}((\tau_A-\tau_B)\ +(\lambda_A-\lambda_B)\ )]-[\mathrm{var}(\tau_A-\tau_B)+\mathrm{var}(\lambda_A-\lambda_B\ )]] \quad (3.2.6)$$

The current study evaluates the variances of the treatment and treatment carry-over effects for the five period cross-over designs as given in (3.2.1) and (3.2.2) .The covariance of treatments and carry-over effects given in (3.2.6) will aid in evaluating the optimality for designs which estimate treatment effects in the presence of carry-over effects.

3.3 Robustness of the (2× 5) Cross-Over Designs against Missing Data.

A useful measure when planning an experiment to reduce or even prevent the possibility of a disconnected eventual design is the concept of minimum number of observations that a planned design is required to lose for the corresponding eventual design to be disconnected. This is referred in what follows as breakdown number of the planned design. Planned designs with a high breakdown number are advantageous on grounds of robustness to missing data.

3.3.1 Robustness of a design (D)

For a given design (D), there are many possible eventual designs (D_e) which could occur. We first consider the robustness concept of breakdown number which was discussed by (Godolphin & Godolphin, 2019) .

3.3.2 Robustness Using Break down Numbers

The break down number (MD) of a planned design is the minimum number of missing observations that result in one disconnected D_e.

This definition implies that there is at least one D_e which is disconnected; this design will consist of MD fewer measurements than could be available from D. Furthermore,

there will usually be several other disconnected eventual designs which have MD or more observations missing when compared with the planned design. When D has break down number MD, then no D_e will be disconnected if fewer than MD observations are lost during the experiment. This D is robust to the unavailability of observations due to subject dropout if MD is relatively high.

If D_1 and D_2 are cross-over designs with the same dimension, then D_1 is said to be more robust than D_2 when their break down numbers satisfy $MD_1 > MD_2$. It follows that if many designs are under consideration, then the design D with the maximum break down number is more robust than the competing design and should be preferred in terms of robustness. When several designs have the same high break down number, then variance considerations should apply to these designs. Evidently a preliminary step is to aim to identify those designs that possess the largest break down numbers. All the five period two treatment designs for four sequences were evaluated and ranked according to their breakdown numbers.

3.3.3 Robustness for Perpetually Connected Designs

A planned design is perpetually connected if all subjects complete the first two periods and the D_e is connected irrespective of subject dropout behavior in succeeding periods.

Thus D is perpetually connected if there is no D_e which is disconnected, conditional on no dropout in the first two periods of study.

The break down number of a perpetually connected design D will be denoted by MD $= \infty$

If several designs are perpetually connected, their robustness should be evaluated using their variances where the design with the minimum variance is taken as the most robust.

3.4 Data analysis based on the Bayesian method for C $(2, 5)$ cross over designs

In crossover designs, the group sequences differ substantially, not only in their means but also in their variances as well. The group sequences are assumed to be normally distributed. The study assumed a non- informative reference prior where the means and variances in the priors are approximately independent and locally uniform. This is because there is no prior information about the likelihood to rely on. In such a case the posterior distributions are the same as the likelihood distributions. The Behrens fisher approximation Bayesian approach was the most ideal technique to analyze the five period cross-over designs .The most robust C $(2, 5, 4)$ cross –over design is considered for analysis.

3.4.1 Determination of Variance for the C $(2, 5, 2)$Cross-Over Design

Let : the k^{th} subject in group1 have $k = 1,2, \dots, n_1$; the k^{th} subject in group2 have $k = 1,2, \dots, n_2$; the k^{th} subject in group3 have $k = 1,2, \dots, n_3$, and the k^{th} subject in group 4 have $k = 1,2, \dots, n_4$.

Assuming that s_{11}^2 is the variance of the first group and s_{21}^2 is the variance of the second group, the pooled variance for the first two groups is given by,

$$s_1^2 = \frac{(n_1-1)s_{11}^2+(n_2-1)s_{21}^2}{(n_1+n_2-2)} \qquad (3.4.1)$$

Similarly, assuming that s_{31}^2 is the variance of the third group and s_{41}^2 is the variance of the fourth group, the pooled variance for the two groups is given by,

$$s_2^2 = \frac{(n_3-1)s_{31}^2+(n_4-1)s_{41}^2}{(n_3+n_4-2)} \qquad (3.4.2)$$

3.4.2 Determination of Variance for the C $(2, 5, 4)$ Cross-Over Design

Let

$$(\tau_A - \tau_B)_1 = \frac{1}{k}(d_{11} - d_{21}) \quad (3.4.3)$$

and

$$(\tau_A - \tau_B)_2 = \frac{1}{m}(d_{31} - d_{41}) \quad (3.4.4)$$

Where; d_{11}, d_{21}, d_{31} & d_{41} are treatment contrasts for groups 1, 2, 3 and 4 respectively?

The variances of these estimators are.

$$V(\tau_A - \tau_B)_1 = \frac{s_1^2}{k^2}\left[\frac{1}{n_1} + \frac{1}{n_2}\right] \quad (3.4.5)$$

$$V(\tau_A - \tau_B)_2 = \frac{s_2^2}{m^2}\left[\frac{1}{n_3} + \frac{1}{n_4}\right] \quad (3.4.6)$$

Note that $n_1, n_2, n_3, \& n_4$ are the sample sizes for groups 1, 2, 3&4 respectively.

A combined estimator of $(\tau_A - \tau_B)_W$ can be obtained by taking a weighted average of the two estimators where the weights are taken to be inversely proportional to the variances of the estimators. That is,

$$W_1 = \frac{1}{V(\tau_A - \tau_B)_1}\ , \quad (3.4.7)$$

and

$$W_2 = \frac{1}{V(\tau_A - \tau_B)_2} \quad (3.4.8)$$

Using (3.4.1), (3.4.2), (3.4.7) and (3.4.8), the combined estimator for treatment effects is given by,

$$(\tau_A - \tau_B)_W = \frac{W_1(\tau_A-\tau_B)_1+W_2(\tau_A-\tau_B)_2}{W_1+W_2} \quad (3.4.9)$$

Thus the variance of (3.4.9) which forms the combined variance estimator is given by,

$$V(\tau_A - \tau_B)_W = (\frac{W_1}{W_1+W_2})^2 V(\tau_A - \tau_B)_1 + (\frac{W_2}{W_1+W_2})^2 V(\tau_A - \tau_B)_2 \quad (3.4.10)$$

The same procedure can be used to obtain $(\lambda_A - \lambda_B)_W$ and $V(\lambda_A - \lambda_B)_W$.

3.4.3 The Bayesian Method

We employ an approximation proposed by Patil (1964), who fits a scaled t distribution to the distribution t.

It is shown by Patil that t is approximately distributed as $t(\delta_i, a^2\left(\frac{s_1^2}{n_1}+\frac{s_2^2}{n_2}\right), b)$ for $i = 1,2$

Where,

$$\delta_1 = [\lambda_A - \lambda_B]_W \ , \quad (3.4.11)$$

$$\delta_2 = [\tau_A - \tau_B]_W \ , \quad (3.4.12)$$

$$a = \sqrt{\left(\frac{b-2}{b}\right) f_1} \ , \quad (3.4.13)$$

$$b = 4 + \frac{f_1^2}{f_2} , \quad (3.4.14)$$

$$f_1 = \left(\frac{v_2}{v_2-2}\right)\cos^2\theta + \left(\frac{v_1}{v_1-2}\right)\sin^2\theta, \quad (3.4.15)$$

$$f_2 = \frac{v_1^2}{(v_2-2)^2(v_2-4)}\cos^4\emptyset + \frac{v_2^2}{(v_2-2)^2(v_2-4)}\sin^4\emptyset, \quad (3.4.16)$$

Where

$$\cos^2\emptyset = \frac{\frac{s_2^2}{n_2}}{\left(\frac{s_1^2}{n_1}+\frac{s_2^2}{n_2}\right)} \ , \quad (3.4.17)$$

v_1 & v_2, are the degrees of freedom given by $n_1 - 2$ and $n_2 - 2$ respectively where $n_1 = n_{11} + n_{21}$, and $n_2 = n_{31} + n_{41}$.

From (3.3.17) $\sin^2\emptyset = 1 - \cos^2\emptyset$. (3.4.18)

To this degree of approximation, the difference of the mean values

$[\tau_A - \tau_B]_W$ and $[\lambda_A - \lambda_B\ ]_W$ are distributed a posterior as;

$$t\left[(\tau_A - \tau_B)_W, a^2\left(\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}\right), b\right] \ \&\ t\left[(\lambda_A - \lambda_B)_W, a^2\left(\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}\right), b\right] \quad (3.4.19)$$

The (1- $\propto$) H.P.D intervals are given by;

$$(\tau_A - \tau_B)_W \pm (a)\left(\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}\right)^{\frac{1}{2}} t_{\frac{\alpha}{2}(b,95\%)} \quad (3.4.20)$$

For treatment effects and

$$(\lambda_A - \lambda_B)_W \pm t_{\frac{\alpha}{2}}(a)\left(\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}\right)^{\frac{1}{2}} t_{\frac{\alpha}{2}(b,95\%)} \quad (3.4.21)$$

For carry-over effects.

3.4.4 Interpretation of the Bayesian Approximation Method

The strategy was to use a non-informative prior to produce the posterior distribution which was used to obtain the highest posterior density (H.P.D) interval and to test the null hypotheses as given in (Patil, 1964).

Different values of $(\tau_A - \tau_B)_W$, $(\lambda_A - \lambda_B)_W$ and $(\tau_A - \tau_B)_W / (\lambda_A - \lambda_B)_W$ were tested and a directional hypothesis tests and a probabilistic statements regarding the parameter estimates were given and the whole posterior distribution was used. The null hypothesis of $H_0: (\lambda_A - \lambda_B)_W = 0$, $H_0: (\tau_A - \tau_B)_W = 0$, and $H_0: (\tau_A - \tau_B)_W / (\lambda_A - \lambda_B)_W = 0$, were tested at **α**=5%.

If in the 95 % HPD interval, the probability of the effects of interest greater than zero was 1 or relatively higher than 0.2, the null hypothesis was rejected. Otherwise the null hypothesis was not rejected.

3.4.5 Student's *t*-test

The $t-$ test was used to validate the results obtained by the Bayesian method of analysis.

From (3.4.9), (3.4.10), (3.4.11) and (3.4.12), the calculated t values for treatment effects and carry-over effects are given by,

$$t_c = \frac{(\tau_A - \tau_B)_W}{\sqrt{V(\tau_A - \tau_B)_W}} \ , \tag{3.4.22}$$

and

$$t_c = \frac{(\lambda_A - \lambda_B)_W}{\sqrt{V(\lambda_A - \lambda_B)_W}} \ . \tag{3.4.23}$$

A simple approximation to the degrees of freedom of the estimated variance of the combined estimator was obtained using the result given by Satterthwaite (1946).

Let,

$$a_1 = \frac{W_1}{W_1 + W_2} \ , \tag{3.4.24}$$

$$a_2 = \frac{W_2}{W_1 + W_2} \ , \tag{3.4.25}$$

$$V_1 = \mathrm{Var}(\tau_A - \tau_B)_1 \ , \tag{3.4.26}$$

$$V_2 = \mathrm{Var}(\tau_A - \tau_B)_2 \ , \tag{3.4.27}$$

And

$$V_W = \mathrm{Var}(\tau_A - \tau_B)_W \ . \tag{3.4.28}$$

Similarly, let f_1 , f_2 and f_w be the degrees of freedom respectively, of the estimates of $V_1, V_2 \& V_W$

Then $f_w = \frac{(a_1V_1+a_2V_2)^2}{\frac{(a_1V_1)^2}{f_1}+\frac{(a_2V_2)^2}{f_2}}$. (3.4.30)

By comparing the tabulated value at f_w degrees of freedom in (3.4.30) with the calculated value from (3.4.22) and (3.4.23), the null hypothesis is rejected if the calculated value is greater than the tabulated value at 95% confidence interval.

3.4.6 Plotting the Data

3.4.6.1 Subject Profiles Plot

The objective of cross-over trial is to focus attention on within- individual treatment differences. A good plot for displaying these differences is the subject profiles plot. In this case, subject profiles graphs were plotted for each group to represent the change in each individual's response over two treatments periods. For each value of k, the pairs of points $(y_{11k}, y_{12k}, y_{13k}, y_{14k}, y_{15k}), (y_{21k}, y_{22k}, y_{23k}, y_{24k}, y_{25k})$,

and

$(y_{31k}, y_{32k}, y_{33k}, y_{34k}, y_{35k}), (y_{41k}, y_{42k}, y_{43k}, y_{44k}, y_{45k})$, were plotted.

This plot helped to identify the general trend and ascertain the effectiveness of treatment B (the new treatment) with regard to treatment A (the standard treatment).

3.4.6.2 Group by Periods Plot

In this case, the graphs that compared the average values over each group for each period were plotted. The eight group by period's means $\bar{y}_{1i.}, \bar{y}_{1j.}, \bar{y}_{2i.}, \bar{y}_{2j.}, \bar{y}_{3i.}, \bar{y}_{3j.}, \bar{y}_{4i.}, \& \bar{y}_{4j.}$ for $i \; and \; j = 1,2,3,4 \; and \; 5$ respectively, against their corresponding period labels were plotted and joined. On the graph, the means were labeled in terms of the group and treatments they represented

i.e. as 1A, 1B; and 2B, 2A for the first two groups respectively. In this regard, 1A was joined with 2A and 2B with 1B and the same procedure was applied for the 3rd and 4th groups respectively .This plot was used to ascertain presence of treatment by period interaction.

CHAPTER FOUR: RESULTS AND DISCUSSIONS

4.0 Introduction

In this chapter, the direct treatments and treatments carry-over effects for (2×5) cross-over designs are presented using (BLUE), Their optimality criteria and robustness for missing data are established and the treatment effects and carry-over effects for the optimum and most robust design are analyzed using the Bayesian approximation method.

4.1 Estimation of the direct treatments and treatments carry-over effects for (2×5) cross-over designs using Best Linear Unbiased Estimation method (BLUE).

In higher order five period cross-over designs with two treatments, thirty two possible treatments sequences can result to ; AAAAA, BAAAA, ABAAA, AABAA, AAABA, AAAAB, BBAAA, BABAA,BAABA, BAAAB, ABBAA, ABABA, ABAAB, AABBA, AABAB, AAABB, and their duals. A combination of particular group sequences with their respective duals gives

C (2, 5, 2) cross over designs. Similarly, combinations of pairs of C (2, 5, 2) gives C (2, 5, 4) crossover designs. The following are the C (2, 5. 2) designs that were obtained;

4.1.1 Five Period Two Treatments Design for Sequence BAAAA and its Dual (Design 1)

The design is represented as given in Table 4.1.1 below.

Table 4.1.1: C $(2\times 5\times 2)$ Design 1

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAA	B	A	A	A	A
ABBBB	A	B	B	B	B

Substituting model (3.1.3) to Table (4.1.1) gives;

Table 4.1.2: Expected Values for C (2× 5 × 2) Design 1

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_A$
ABBBB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_B$

4.1.1.1 Direct Treatments Estimate for Design 1 using (BLUE)

The contrasts C_1 and C_2 , identified from table 4.1.2 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_1) = E(Y_{11} + Y_{12} - Y_{13} + Y_{14} + Y_{15}) = 3\ \mu + (\pi_1 + \pi_2 - \pi_3 + \pi_4 + \pi_5) + 2\ \tau_A + \tau_B + (\lambda_A + \lambda_B)$$

$$E(C_2) = E(Y_{21} + Y_{22} - Y_{23} + Y_{24} + Y_{25}) = 3\mu + (\pi_1 + \pi_2 - \pi_3 + \pi_4 + \pi_5) + 2\ \tau_B + \tau_A + (\lambda_A + \lambda_B)$$

The treatments difference is obtained by finding difference between the two contrasts.

Thus,

$$\tau_A - \tau_B = C_1 - C_2 \quad . \tag{4.1.1}$$

4.1.2 Five Period Two Treatments Design for Sequence ABAAA and its Dual (Design 2)

The design is represented as given in Table 4.1.3 below,

Table 4.1.3: C (2× 5 × 2) Design 2

SEQ	p_1	p_2	p_3	p_4	p_5
ABAAA	A	B	A	A	A
BABBB	B	A	B	B	B

Substituting model (3.1.3) to Table (4.1.3) gives;

Table 4.1.4: Expected values for C (2× 5 × 2) Design 2

SEQ	p_1	p_2	p_3	p_4	p_5
ABAAA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_A$
BABBB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_B$

4.1.2.1: Direct Treatments Estimate for Design 2 using (BLUE)

The contrasts C_3 and C_4 , identified from Table 4.1.4 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_3) = E(Y_{11} + Y_{12} + Y_{13} - Y_{14} + Y_{15}) = 3\ \mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 + \pi_5) + 2\ \tau_A + \tau_B + (\lambda_A + \lambda_B)$$

$$E(C_4) = E(Y_{21} + Y_{22} + Y_{23} - Y_{24} + Y_{25}) = 3\mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 + \pi_5) + 2\ \tau_B + \tau_A + (\lambda_A + \lambda_B),$$

From (3.1.4) the treatment difference is obtained by finding difference between the two contrasts.

Thus,

$$\tau_A - \tau_B = C_3 - C_4 \qquad (4.1.2)$$

4.1.3 Five Period Two Treatments Design for Sequence AABAA and its Dual (Design 3)

The design is represented as given in Table 4.1.5 below.

Table 4.1.5: C (2× 5 × 2) Design 3

SEQ	p_1	p_2	p_3	p_4	p_5
AABAA	A	A	B	A	A
BBABB	B	B	A	B	B

Substituting model (3.1.3) to table (4.1.5) gives;

Table 4.1.6: Expected values for C (2× 5 × 2) Design 3

SEQ	p_1	p_2	p_3	p_4	p_5
AABAA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_A$
BBABB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_B$

4.1.3.1 Direct Treatments Estimate for Design 3 using (BLUE)

The contrasts C_5 and C_6 , identified from Table 4.1.6 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_5) = E(Y_{11} - Y_{12} + Y_{13} + Y_{14} + Y_{15}) = 3\ \mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 + \pi_5) + 2\ \tau_A + \tau_B + (\lambda_A + \lambda_B)$$

$$E(C_6) = E(Y_{21} - Y_{22} + Y_{23} + Y_{24} + Y_{25}) = 3\mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 + \pi_5) + 2\ \tau_B + \tau_A + (\lambda_A + \lambda_B$$

From (3.1.4), the treatment difference is obtained by finding difference between the two contrasts.

Thus,

$$\tau_A - \tau_B = C_5 - C_6 \qquad (4.1.3)$$

4.1.4 Five Period Two Treatments Design for Sequence AAABA and its Dual (Design 4)

The design is represented as given in Table 4.1.7 below.

Table 4.1.7: C (2× 5 × 2) Design 4

SEQ	p_1	p_2	p_3	p_4	p_5
AAABA	A	A	A	B	A
BBBAB	B	B	B	A	B

Substituting model (3.1.3) to Table (4.1.7) gives;

Table 4.1.8: Expected values for C (2× 5 × 2) Design 4

SEQ	p_1	p_2	p_3	p_4	p_5
AAABA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_B$
BBBAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_A$

4.1.4.1: Direct Treatments Estimate for Design 4 using (BLUE)

The contrasts C_7 and C_8 , identified from Table 4.1.8 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_7) = E(Y_{11} - Y_{12} + Y_{13} + Y_{14} + Y_{15}) = 3\ \mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 + \pi_5) + (2\tau_A + \tau_B) + (\lambda_A + \lambda_B)$$

$$E(C_8) = E(Y_{21} - Y_{22} + Y_{23} + Y_{24} + Y_{25}) = 3\ \mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 + \pi_5) + (2\tau_B + \tau_A) + (\lambda_A + \lambda_B)$$

From (3.1.4), the treatment difference is obtained by finding difference between the two contrasts,

Thus,

$$\tau_A - \tau_B = C_7 - C_8 \qquad (4.1.4)$$

4.1.5 Five Period Two Treatments Design for Sequence AAAAB and its Dual (Design 5)

The design is represented as given in Table 4.1.9 below.

Table 4.1.9: C (2× 5 × 2) Design 5

SEQ	p_1	p_2	p_3	p_4	p_5
AAAAB	A	A	A	A	B
BBBBA	B	B	B	B	A

Substituting model (3.1.3) to table (4.1.9) gives;

Table 4.1.10: Expected values for C (2× 5 × 2) Design 5

SEQ	p_1	p_2	p_3	p_4	p_5
AAAAB	$\mu+\pi_1$ $+\tau_A$	$\mu+\pi_2+$ $\tau_A+\lambda_A$	$\mu+\pi_3+$ $\tau_A+\lambda_A$	$\mu+\pi_4$ $+\tau_A+\lambda_A$	$\mu+\pi_5$ $+\tau_B+\lambda_A$
BBBBA	$\mu+\pi_1$ $+\tau_B$	$\mu+\pi_2+$ $\tau_B+\lambda_B$	$\mu+\pi_3+$ $\tau_B+\lambda_B$	$\mu+\pi_4$ $+\tau_B+\lambda_B$	$\mu+\pi_5$ $+\tau_A+\lambda_B$

4.1.5.1 Direct Treatments Estimate for Design 5 using (BLUE)

The contrasts C_9andC_{10} , identified from Table 4.1.10 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_9) = E(-Y_{11} + Y_{12} - Y_{13} + Y_{14} - Y_{15}) = -\mu - (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) - \tau_B,$$

$$E(C_{10}) = E(-Y_{21} + Y_{22} - Y_{23} + Y_{24} - Y_{25}) = -\mu - (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) - \tau_A ,$$

Thus (3.1.4) is obtained by finding difference between the two contrasts,

$$\tau_A - \tau_B = C_9 - C_{10} \qquad (4.1.5)$$

4.1.6 Five Period Two Treatments of Sequence BBAAA and its Dual (Design 6)

The design is represented as given in Table 4.1.11 below.

Table 4.1.11: C (2× 5 × 2) Design 6

SEQ	p_1	p_2	p_3	p_4	p_5
BBAAA	B	B	A	A	A
AABBB	A	A	B	B	B

Substituting model (3.1.3) to table (4.1.11) gives;

Table 4.1.12: Expected values for C (2× 5 × 2) Design 6

SEQ	p_1	p_2	p_3	p_4	p_5
BBAAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_A$
AABBB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_B$

4.1.6.1 Direct Treatments Estimate for Design 6 using (BLUE)

The contrasts C_{11} and C_{12} , identified from Table 4.1.12 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_{11}) = E(Y_{11} - Y_{12} + Y_{13} - Y_{14} + Y_{15}) = \mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + \tau_A$$

$$E(C_{12}) = E(Y_{21} - Y_{22} + Y_{23} - Y_{24} + Y_{25}) = \mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + \tau_B$$

Thus (3.1.4) is obtained by finding difference between the two contrasts given by,

$$\tau_A - \tau_B = C_{11} - C_{12} \qquad (4.1.6)$$

4.1.6.2 Carryover Treatments Effects Estimate for Design 6 using (BLUE)

The contrasts C_{13} and C_{14} , identified from Table 4.1.12 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(C_{13}) = \frac{1}{5}E(Y_{11} - Y_{12} - 2Y_{13} + Y_{14} + Y_{15}) = \frac{1}{5}[(\pi_1 - \pi_2 - 2\pi_3 + \pi_4 + \pi_5) + 2\lambda_A - 3\lambda_B]$$

$$E(C_{14}) = \frac{1}{5}E(Y_{21} - Y_{22} - 2Y_{23} + Y_{24} + Y_{25}) = \frac{1}{5}[(\pi_1 - \pi_2 - 2\pi_3 + \pi_4 + \pi_5) - 3\lambda_A + 2\lambda_B]$$

From (3.1.5), the carryover difference is obtained by finding difference between the two contrasts,

Thus, $\lambda_A - \lambda_B = C_{13} - C_{14}$ (4.1.7)

4.1.7 Five Period Two Treatments Design for Sequence BABAA and its Dual (Design 7)

The design is represented as given in Table 4.1.13 below.

Table 4.1.13: C (2× 5 × 2) Design 7

SEQ	p_1	p_2	p_3	p_4	p_5
BABAA	B	A	B	A	A
ABABB	A	B	A	B	B

Substituting model (3.1.3) to Table (4.1.13) gives;

Table 4.1.14: Expected values for C (2× 5 × 2) Design 7

SEQ	p_1	p_2	p_3	p_4	p_5
B A B A A	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_A$
A B A B B	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_B$

4.1.7.1 Direct Treatments Estimate for Design 7 using (BLUE)

The contrasts $C_{15}$and C_{16} , identified from Table 4.1.14 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_{15}) = E(Y_{11} - Y_{12} - Y_{13} + Y_{14} + Y_{15}) = \mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + \tau_A$$

$$E(C_{16}) = E(Y_{21} - Y_{22} - Y_{23} + Y_{24} + Y_{25}) = \mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + \tau_B$$

From (3.1.4), the treatment difference is obtained by finding difference between the two contrasts,

Thus,

$$\tau_A - \tau_B = C_{15} - C_{16} \qquad (4.1.8)$$

4.1.7.2: Carryover Treatments Effects Estimate for Design 7 using (BLUE)

The contrasts C_{17} and C_{18} , identified from Table 4.1.14 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(C_{17}) = E(Y_{11} - 2Y_{12} - Y_{13} + Y_{14} + Y_{15}) = (\pi_1 - 2\pi_2 - \pi_3 + \pi_4 + \pi_5) - \lambda_B$$

$$E(C_{18}) = E(Y_{21} - 2Y_{22} - Y_{23} + Y_{24} + Y_{25}) = (\pi_1 - 2\pi_2 - \pi_3 + \pi_4 + \pi_5) - \lambda_A$$

From (3.1.5), the carryover difference is obtained by finding difference between the two contrasts,

Thus,

$$\lambda_A - \lambda_B = C_{17} - C_{18} \qquad (4.1.9)$$

4.1.8 Five Period Two Treatments Design for Sequence BAABA and its Dual (Design 8)

The design is represented as given in Table 4.1.15 below.

Table 4.1.15: C (2× 5 × 2) Design 8

SEQ	p_1	p_2	p_3	p_4	p_5
BAABA	B	A	A	B	A
ABBAB	A	B	B	A	B

Substituting model (3.1.3) to Table (4.1.15) gives;

Table 4.1.16: Expected values for C (2× 5 × 2) Design 8

SEQ	p_1	p_2	p_3	p_4	p_5
BAABA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_B$
ABBAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_A$

4.1.8.1 Direct Treatments Estimate for Design 8 using (BLUE)

The contrasts C_{19}andC_{20} , identified from Table 4.1.16 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_{19}) = \frac{1}{3}E(Y_{11} - Y_{12} + Y_{13} - Y_{14} + Y_{15}) = \frac{1}{3}\ [\ \mu\ +\ (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5)\ +\ 3\tau_A\ ]$$

$$E(C_{20}) = \frac{1}{3}E(Y_{21} - Y_{22} + Y_{23} - Y_{24} + Y_{25}) = \frac{1}{3}[\mu\ +\ (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5)\ +\ 3\tau_B\ ]$$

From (3.1.5), the treatment difference is obtained by finding difference between the two contrasts,

Thus,

$$\tau_A - \tau_B = C_{19} - C_{20} \qquad (4.1.10)$$

4.1.8.2 Carryover Treatments Effects Estimate for Design 8 using (BLUE)

The contrasts C_{21} and C_{22} , identified from Table 4.1.16 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(C_{21}) = E(Y_{11} + Y_{12} + Y_{13} - Y_{14} - Y_{15}) = \mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 - 2\pi_5) - \lambda_B$$

$$E(C_{22}) = E(Y_{21} + Y_{22} + Y_{23} - Y_{24} - Y_{25}) = \mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 - 2\pi_5) - \lambda_A$$

From (3.1.5), the carryover difference is obtained by finding difference between the two contrasts,

Thus,

$$\lambda_A - \lambda_B = C_{21} - C_{22} \qquad (4.1.11)$$

4.1.9 Five Period Two Treatments Design for Sequence BAABA and its Dual (Design 9)

The design is represented as given in Table 4.1.17 below.

Table 4.1.17: C (2× 5 × 2) Design (9)

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAB	B	A	A	A	B
ABBBA	A	B	B	B	A

Substituting model (3.1.3) to table (4.1.17) gives;

Table 4.1.18: Expected values for C (2× 5 × 2) Design (9)

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_A$
ABBBA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_B$

4.1.9.1 Direct Treatments Estimate for Design 9 using (BLUE)

The contrasts C_{23}andC_{24} , identified from Table 19 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_{23}) = E(-Y_{11} - Y_{12} - Y_{13} + Y_{14} - Y_{15}) = -\mu + (-\pi_1 - \pi_2 - \pi_3 + \pi_4 - \pi_5) - (2\tau_B + \tau_A) - (\lambda_A + \lambda_B)$$

$$E(C_{24}) = E(-Y_{21} - Y_{22} - Y_{23} + Y_{24} - Y_{25}) = -\mu + (-\pi_1 - \pi_2 - \pi_3 + \pi_4 - \pi_5) - (2\tau_A + \tau_B) - (\lambda_A + \lambda_B)$$

From (3.1.4), the treatment difference is obtained by finding difference between the two contrasts,

Thus,

$$\tau_A - \tau_B = C_{23} - C_{24} \qquad (4.1.12)$$

4.1.9.2 Carryover Treatments Effects Estimate for Design 9 using (BLUE)

The contrasts C_{25}andC_{26} , identified from Table 4.1.18 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(C_{25}) = \frac{1}{3}E[(Y_{11} - 2Y_{12} + Y_{13} + Y_{14} - Y_{15})] = \frac{1}{3}[2\mu + (\pi_1 - 2\pi_2 + \pi_3 + \pi_4 - \pi_5) - 2\lambda_B + \lambda_A]$$

$$E(C_{26}) = \frac{1}{3}E[(Y_{21} - 2Y_{22} + Y_{23} + Y_{24} - Y_{25})] = \frac{1}{3}[2\mu + (\pi_1 - 2\pi_2 + \pi_3 + \pi_4 - \pi_5) - 2\lambda_A + \lambda_B]$$

From (3.1.5), the carryover difference is obtained by finding difference between the two contrasts,

Thus,

$$\lambda_A - \lambda_B = C_{25} - C_{26} \qquad (4.1.13)$$

4.1.10 Five Period Two Treatments Design for Sequence ABBAA and its Dual (Design10)

The design is represented as given in Table 4.1.19 below.

Table 4.1.19: C (2× 5 × 2) Design 10

SEQ	p_1	p_2	p_3	p_4	p_5
ABBAA	A	B	B	A	A
BAABB	B	A	A	B	B

Substituting model (3.1.3) to Table (4.1.19) gives;

Table 4.1.20: Expected values for C (2× 5 × 2), Design 10

SEQ	p_1	p_2	p_3	p_4	p_5
ABBAA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_A$
BAABB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_B$

4.1.10.1 Direct Treatments Estimate for Design10 using (BLUE)

The contrasts $C_{27}$and C_{28} , identified from Table 4.1.20 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_{27}) = E(Y_{11} - Y_{12} + Y_{13} - Y_{14} + Y_{15}) = \mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + (\tau_A)$$

$$E(C_{28}) = E(Y_{21} - Y_{22} + Y_{23} - Y_{24} + Y_{25}) = \mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + (\tau_B)$$

From (3.1.4), the treatment difference is obtained by finding difference between the two contrasts,

Thus,

$$\tau_A - \tau_B = C_{27} - C_{28} \qquad (4.1.14)$$

4.1.10.2: Carryover Treatments Effects Estimate for Design 10 using (BLUE)

The contrasts C_{29} and C_{30} , identified from Table 4.1.20 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(C_{29}) = \frac{1}{3}E[(Y_{11} + Y_{12} + Y_{13} - 2Y_{14} + Y_{15})] = \frac{1}{3}[2\mu + (\pi_1 + \pi_2 - \pi_3 - 2\pi_4 + \pi_5) - \lambda_B + 2\lambda_A]$$

$$E(C_{30}) = \frac{1}{3}E[(Y_{21} + Y_{22} + Y_{23} - 2Y_{24} + Y_{25})] = \frac{1}{3}[2\mu + (\pi_1 + \pi_2 - \pi_3 - 2\pi_4 + \pi_5) - \lambda_A + 2\lambda_B]$$

From (3.1.5), the treatment difference is obtained by finding difference between the two contrasts,

Thus,

$$\lambda_A - \lambda_B = C_{29} - C_{30} \qquad (4.1.15)$$

4.1.11 Five Period Two Treatments Design for Sequence ABABA and its Dual (Design11)

The design is represented as given in Table 4.1.21 below.

Table 4.1.21: C (2× 5 × 2) Design 11

SEQ	p_1	p_2	p_3	p_4	p_5
ABABA	A	B	A	B	A
BABAB	B	A	B	A	B

Substituting model (3.1.3) to Table (4.1.21) gives;

Table 4.1.22: Expected values for C (2× 5 × 2) Design 11

SEQ	p_1	p_2	p_3	p_4	p_5
A B A B A	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_B$
B A B A B	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_A$

4.1.11.1 Direct Treatments Estimate for Design11 using (BLUE)

The contrasts $C_{31}$and C_{32} , identified from Table 4.1.22 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_{31}) = E(Y_{11} + Y_{12} + Y_{13} + Y_{14} + Y_{15}) = 5\mu + (\pi_1 + \pi_2 + \pi_3 + \pi_4 + \pi_5) + (3\tau_A + 2\tau_B) + 2(\lambda_A + \lambda_B)$$

$$E(C_{32}) = E(Y_{21} + Y_{22} + Y_{23} + Y_{24} + Y_{25}) = 5\mu + (\pi_1 + \pi_2 + \pi_3 + \pi_4 + \pi_5) + (2\tau_A + 3\tau_B) + 2(\lambda_A + \lambda_B)$$

From (3.1.4), the treatment difference is obtained by finding difference between the two contrasts,

Thus,

$$\tau_A - \tau_B = C_{31} - C_{32} \qquad (4.1.16)$$

4.1.11.2 Carryover Treatments Effects Estimate for Design 11 using (BLUE)

The contrasts C_{33} and C_{34} , identified from Table 4.1.22 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(C_{33}) = E(Y_{11} + 2Y_{12} + Y_{13} + Y_{14} + Y_{15}) = 6\mu + (\pi_1 + 2\pi_2 + \pi_3 + \pi_4 + \pi_5) + (3\tau_A + 3\tau_B) + (3\lambda_A + 2\lambda_B)$$

$$E(C_{34}) = E(Y_{21} + 2Y_{22} + Y_{23} + Y_{24} + Y_{25}) = 6\mu + (\pi_1 + 2\pi_2 + \pi_3 + \pi_4 + \pi_5) + (3\tau_A + 3\tau_B) + (2\lambda_A + 3\lambda_B)$$

From (3.1.5), the carryover difference is obtained by finding difference between the two contrasts,

Thus,

$$\lambda_A - \lambda_B = C_{33} - C_{34} \qquad (4.1.17)$$

4.1.12: Five Period Two Treatments of Sequence ABABA and its Dual (Design12)

The design is represented as given in Table 4.1.23 below.

Table 4.1.23: C (2× 5 × 2) Design 12

SEQ	p_1	p_2	p_3	p_4	p_5
ABAAB	A	B	A	A	B
BABBA	B	A	B	B	A

Substituting model (3.1.3) to table (4.1.23) gives;

Table 4.1.24: Expected values for (2× 5 × 2) Design 12

SEQ	p_1	p_2	p_3	p_4	p_5
ABAAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_A$
BABBA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_B$

4.1.12.1 Direct Treatments Estimate for Design12 using (BLUE)

The contrasts C_1andC_2 , identified from Table 4.1.24 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_{35}) = E(-Y_{11} - Y_{12} - Y_{13} + Y_{14} - Y_{15}) = -3\mu + (-\pi_1 - \pi_2 - \pi_3 + \pi_4 - \pi_5) - (\tau_A + 2\tau_B) - (\lambda_A + \lambda_B)$$

$$E(C_{36}) = E(-Y_{21} - Y_{22} - Y_{23} + Y_{24} - Y_{25}) = -3\mu + (-\pi_1 - \pi_2 - \pi_3 + \pi_4 - \pi_5) - (2\tau_A + \tau_B) - (\lambda_A + \lambda_B)$$

From (3.1.4), the treatment difference is obtained by finding difference between the two contrasts,

Thus,

$$\tau_A - \tau_B = C_{35} - C_{36} \qquad (4.1.18)$$

4.1.12.2 Carryover Treatments Effects Estimate for Design 12 using (BLUE)

The contrasts C_{37}andC_{38} , identified from Table 4.1.24 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(C_{37}) = \frac{1}{3}E(-Y_{11} + Y_{12} - Y_{13} + 2Y_{14} - Y_{15}) = \frac{1}{3}[(-\pi_1 + \pi_2 - \pi_3 + 2\pi_4 - \pi_5) + 2\lambda_A - \lambda_B]$$

$$E(C_{38}) = \frac{1}{3}E(-Y_{21} + Y_{22} - Y_{23} + 2Y_{24} - Y_{25}) = \frac{1}{3}[(-\pi_1 + \pi_2 - \pi_3 + 2\pi_4 - \pi_5) + 2\lambda_B - \lambda_A]$$

From (3.1.5), the carryover difference is obtained by finding difference between the two contrasts. Thus,

$$\lambda_A - \lambda_B = C_{37} - C_{38} \qquad (4.1.19)$$

4.1.13 Five Period Two Treatments Design for Sequence AABBA and its Dual (Design13)

The design is represented as given in Table 4.1.25 below.

Table 4.1.25: C (2× 5 × 2) Design 13

SEQ	p_1	p_2	p_3	p_4	p_5
AABBA	A	A	B	B	A
BBAAB	B	B	A	A	B

Substituting model (3.1.3) to Table (4.1.25) gives;

Table 4.1.26: Expected values for (2× 5 × 2) Design 13

SEQ	p_1	p_2	p_3	p_4	p_5
AABBA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_B$
BBAAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_A$

4.1.13.1 Direct Treatments Estimate for Design13 using (BLUE)

The contrasts C_{39}andC_{40} , identified from table 4.1.26 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_{39}) = E(Y_{11} - Y_{12} + Y_{13} - Y_{14} + Y_{15}) = \mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + (\tau_A)$$

$$E(C_{40}) = E(Y_{21} - Y_{22} + Y_{23} - Y_{24} + Y_{25}) = \mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + (\tau_B)$$

From (3.1.4), the treatment difference is obtained by finding difference between the two contrasts,

Thus,

$$\tau_A - \tau_B = C_{39} - C_{40} \qquad (4.1.20)$$

4.1.13.2 Carryover Treatments Effects Estimate for Design 13 using (BLUE)

The contrasts $C_{41}$and C_{42} , identified from Table 4.1.26 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(C_{41}) = E(-Y_{11} + 2Y_{12} - Y_{13} + Y_{14} - Y_{15}) = (-\pi_1 + 2\pi_2 - \pi_3 + \pi_4 - \pi_5) + \lambda_A$$

$$E(C_{42}) = E(-Y_{21} + 2Y_{22} - Y_{23} + Y_{24} - Y_{25}) = (-\pi_1 + 2\pi_2 - \pi_3 + \pi_4 - \pi_5) + \lambda_B$$

From (3.1.5), the carryover difference is obtained by finding difference between the two contrasts. Thus,

$$\lambda_A - \lambda_B = C_{41} - C_{42} \qquad (4.1.21)$$

4.1.14 Five Period Two Treatments Design for Sequence AABAB and its Dual (Design14)

The design is represented as given in Table 4.1.27 below.

Table 4.1.27: C (2× 5 × 2) Design 14

SEQ	p_1	p_2	p_3	p_4	p_5
AABAB	A	A	B	A	B
BBABA	B	B	A	B	A

Substituting model (3.1.3) to Table (4.1.27) gives;

Table 4.1.28: Expected values for C (2× 5 × 2) Design 14

SEQ	p_1	p_2	p_3	p_4	p_5
A A B A B	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_A$
B B A B A	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_B$

4.1.14.1 Direct Treatments Estimate for Design14 using (BLUE)

The contrasts C_{43}andC_{44} , identified from Table 4.1.28 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_{43}) = E(-Y_{11} + Y_{12} - Y_{13} - Y_{14} - Y_{15}) = -3\mu + (-\pi_1 + \pi_2 - \pi_3 - \pi_4 - \pi_5) - (2\tau_B + \tau_A) - (\lambda_A + \lambda_B)$$

$$E(C_{44}) = E(-Y_{21} + Y_{22} - Y_{23} - Y_{24} - Y_{25}) = -3\mu + (-\pi_1 + \pi_2 - \pi_3 - \pi_4 - \pi_5) - (2\tau_A + \tau_B) - (\lambda_A + \lambda_B)$$

From (3.1.4), the treatment difference is obtained by finding difference between the two contrasts. Thus,

$$\tau_A - \tau_B = C_{43} - C_{44} \qquad (4.1.22)$$

4.1.14.2: Carryover Treatments Effects Estimate for Design 14 using (BLUE)

The contrasts C_{45} and C_{46} , identified from Table 4.1.28 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(C_{45}) = \frac{1}{3} E(-Y_{11} + 2Y_{12} + Y_{13} - Y_{14} - Y_{15}) = \frac{1}{3}[(-\pi_1 + 2\pi_2 + \pi_3 - \pi_4 - \pi_5) + 2\lambda_A - \lambda_B]$$

$$E(C_{46}) = \frac{1}{3} E(-Y_{21} + 2Y_{22} + Y_{23} - Y_{24} - Y_{25}) = \frac{1}{3}[(-\pi_1 + 2\pi_2 + \pi_3 - \pi_4 - \pi_5) + 2\lambda_B - \lambda_A]$$

From (3.1.4), the carryover difference is obtained by finding difference between the two contrasts. Thus,

$$\lambda_A - \lambda_B = C_{45} - C_{46} \qquad (4.1.23)$$

4.1.15 Five Period Two Treatments Design for Sequence ABABA and its Dual (Design15)

The design is represented as given in Table 4.1.29.

Table 4.1.29: C (2× 5 × 2) Design 15

SEQ	p_1	p_2	p_3	p_4	p_5
AAABB	A	A	B	A	B
BBABA	B	B	A	B	A

Substituting model (3.1.3) to table (4.1.29) gives;

Table 4.1.30: Expected Values for C (2× 5 × 2) Design 15

SEQ	p_1	p_2	p_3	p_4	p_5
AAABB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_B$
BBBAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_A$

4.1.15.1 Direct Treatments Estimate for Design15 using (BLUE)

The contrasts C_{47}andC_{48} , identified from Table 4.1.30 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(C_{47}) = \frac{1}{3}E[(Y_{11} + Y_{12} + Y_{13} - Y_{14} + Y_{15})] = \frac{1}{3}[3\mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 + \pi_5) + 3\tau_A + (\lambda_A + \lambda_B)]$$

$$E(C_{48}) = \frac{1}{3}E[(Y_{21} + Y_{22} + Y_{23} - Y_{24} + Y_{25})] = \frac{1}{3}[3\mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 + \pi_5) + 3\tau_B + (\lambda_A + \lambda_B)]$$

From (3.1.4), the treatment difference is obtained by finding difference between the two contrasts. Thus,

$$\tau_A - \tau_B = C_{47} - C_{48} \qquad (4.1.24)$$

4.1.15.2 Carryover Treatments Effects Estimate for Design 15 using (BLUE)

The contrasts C_{49}andC_{50} , identified from Table 4.1.30 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$E(C_{49}) = \frac{1}{3}\, E(-Y_{11} - Y_{12} + 2Y_{13} + Y_{14} - Y_{15}) = \frac{1}{3}[(-\pi_1 - \pi_2 + 2\pi_3 + \pi_4 - \pi_5) + 2\lambda_A - \lambda_B]$

$E(C_{50}) = \frac{1}{3}\, E(-Y_{21} - Y_{22} + 2Y_{23} + Y_{24} - Y_{25}) = \frac{1}{3}[(-\pi_1 - \pi_2 + 2\pi_3 + \pi_4 - \pi_5) + 2\lambda_B - \lambda_A]$

From (3.1.5), the carryover difference is obtained by finding difference between the two contrasts. Thus,

$$\lambda_A - \lambda_B = C_{49} - C_{50} \qquad (4.1.25)$$

4.1.16: Five Periods, Two Treatments, and four sequence design $(\mathbf{D_1 + D_2})$

The design is represented as given in Table 4.1.31 below.

Table 4.1.31: C (2× 5 × 4) Design 16

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAA	B	A	A	A	A
ABBBB	A	B	B	B	B
ABAAA	A	B	A	A	A
BABBB	B	A	B	B	B

Substituting model (3.1.3) to table (4.1.31) gives;

Table 4.1.32: Expected values for C (2× 5 × 4) Design 16

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_A$
ABBBB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_B$
ABAAA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_A$
BABBB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_B$

4.1.16.1: Direct Treatments Estimate for Design16 using (BLUE)

The contrasts $d_1, d_2, d_3$and d_4 , identified from table 4.1.32 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(d_1) = \frac{1}{2}E(Y_{11} - Y_{12} - Y_{13} + Y_{14} + Y_{15}) = \frac{1}{2}[3 \quad \mu \quad + \quad (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + (\tau_B) + (\lambda_A - \lambda_B)]$$

$$E(d_2) = \frac{1}{2}E(Y_{21} - Y_{22} - Y_{23} + Y_{24} + Y_{25}) = \frac{1}{2} \quad [3\mu \quad + \quad (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + (\tau_A) + (\lambda_B - \lambda_A)]$$

$$E(d_3) = \frac{1}{2}E(Y_{31} + Y_{32} - Y_{33} + Y_{34} - Y_{35}) = \frac{1}{2}[3 \quad \mu \quad + \quad (\pi_1 + \pi_2 - \pi_3 + \pi_4 - \pi_5) + (\tau_B) + (\lambda_A - \lambda_B)]$$

$$E(d_4) = \frac{1}{2}E(Y_{41} + Y_{42} - Y_{43} + Y_{44} - Y_{45}) = \frac{1}{2}[3\mu + (\pi_1 + \pi_2 - \pi_3 + \pi_4 - \pi_5) + (\tau_A) + (\lambda_B - \lambda_A)]$$

Thus (3.1.4) is obtained by finding the sum of the four contrasts,

$$\tau_A - \tau_B = (d_1 + d_2 + d_3 + d_4) \qquad (4.1.26)$$

4.1.16.1 Carryover Treatments Estimate for Design16 using (BLUE)

The contrasts $d_5, d_6, d_7$and d_8 , identified from table 4.1.32 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_5) = \frac{1}{4}E(Y_{11} - Y_{12} - Y_{13} + Y_{14} + Y_{15}) = \frac{1}{4}[\ \mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + \tau_B + (\lambda_A - \lambda_B)]$$

$$E(d_6) = \frac{1}{4}E(Y_{21} - Y_{22} - Y_{23} + Y_{24} + Y_{25}) = \frac{1}{4}\ [\mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) \quad + \tau_A + (\lambda_B - \lambda_A)]$$

$E(d_7) = \frac{1}{4}E(Y_{31} + Y_{32} + Y_{33} - Y_{34} - Y_{35}) = \frac{1}{4}[\ \mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 - \pi_5) + \tau_B + (\lambda_B - \lambda_A)]$

$E(d_8) = \frac{1}{4}E(Y_{41} + Y_{42} + Y_{43} - Y_{44} - Y_{45}) = \frac{1}{4}[\mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 - \pi_5) + \tau_A + (\lambda_A - \lambda_B)]$

Thus (3.1.5) is obtained by finding difference between the four contrasts,

$\lambda_A - \lambda_B = (d_5 - d_6 - d_7 + d_8)$ (4.1.27)

4.1.17 Five Periods, Two Treatments, and four sequence design $(\mathbf{D_1 + D_3})$

The design is represented as given in Table 4.1.33 below.

Table 4.1.33: C (2× 5 × 4) Design 17

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAA	B	A	A	A	A
ABBBB	A	B	B	B	B
AABAA	A	A	B	A	A
BBABB	B	B	A	B	B

Substituting model (3.1.3) to Table (4.1.33) gives;

Table 4.1.34: Expected values for C (2× 5 × 4) Design 17

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_A$
ABBBB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_B$
A ABAA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_A$
BBABB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_B$

4.1.17.1 Direct Treatments Estimate for Design17 using (BLUE)

The contrasts d_9, d_{10}, d_{11} and d_{12} , identified from Table 4.1.34 in such a way that (3.1.6), and (3.1.8) are satisfied are given by

$$E(d_9) = \frac{1}{2}E(Y_{11} + Y_{12} - Y_{13} + Y_{14} + Y_{15}) = \frac{1}{2}[\ 3\ \mu + (\pi_1 + \pi_2 - \pi_3 + \pi_4 + \pi_5) + 2\ \tau_A + \tau_B + (\lambda_A + \lambda_B)]$$

$$E(d_{10}) = \frac{1}{2}E(Y_{21} + Y_{22} - Y_{23} + Y_{24} + Y_{25}) = \frac{1}{2}[3\mu + (\pi_1 + \pi_2 - \pi_3 + \pi_4 + \pi_5) + 2\ \tau_B + \tau_A + (\lambda_A + \lambda_B)]$$

$$E(d_{11}) = \frac{1}{2}E(Y_{31} - Y_{32} + Y_{33} + Y_{34} + Y_{35}) = \frac{1}{2}[\ 3\ \mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 + \pi_5) + 2\ \tau_A + \tau_B + (\lambda_A + \lambda_B)]$$

$$E(d_{12}) = \frac{1}{2}E(Y_{41} - Y_{42} + Y_{43} + Y_{44} + Y_{45}) = \frac{1}{2}[3\mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 + \pi_5) + 2\ \tau_B + \tau_A + (\lambda_A + \lambda_B)]$$

Thus (3.1.4) is obtained by finding the sum and differences of the four contrasts as shown below,

$$\tau_A - \tau_B = (d_9 - d_{10}) + (d_{11} - d_{12}) \qquad (4.1.28)$$

4.1.17.2 Carryover Treatments Estimate for Design17 using (BLUE)

The contrasts d_{13}, d_{14}, d_{15} and d_{16} , identified from Table 4.1.34 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_{13}) = \frac{1}{4}E(Y_{11} - Y_{12} - Y_{13} - Y_{14} + Y_{15}) = \frac{1}{4}[\ 2\ \mu\ +\ (\pi_1 - \pi_2 - \pi_3 - \pi_4 + \pi_5) + (2\ \tau_A - \tau_B) + (3\lambda_A - \lambda_B)]$$

$$E(d_{14}) = \frac{1}{4}E(Y_{21} - Y_{22} - Y_{23} - Y_{24} + Y_{25}) = \frac{1}{4}\ [2\mu\ +\ (\pi_1 - \pi_2 - \pi_3 - \pi_4 + \pi_5) + (\ 2\ \tau_B - \tau_A) + (3\lambda_B - \lambda_A)]$$

$$E(d_{15}) = \frac{1}{4}E(Y_{31} + Y_{32} - Y_{33} - Y_{34} - Y_{35}) = \frac{1}{4}[\ 2\ \mu\ +\ (\pi_1 + \pi_2 - \pi_3 - \pi_4 - \pi_5)$$

$$-(\tau_B) - (\lambda_B + \lambda_A)]$$

$$E(d_{16}) = \frac{1}{4}E(Y_{41} + Y_{42} - Y_{43} - Y_{44} - Y_{45}) = \frac{1}{4}\ \ [2\mu\ +\ (\pi_1 + \pi_2 - \pi_3 - \pi_4 - \pi_5)$$

$$-(\tau_A) -\ (\lambda_A + \lambda_B)]$$

Thus (3.1.5) is obtained by finding difference between the four contrasts,

$$\lambda_A - \lambda_B = (d_{13} - d_{14} - 3d_{15} + 3d_{16}) \qquad (4.1.29)$$

4.1.18 Five Periods, Two Treatments, and four sequence design $(\mathbf{D_1 + D_4})$

The design is represented as given in Table 4.1.35 below.

Table 4.1.35: C (2× 5 × 4) Design 18

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAA	B	A	A	A	A
ABBBB	A	B	B	B	B
AAABA	A	A	A	B	A
BBBAB	B	B	B	A	B

Substituting model (3.1.3) to Table (4.1.35) gives;

Table 4.1.36: Expected values for C (2× 5 × 4) Design 18

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_A$
ABBBB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_B$
A AABA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_B$
BBBAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_A$

4.1.18.1 Direct Treatments Estimate for Design18 using (BLUE)

The contrasts $d_{17}, d_{18}, d_{19}$and d_{20} , identified from Table 4.1.36 in such a way that (3.1.6), and (3.1.8) are satisfied are given by

$E(d_{17}) = \frac{1}{2}E(Y_{11} + Y_{12} - Y_{13} + Y_{14} + Y_{15}) = \frac{1}{2}[\ 3\ \mu + (\pi_1 + \pi_2 - \pi_3 + \pi_4 + \pi_5) + 2\ \tau_A + \tau_B + (\lambda_A + \lambda_B)]$,

$E(d_{18}) = \frac{1}{2}E(Y_{21} + Y_{22} - Y_{23} + Y_{24} + Y_{25}) = \frac{1}{2}[3\mu + (\pi_1 + \pi_2 - \pi_3 + \pi_4 + \pi_5) + 2\ \tau_B + \tau_A + (\lambda_A + \lambda_B)]$,

$E(d_{19}) = \frac{1}{2}E(Y_{31} - Y_{32} + Y_{33} + Y_{34} + Y_{35}) = \frac{1}{2}[\ 3\ \mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 + \pi_5) + 2\ \tau_A + \tau_B + (\lambda_A + \lambda_B)]$,

$E(d_{20}) = \frac{1}{2}E(Y_{41} - Y_{42} + Y_{43} + Y_{44} + Y_{45}) = \frac{1}{2}[3\mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 + \pi_5) + 2\ \tau_B + \tau_A + (\lambda_A + \lambda_B)]$.

Thus (3.1.4) is obtained by finding the sum and differences of the four contrasts as shown below,

$$\tau_A - \tau_B = (d_{17} - d_{18}) + (d_{19} - d_{20}) \qquad (4.1.30)$$

4.1.18.2 Carryover Treatments Estimate for Design18 using (BLUE)

The contrasts $d_{21}, d_{22}, d_{23}$and d_{24} , identified from Table 4.1.36 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$E(d_{21}) = \frac{1}{4}E(Y_{11} - Y_{12} - Y_{13} - Y_{14} + Y_{15}) = \frac{1}{4}[\ 2\ \mu + (\pi_1 - \pi_2 - \pi_3 - \pi_4 + \pi_5) + (2\ \tau_A - \tau_B) + (3\lambda_A - \lambda_B)]$

$E(d_{22}) = \frac{1}{4}E(Y_{21} - Y_{22} - Y_{23} - Y_{24} + Y_{25}) = \frac{1}{4}\ [2\mu + (\pi_1 - \pi_2 - \pi_3 - \pi_4 + \pi_5) + (\ 2\ \tau_B - \tau_A) + (3\lambda_B - \lambda_A)]$

$$E(d_{23}) = \frac{1}{4}E(Y_{31} + Y_{32} - Y_{33} - Y_{34} - Y_{35}) = \frac{1}{4}[\ 2\ \mu\ +\ (\pi_1 + \pi_2 - \pi_3 - \pi_4 - \pi_5)$$

$$-(\tau_B) - (\lambda_B + \lambda_A)]$$

$$E(d_{24}) = \frac{1}{4}E(Y_{41} + Y_{42} - Y_{43} - Y_{44} - Y_{45}) = \frac{1}{4}\ \ [2\mu\ +\ (\pi_1 + \pi_2 - \pi_3 - \pi_4 - \pi_5)$$

$$-(\tau_A) -\ (\lambda_A + \lambda_B)]$$

Thus (3.1.5) is obtained by finding difference between the four contrasts,

$$\lambda_A - \lambda_B = (d_{21} - d_{22} - 3d_{23} + 3_{24}) \qquad (4.1.31)$$

4.1.19: Five Periods, Two Treatments, and four sequence design $(\mathbf{D_3 + D_4})$

The design is represented as given in Table 4.1.37 below.

Table 4.1.37: C (2× 5 × 4) Design 19

SEQ	p_1	p_2	p_3	p_4	p_5
AABAA	A	A	B	A	A
BBABB	B	B	A	B	B
AAABA	A	A	A	B	A
BBBAB	B	B	B	A	B

Substituting model (3.1.3) to Table (4.1.37) gives;

Table 4.1.38: Expected values for C (2× 5 × 4) Design 19

SEQ	p_1	p_2	p_3	p_4	p_5
AABAA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_A$
BBABB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_B$
A AABA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_B$
BBBAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_A$

4.1.19.1 Direct Treatments Estimate for Design19 using (BLUE)

The contrasts d_{21}, d_{22}, d_{23} and d_{24} , identified from Table 4.1.38 in such a way that (3.1.6), and (3.1.8) are satisfied are given by

$$E(d_{21}) = \frac{1}{2}E(Y_{11} - Y_{12} + Y_{13} + Y_{14} + Y_{15}) = \frac{1}{2}[3\ \mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 + \pi_5) + 2\ \tau_A + \tau_B + (\lambda_A + \lambda_B)]$$

$$E(d_{22}) = \frac{1}{2}E(Y_{21} - Y_{22} + Y_{23} + Y_{24} + Y_{25}) = \frac{1}{2}[3\mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 + \pi_5) + 2\ \tau_B + \tau_A + (\lambda_A + \lambda_B)]$$

$$E(d_{23}) = \frac{1}{2}E(Y_{31} - Y_{32} + Y_{33} + Y_{34} + Y_{35}) = \frac{1}{2}[3\ \mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 + \pi_5) + (2\tau_A + \tau_B) + (\lambda_A + \lambda_B)]$$

$$E(d_{24}) = \frac{1}{2}E(Y_{41} - Y_{42} + Y_{43} + Y_{44} + Y_{45}) = \frac{1}{2}[3\ \mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 + \pi_5) + (2\tau_B + \tau_A) + (\lambda_A + \lambda_B)]$$

Thus (3.1.4) is obtained by finding the sum of the differences of the four contrasts given by,

$$\tau_A - \tau_B = (d_{21} - d_{22}) + (d_{23} - d_{24}) \qquad (4.1.32)$$

4.1.19.2 Carryover Treatments Estimate for Design18 using (BLUE)

The contrasts d_{25}, d_{26}, d_{27} and d_{28} , identified from Table 4.1.38 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_{25}) = \frac{1}{4}E(Y_{11} - Y_{12} + Y_{13} + Y_{14} - Y_{15}) = \frac{1}{4}\ [\ \mu\ +\ (\pi_1 - \pi_2 + \pi_3 + \pi_4 - \pi_5) + (\tau_B)\ + (\lambda_B - \lambda_A)],$$

$$E(d_{26}) = \frac{1}{4}E(Y_{21} - Y_{22} + Y_{23} + Y_{24} - Y_{25}) = \frac{1}{4}[\mu\ +\ (\pi_1 - \pi_2 + \pi_3 + \pi_4 - \pi_5)\ +\ (\tau_A) + (\lambda_A - \lambda_B)],$$

$$E(d_{27}) = \frac{1}{4}E(Y_{31} - Y_{32} + Y_{33} + Y_{34} - Y_{35}) = \frac{1}{4}[\ \mu\ +\ (\pi_1 - \pi_2 + \pi_3 + \pi_4 - \pi_5)\ +\ (\tau_B) + (\lambda_A - \lambda_B)],$$

$E(d_{28}) = \frac{1}{4}E(Y_{41} - Y_{42} + Y_{43} + Y_{44} - Y_{45}) = \frac{1}{4}[\ \mu\ +\ (\pi_1 - \pi_2 + \pi_3 + \pi_4 - \pi_5)\ +$

$(\tau_A)+(\lambda_B - \lambda_A)]$,

Thus (3.1.5) is obtained by finding difference between the four contrasts,

$$\lambda_A - \lambda_B=(d_{26} - d_{25}) + (d_{27} - d_{28}) \qquad (4.1.33)$$

4.1.20 Five Periods, Two Treatments, and four sequence design $(\mathbf{D_5 + D_6})$

The design is represented as given in Table 4.1.39 below.

Table 4.1.39: C (2× 5 × 4) Design 20

SEQ	p_1	p_2	p_3	p_4	p_5
AAAAB	A	A	A	A	B
BBBBA	B	B	B	B	A
BBAAA	B	B	A	A	A
AABBB	A	A	B	B	B

Substituting model (3.1.3) to Table (4.1.39) gives;

Table 4.1.40: Expected values for C (2× 5 × 4) Design 20

SEQ	p_1	p_2	p_3	p_4	p_5
AAAAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_A$
BBBBA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_B$
BBAAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_A$
AABBB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_B$

4.1.20.1: Direct Treatments Estimate for Design 20 using (BLUE)

The contrasts d_{29}, d_{30}, d_{31} and d_{32} , identified from Table 4.1.40 in such a way that (3.1.6), and (3.1.8) are satisfied are given by

$E(d_{29}) = \frac{1}{2}E(-Y_{11} + Y_{12} - Y_{13} + Y_{14} - Y_{15})= -\mu - (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) - \tau_B$

$$E(d_{30}) = \frac{1}{2}E(-Y_{21} + Y_{22} - Y_{23} + Y_{24} - Y_{25}) = -\mu - (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) - \tau_A$$

$$E(d_{31}) = \frac{1}{2}E(Y_{31} - Y_{32} + Y_{33} - Y_{34} + Y_{35}) = \mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + \tau_A$$

$$E(d_{32}) = \frac{1}{2}E(Y_{41} - Y_{42} + Y_{43} - Y_{44} + Y_{45}) = \mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + \tau_B$$

Thus (3.1.4) is obtained by finding the sum and differences of the four contrasts as shown below,

$$\tau_A - \tau_B = (d_{29} - d_{30}) + (d_{31} - d_{32}) \qquad (4.1.34)$$

4.1.20.2: Carryover Treatments Estimate for Design20 using (BLUE)

The contrasts d_{33}, d_{34}, d_{35} and d_{37} , identified from Table 4.1.40 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_{33}) = \frac{1}{4}E(Y_{11} - Y_{12} + Y_{13} + Y_{14} - Y_{15}) = \frac{1}{4}[\ 3\mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 - \pi_5) + (2\tau_A - \tau_B)\ ],$$

$$E(d_{34}) = \frac{1}{4}E(Y_{21} - Y_{22} + Y_{23} + Y_{24} - Y_{25}) = \frac{1}{4}[3\mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 - \pi_5) + (2\tau_B - \tau_A)\ ],$$

$$E(d_{35}) = \frac{1}{4}E(Y_{31} + Y_{32} - Y_{33} + Y_{34} + Y_{35}) = \frac{1}{4}[4\ \mu + (\pi_1 + \pi_2 - \pi_3 + \pi_4 + \pi_5) + (\tau_A + 2\tau_B) + 2(\lambda_A + \lambda_B)],$$

$$E(d_{36}) = \frac{1}{4}E(Y_{41} + Y_{42} - Y_{43} + Y_{44} + Y_{45}) = \frac{1}{4}[\ 4\mu + (\pi_1 + \pi_2 - \pi_3 + \pi_4 + \pi_5) + (2\tau_A + \tau_B) + 2(\lambda_B + \lambda_A)],$$

Thus (3.1.5) is obtained by finding difference between the four contrasts,

$$\lambda_A - \lambda_B = (d_{33} - d_{34}) - (d_{35} + d_{36}) \qquad (4.1.35)$$

4.1.21: Five Periods, Two Treatments, and four sequence design $(\mathbf{D_7 + D_8})$

The design is represented as given in Table 4.1.41 below.

Table 4.1.41: C (2× 5 × 4) Design 21

SEQ	p_1	p_2	p_3	p_4	p_5
BABAA	B	A	B	A	A
ABABB	A	B	A	B	B
BAABA	B	A	A	B	A
ABBAB	A	B	B	A	B

Substituting model (3.1.3) to Table (4.1.41) gives;

Table 4.1.42: Expected values for C (2× 5 × 4) Design 21

SEQ	p_1	p_2	p_3	p_4	p_5
BABAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_A$
ABABB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_B$
BA ABA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_B$
ABBAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_A$

4.1.21.1 Direct Treatments Estimate for Design 21 using (BLUE)

The contrasts $d_{37}, d_{38}, d_{39}$and d_{40} , identified from Table 4.1.42 in such a way that (3.1.6), and (3.1.8) are satisfied are given by

$$E(d_{37}) = \frac{1}{4}E(Y_{11} - Y_{12} - Y_{13} + Y_{14} + Y_{15}) = \frac{1}{4}[\ \mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + \tau_A\ ]$$

$$E(d_{38}) = \frac{1}{4}E(Y_{21} - Y_{22} - Y_{23} + Y_{24} + Y_{25}) = \frac{1}{4}[\mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + \tau_B\ ]$$

$$E\ (d_{39}) = \frac{1}{12}E(Y_{31} - Y_{32} + Y_{33} - Y_{34} + Y_{35}) = \frac{1}{12}[\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + 3\tau_A\ ]$$

$$E(d_{40}) = \frac{1}{12}E(Y_{41} - Y_{42} + Y_{43} - Y_{44} + Y_{45}) = \frac{1}{12}[\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + 3\tau_B\ ]$$

Thus (3.1.4) is obtained by finding the sum and differences of the four contrasts as shown below,

$$\tau_A - \tau_B = (d_{37} - d_{38}) + (d_{39} - d_{40}) \quad (4.1.36)$$

4.1.21.2 Carryover Treatments Estimate for Design 21 using (BLUE)

The contrasts d_{41}, d_{42}, d_{43} and d_{44} , identified from table 4.1.42 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_{41}) = \frac{1}{2}E\left[(Y_{11} - 2Y_{12} - Y_{13} + Y_{14} + Y_{15})\right] = \frac{1}{2}[(\pi_1 - 2\pi_2 - \pi_3 + \pi_4 + \pi_5) - \lambda_B]$$

$$E(d_{42}) = \frac{1}{2}E[\ (Y_{21} - 2Y_{22} - Y_{23} + Y_{24} + Y_{25})] = \frac{1}{2}[(\pi_1 - 2\pi_2 - \pi_3 + \pi_4 + \pi_5) - \lambda_A]$$

$$E(d_{43}) = \frac{1}{2}E[(Y_{31} + Y_{32} + Y_{33} - Y_{34} - Y_{35})] = \frac{1}{2}[\ \mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 - 2\pi_5) - \lambda_B]$$

$$E(d_{44}) = \frac{1}{2}\ E[(Y_{41} + Y_{42} + Y_{43} - Y_{44} - Y_{45})] = \frac{1}{2}[\ \mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 - 2\pi_5) - \lambda_A]$$

Thus (3.1.5) is obtained by finding difference between the four contrasts,

$$\lambda_A - \lambda_B = (d_{41} - d_{42}) + (d_{43} - d_{44}) \quad (4.1.37)$$

4.1.22 Five Periods, Two Treatments, and four sequence design $(\mathbf{D_9 + D_{10}})$

The design is represented as given in Table 4.1.43 below.

Table 4.1.43: C (2× 5 × 4) Design 22

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAB	B	A	A	A	B
ABBBA	A	B	B	B	A
ABBAA	A	B	B	A	A
BAABB	B	A	A	B	B

Substituting model (3.1.3) to Table (4.1.43) gives;

Table 4.1.44: Expected values of C (2× 5 × 4) Design 22

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAB	$\mu+\pi_1$ $+\tau_B$	$\mu+\pi_2+$ $\tau_A+\lambda_B$	$\mu+\pi_3+$ $\tau_A+\lambda_A$	$\mu+\pi_4+$ $\tau_A+\lambda_A$	$\mu+\pi_5+$ $\tau_B+\lambda_A$
ABBBA	$\mu+\pi_1$ $+\tau_A$	$\mu+\pi_2+$ $\tau_B+\lambda_A$	$\mu+\pi_3+$ $\tau_B+\lambda_B$	$\mu+\pi_4+$ $\tau_B+\lambda_B$	$\mu+\pi_5+$ $\tau_A+\lambda_B$
ABBAA	$\mu+\pi_1$ $+\tau_A$	$\mu+\pi_2+$ $\tau_B+\lambda_A$	$\mu+\pi_3+$ $\tau_B+\lambda_B$	$\mu+\pi_4+$ $\tau_A+\lambda_B$	$\mu+\pi_5+$ $\tau_A+\lambda_A$
BAABB	$\mu+\pi_1$ $+\tau_B$	$\mu+\pi_2+$ $\tau_A+\lambda_B$	$\mu+\pi_2+$ $\tau_A+\lambda_A$	$\mu+\pi_4+$ $\tau_B+\lambda_A$	$\mu+\pi_5+$ $\tau_B+\lambda_B$

4.1.22.1: Direct Treatments Estimate for Design 22 using (BLUE)

The contrasts $d_{45}, d_{46}, d_{47}$and d_{48} , identified from Table 4.1.44 in such a way that (3.1.6), and (3.1.8) are satisfied are given by

$$E(d_{45}) = \frac{1}{2}E(-Y_{11} - Y_{12} - Y_{13} + Y_{14} - Y_{15}) = \frac{1}{2}[-\mu + (-\pi_1 - \pi_2 - \pi_3 + \pi_4 - \pi_5) - (2\tau_B + \tau_A) - (\lambda_A + \lambda_B)]$$

$$E(d_{46}) = \frac{1}{2}E(-Y_{21} - Y_{22} - Y_{23} + Y_{24} - Y_{25}) = \frac{1}{2}[-\mu + (-\pi_1 - \pi_2 - \pi_3 + \pi_4 - \pi_5) - (2\tau_A + \tau_B) - (\lambda_A + \lambda_B)]$$

$$E(d_{47}) = \frac{1}{2}E(Y_{31} - Y_{32} + Y_{33} - Y_{34} + Y_{35}) = \frac{1}{2}[\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + (\tau_A)]$$

$$E(d_{48}) = \frac{1}{2}E(Y_{41} - Y_{42} + Y_{43} - Y_{44} + Y_{45}) = \frac{1}{2}[\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + (\tau_B)]$$

Thus (3.1.4) is obtained by finding the sum and differences of the four contrasts as shown below,

$$\tau_A - \tau_B = (d_{45} - d_{46}) + (d_{47} - d_{48}) \qquad (4.1.38)$$

4.1.22.2: Carryover Treatments Estimate for Design 22 using (BLUE)

The contrasts d_{49}, d_{50}, d_{51} and d_{52} , identified from Table 4.1.44 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_{49}) = \frac{1}{6}E[(Y_{11} - 2Y_{12} + Y_{13} + Y_{14} - Y_{15})] = \frac{1}{6}[2\mu + (\pi_1 - 2\pi_2 + \pi_3 + \pi_4 - \pi_5) - 2\lambda_B + \lambda_A]$$

$$E(d_{50}) = \frac{1}{6}E[(Y_{21} - 2Y_{22} + Y_{23} + Y_{24} - Y_{25})] = \frac{1}{6}[2\mu + (\pi_1 - 2\pi_2 + \pi_3 + \pi_4 - \pi_5) - 2\lambda_A + \lambda_B]$$

$$E(d_{51}) = \frac{1}{6}E[(Y_{31} + Y_{32} + Y_{33} - 2Y_{34} + Y_{35})] = \frac{1}{6}[2\mu + (\pi_1 + \pi_2 - \pi_3 - 2\pi_4 + \pi_5) - \lambda_B + 2\lambda_A]$$

$$E(d_{52}) = \frac{1}{6}E[(Y_{41} + Y_{42} + Y_{43} - 2Y_{44} + Y_{45})] = \frac{1}{6}[2\mu + (\pi_1 + \pi_2 - \pi_3 - 2\pi_4 + \pi_5) - \lambda_A + 2\lambda_B]$$

Thus (3.1.5) is obtained by finding difference between the four contrasts,

$$\lambda_A - \lambda_B = (d_{49} - d_{50}) + (d_{51} - d_{52}) \qquad (4.1.39)$$

4.1.23: Five Periods, Two Treatments, and four sequence design $(\mathbf{D_{11} + D_{12}})$

The design is represented as given in Table 4.1. 45 below.

Table 4.1.45: C (2× 5 × 4) Design 23

SEQ	p_1	p_2	p_3	p_4	p_5
ABABA	A	B	A	B	A
BABAB	B	A	B	A	B
ABAAB	A	B	A	A	B
BABBA	B	A	B	B	A

Substituting model (3.1.3) to Table (4.1.45) gives;

Table 4.1.46: Expected values for C (2× 5 × 4) Design 23

SEQ	p_1	p_2	p_3	p_4	p_5
ABABA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_B$
BABAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_A$
ABAAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_A$
BABBA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_B$

4.1.23.1: Direct Treatments Estimate for Design 23 using (BLUE)

The contrasts d_{53}, d_{54}, d_{55} and d_{56} , identified from table 4.1.46 in such a way that (3.1.6), and (3.1.8) are satisfied are given by

$E(d_{53}) = \frac{1}{2}E(Y_{11} + Y_{12} + Y_{13} + Y_{14} + Y_{15}) = \frac{1}{2}$ $[5\mu + (\pi_1 + \pi_2 + \pi_3 + \pi_4 + \pi_5) + (3\tau_A + 2\tau_B) + 2(\lambda_A + \lambda_B)]$,

$E(d_{54}) = \frac{1}{2}E(Y_{21} + Y_{22} + Y_{23} + Y_{24} + Y_{25}) = \frac{1}{2}$ $[5\mu + (\pi_1 + \pi_2 + \pi_3 + \pi_4 + \pi_5) + (2\tau_A + 3\tau_B) + 2(\lambda_A + \lambda_B)]$,

$E(d_{55}) = \frac{1}{2}E(-Y_{31} - Y_{32} - Y_{33} + Y_{34} - Y_{35}) = \frac{1}{2}$ $[-3\mu + (-\pi_1 - \pi_2 - \pi_3 + \pi_4 - \pi_5) - (\tau_A + 2\tau_B) - (\lambda_A + \lambda_B)]$,

$E(d_{56}) = \frac{1}{2}E(-Y_{41} - Y_{42} - Y_{43} + Y_{44} - Y_{45}) = \frac{1}{2}$ $[-3\mu + (-\pi_1 - \pi_2 - \pi_3 + \pi_4 - \pi_5) - (2\tau_A + \tau_B) - (\lambda_A + \lambda_B)]$,

Thus (3.1.4) is obtained by finding the sum of the differences of the four contrasts as shown below,

$$\tau_A - \tau_B = (d_{53} - d_{54}) + (d_{55} - d_{56}) \qquad (4.1.40)$$

4.1.23.2: Carryover Treatments Estimate for Design 23 using (BLUE)

The contrasts $d_{57}, d_{58}, d_{59}$and d_{60} , identified from Table 4.1.46 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$E(d_{57}) = \frac{1}{2}E(Y_{11} + 2Y_{12} + Y_{13} + Y_{14} + Y_{15}) = \frac{1}{2}[6\mu + (\pi_1 + 2\pi_2 + \pi_3 + \pi_4 + \pi_5) + (3\tau_A + 3\tau_B) + (3\lambda_A + 2\lambda_B)]$

$E(d_{58}) = \frac{1}{2}E(Y_{21} + 2Y_{22} + Y_{23} + Y_{24} + Y_{25}) = \frac{1}{2}[6\mu + (\pi_1 + 2\pi_2 + \pi_3 + \pi_4 + \pi_5) + (3\tau_A + 3\tau_B) + (2\lambda_A + 3\lambda_B)]$

$E(d_{59}) = \frac{1}{6}E(-Y_{31} + Y_{32} - Y_{33} + 2Y_{34} - Y_{35}) = \frac{1}{6}[(-\pi_1 + \pi_2 - \pi_3 + 2\pi_4 - \pi_5) + 2\lambda_A - \lambda_B]$

$E(d_{60}) = \frac{1}{6}E(-Y_{41} + Y_{42} - Y_{43} + 2Y_{44} - Y_{45}) = \frac{1}{6}[(-\pi_1 + \pi_2 - \pi_3 + 2\pi_4 - \pi_5) + 2\lambda_B - \lambda_A]$

Thus (3.1.5) is obtained by finding difference between the four contrasts,

$$\lambda_A - \lambda_B = (d_{57} - d_{58}) + (d_{59} - d_{60}) \qquad (4.1.41)$$

4.1.24: Five Periods, Two Treatments, and four sequence design $(\mathbf{D_{13} + D_{14}})$

The design is represented as given in Table 4.1.47 below.

Table 4.1.47: C (2× 5 × 4) Design 24

SEQ	p_1	p_2	p_3	p_4	p_5
AABBA	A	A	B	B	A
BBAAB	B	B	A	A	B
AABAB	A	A	B	A	B
BBABA	B	B	A	B	A

Substituting model (3.1.3) to Table (4.1.47) gives;

Table 4.1.48: Expected values for C (2× 5 × 4) Design 24

SEQ	p_1	p_2	p_3	p_4	p_5
AABBA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_B$
BBAAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_A$
AABAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_A$
BBABA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_B$

4.1.24.1 Direct Treatments Estimate for Design 24 using (BLUE)

The contrasts d_{61}, d_{62}, d_{63} and d_{64} , identified from Table 4.1.48 in such a way that (3.1.6), and (3.1.8) are satisfied are given by

$$E(d_{61}) = \frac{1}{2}E(Y_{11} - Y_{12} + Y_{13} - Y_{14} + Y_{15}) = \frac{1}{2}[\ \mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + (\tau_A)\ ]$$

$$E(d_{62}) = \frac{1}{2}E(Y_{21} - Y_{22} + Y_{23} - Y_{24} + Y_{25}) = \frac{1}{2}[\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + (\tau_B)\ ]$$

$$E(d_{63}) = \frac{1}{2}E(-Y_{11} + Y_{12} - Y_{13} - Y_{14} - Y_{15}) = \frac{1}{2}[-3\mu + (-\pi_1 + \pi_2 - \pi_3 - \pi_4 - \pi_5) - (2\tau_B + \tau_A) - (\lambda_A + \lambda_B)]$$

$$E(d_{64}) = \frac{1}{2}E(-Y_{21} + Y_{22} - Y_{23} - Y_{24} - Y_{25}) = \frac{1}{2}[-3\mu + (-\pi_1 + \pi_2 - \pi_3 - \pi_4 - \pi_5) - (2\tau_A + \tau_B) - (\lambda_A + \lambda_B)]$$

Thus (3.1.4) is obtained by finding the sum and differences of the four contrasts as shown below,

$$\tau_A - \tau_B = (d_{61} - d_{62}) + (d_{63} - d_{64}) \qquad (4.1.42)$$

4.1.24.2: Carryover Treatments Estimate for Design 24 using (BLUE)

The contrasts d_{65}, d_{66}, d_{67} and d_{68} , identified from Table 4.1.48 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$E(d_{65}) = \frac{1}{2}E\,(-Y_{11} + 2Y_{12} - Y_{13} + Y_{14} - Y_{15}) = \frac{1}{2}[\,(-\pi_1 + 2\pi_2 - \pi_3 + \pi_4 - \pi_5) + \lambda_A]$

$E(d_{66}) = \frac{1}{2}\,E(-Y_{21} + 2Y_{22} - Y_{23} + Y_{24} - Y_{25}) = \frac{1}{2}[(-\pi_1 + 2\pi_2 - \pi_3 + \pi_4 - \pi_5) + \lambda_B]$

$E(d_{67}) = \frac{1}{6}\,E(-Y_{11} + 2Y_{12} + Y_{13} - Y_{14} - Y_{15}) = \frac{1}{6}[(-\pi_1 + 2\pi_2 + \pi_3 - \pi_4 - \pi_5) + 2\lambda_A - \lambda_B]$

$E(d_{68}) = \frac{1}{6}\,E(-Y_{21} + 2Y_{22} + Y_{23} - Y_{24} - Y_{25}) = \frac{1}{6}\quad[(-\pi_1 + 2\pi_2 + \pi_3 - \pi_4 - \pi_5) + 2\lambda_B - \lambda_A]$

Thus (3.1.5) is obtained by finding difference between the four contrasts,

$$\lambda_A - \lambda_B = (d_{65} - d_{66}) + (d_{67} - d_{68}) \qquad (4.1.43)$$

4.1.25 Five Periods, Two Treatments, and four sequence design $(\mathbf{D_{14} + D_{15}})$

The design is represented as given in Table 4.1.49 below.

Table 4.1. 49: C (2× 5 × 4) Design 25

SEQ	p_1	p_2	p_3	p_4	p_5
AABAB	A	A	B	A	B
BBABA	B	B	A	B	A
AAABB	A	A	A	B	B
BBBAA	B	B	B	A	A

Substituting model (3.1.3) to Table (4.1.49) gives;

Table 4.1.50: Expected values for C (2× 5 × 4) Design 25

SEQ	p_1	p_2	p_3	p_4	p_5
AABAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_A$
BBABA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_B$
AAABB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_B$
BBBAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_A$

4.1.25.1 Direct Treatments Estimate for Design 25 using (BLUE)

The contrasts d_{69}, d_{70}, d_{71} and d_{72} , identified from Table 4.1.50 in such a way that (3.1.6), and (3.1.8) are satisfied are given by

$$E(d_{69}) = \frac{1}{2}E(-Y_{11} + Y_{12} - Y_{13} - Y_{14} - Y_{15}) = \frac{1}{2}[-3\mu + (-\pi_1 + \pi_2 - \pi_3 - \pi_4 - \pi_5) - (2\tau_B + \tau_A) - (\lambda_A + \lambda_B)]$$

$$E(d_{70}) = \frac{1}{2}E(-Y_{21} + Y_{22} - Y_{23} - Y_{24} - Y_{25}) = \frac{1}{2}[-3\mu + (-\pi_1 + \pi_2 - \pi_3 - \pi_4 - \pi_5) - (2\tau_A + \tau_B) - (\lambda_A + \lambda_B)]$$

$$E(d_{71}) = \frac{1}{6}E[(Y_{31} + Y_{32} + Y_{33} - Y_{34} + Y_{35})] = \frac{1}{6}[3\mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 + \pi_5) + 3\tau_A + (\lambda_A + \lambda_B)]$$

$$E(d_{72}) = \frac{1}{6}E[(Y_{41} + Y_{42} + Y_{43} - Y_{44} + Y_{45})] = \frac{1}{6}[3\mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 + \pi_5) + 3\tau_B + (\lambda_A + \lambda_B)]$$

Thus (3.1.4) is obtained by finding the sum of the differences of the four contrasts as shown below,

$$\tau_A - \tau_B = (d_{69} - d_{70}) + (d_{71} - d_{72}) \qquad (4.1.44)$$

4.1.25.2: Carryover Treatments Estimate for Design 25 using (BLUE)

The contrasts d_{73}, d_{74}, d_{75} and d_{76} , identified from Table 4.1.50 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_{73}) = \frac{1}{6}E(-Y_{11} + 2Y_{12} + Y_{13} - Y_{14} - Y_{15}) = \frac{1}{6}[(-\pi_1 + 2\pi_2 + \pi_3 - \pi_4 - \pi_5) + 2\lambda_A - \lambda_B]$$

$$E(d_{74}) = \frac{1}{6}E(-Y_{21} + 2Y_{22} + Y_{23} - Y_{24} - Y_{25}) = \frac{1}{6}[(-\pi_1 + 2\pi_2 + \pi_3 - \pi_4 - \pi_5) + 2\lambda_B - \lambda_A]$$

$$E(C_{75}) = \frac{1}{6}\, E(-Y_{31} - Y_{32} + 2Y_{33} + Y_{34} - Y_{35}) \quad = \quad \frac{1}{6}[(-\pi_1 - \pi_2 + 2\pi_3 + \pi_4 - \pi_5) + 2\,\lambda_A - \lambda_B]$$

$$E(C_{76}) = \frac{1}{6}\, E(-Y_{41} - Y_{42} + 2Y_{43} + Y_{44} - Y_{45}) = \frac{1}{6} \qquad [(-\pi_1 - \pi_2 + 2\pi_3 + \pi_4 - \pi_5) + 2\lambda_B - \lambda_A]$$

Thus (3.1.5) is obtained by finding difference between the four contrasts,

$$\lambda_A - \lambda_B = (d_{73} - d_{74}) + (d_{75} - d_{76}) \qquad (4.1.45)$$

4.1.26: Five Periods, Two Treatments, and four sequence design $(\mathbf{D_4 + D_5})$

The design is represented as given in Table 4.1.51 below.

Table 4.1.51: C (2× 5 × 4) Design 26

SEQ	p_1	p_2	p_3	p_4	p_5
AAABA	A	A	A	B	A
BBBAB	B	B	B	A	B
AAAAB	A	A	A	A	B
BBBBA	B	B	B	B	A

Substituting model (3.1.3) to Table (4.1.51) gives;

Table 4.1.52: Expected values for C (2× 5 × 4) Design 26

SEQ	p_1	p_2	p_3	p_4	p_5
AAABA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_B$
BBBAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_A$
AAAAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_A$
BBBBA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_B$

4.1.26.1: Direct Treatments Estimate for Design 26 using (BLUE)

The contrasts $d_{77}, d_{78}, d_{79}$and d_{80} , identified from Table 4.1.52 in such a way that (3.1.6), and (3.1.8) are satisfied are given by

$E(d_{77}) = E(Y_{11} - Y_{12} + Y_{13} + Y_{14} - Y_{15}) = [\mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 - \pi_5) + (\tau_B) + (2\lambda_A - \lambda_B)]$

$E(d_{78}) = E(Y_{21} - Y_{22} + Y_{23} + Y_{24} - Y_{25}) = [\mu + (\pi_1 - \pi_2 + \pi_3 + \pi_4 - \pi_5) + (\tau_A) + (2\lambda_B - \lambda_A)]$

$E(d_{79}) = 3E(Y_{31} + Y_{32} - 2Y_{33} + Y_{34} + Y_{35})] = 3[2\mu + (\pi_1 + \pi_2 - 2\pi_3 + \pi_4 + \pi_5) + (\tau_A + \tau_B) + (\lambda_A)]$

$E(d_{80}) = 3E(Y_{41} + Y_{42} - 2Y_{43} + Y_{44} + Y_{45})] = 3[2\mu + (\pi_1 + \pi_2 - 2\pi_3 + \pi_4 + \pi_5) + (\tau_B + \tau_A) + (\lambda_B)]$

Thus (3.1.4) is obtained by finding the sum and differences of the four contrasts as shown below,

$$\tau_A - \tau_B = (d_{78} - d_{77}) + (d_{79} - d_{80}) \qquad (4.1.46)$$

4.1.26.2 Carryover Treatments Estimate for Design 26 using (BLUE)

The contrasts d_{81}, d_{82}, d_{83} and d_{84} , identified from Table 4.1.52 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$E(d_{81}) = \frac{1}{4}E(Y_{11} - Y_{12} - Y_{13} - Y_{14} + Y_{15}) = \frac{1}{4}[-\mu + (\pi_1 - \pi_2 - \pi_3 - \pi_4 + \pi_5) - (\tau_B) + (\lambda_B - 3\lambda_A)]$

$E(d_{82}) = \frac{1}{4}E(Y_{21} - Y_{22} - Y_{23} - Y_{24} + Y_{25}) = \frac{1}{4}[-\mu + (\pi_1 - \pi_2 - \pi_3 - \pi_4 + \pi_5) - (\tau_A) + (\lambda_A - 3\lambda_B)]$

$E(d_{83}) = \frac{1}{4}E(Y_{31} - Y_{32} - Y_{33} + Y_{34} + Y_{35})] = \frac{1}{4}[\mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + (\tau_B)]$

$E(d_{84}) = \frac{1}{4}E(Y_{41} - Y_{42} - Y_{43} + Y_{44} + Y_{45})] = \frac{1}{4}$ [μ + $(\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + (\tau_A)$]

Thus (3.1.5) is obtained by finding difference between the four contrasts as shown below,

$$\lambda_A - \lambda_B = (d_{84} + d_{82}) - (d_{83} + d_{81}) \quad (4.1.47)$$

4.1.27: Five Periods, Two Treatments, and four sequence design $(\mathbf{D_5 + D_5})$

The design is represented as given in Table 4.1.53 below.

Table 4.1.53: C (2× 5 × 4) Design 27

SEQ	p_1	p_2	p_3	p_4	p_5
AAAAB	A	A	A	B	A
BBBBA	B	B	B	A	B
AAAAB	A	A	A	A	B
BBBBA	B	B	B	B	A

Substituting model (3.1.3) to Table (4.1.53) gives;

Table 4.1.54: Expected values for C (2× 5 × 4) Design 27

SEQ	p_1	p_2	p_3	p_4	p_5
AAAAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_A$
BBBBA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_B$
AAAAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_A$
BBBBA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_B$

4.1.27.1 Direct Treatments Estimate for Design 27 using (BLUE)

The contrasts d_{85}, d_{86}, d_{87} and d_{88} , identified from Table 4.1.54 in such a way that (3.1.6), and (3.1.8) are satisfied are given by

$E(d_{85}) = \frac{1}{3}E(Y_{11} + Y_{12} - 2Y_{13} + Y_{14} - 2Y_{15}) = \frac{1}{3}$ [-μ + $(\pi_1 + \pi_2 - 2\pi_3 + \pi_4 - 2\pi_5)$ $+(\tau_A - 2\tau_B) - 2(\lambda_A)]$

$E(d_{86}) = \frac{1}{3}E(Y_{21} + Y_{22} - 2Y_{23} + Y_{24} - 2Y_{25}) = \frac{1}{3}$ [-μ + $(\pi_1 + \pi_2 - 2\pi_3 - \pi_4 - 2\pi_5)+(\tau_B - 2\tau_A) - 2(\lambda_B)]$

$E(d_{87}) = \frac{2}{3}E(Y_{31} + Y_{32} - 2Y_{33} + Y_{34} + Y_{35})] = \frac{2}{3}$ [2μ + $(\pi_1 + \pi_2 - 2\pi_3 + \pi_4 + \pi_5)$ $+(\tau_A + \tau_B) + (\lambda_A)]$

$E(d_{88}) = \frac{2}{3}E(Y_{41} + Y_{42} - 2Y_{43} + Y_{44} + Y_{45})] = \frac{2}{3}$ [2μ + $(\pi_1 + \pi_2 - 2\pi_3 + \pi_4 + \pi_5)+(\tau_B + \tau_A) + (\lambda_B)]$

Thus (3.1.4) is obtained by finding the sum and differences of the four contrasts as shown below,

$$\tau_A - \tau_B = (d_{85} - d_{86}) + (d_{87} - d_{88}) \quad (4.1.48)$$

4.1.27.2: Carryover Treatments Estimate for Design 27 using (BLUE)

The contrasts d_{89}, d_{90}, d_{91} and d_{92} , identified from Table 4.1.54 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$E(d_{89}) = \frac{1}{2}E(Y_{11} - Y_{12} - Y_{13} - Y_{14} + Y_{15}) = \frac{1}{2}$[-μ + $(\pi_1 - \pi_2 - \pi_3 - \pi_4 + \pi_5)$ $-2\tau_A + \tau_B - 2\lambda_A]$

$E(d_{90}) = \frac{1}{2}E(Y_{21} - Y_{22} - Y_{23} - Y_{24} + Y_{25}) = \frac{1}{2}$[-μ + $(\pi_1 - \pi_2 - \pi_3 - \pi_4 + \pi_5) - 2\tau_B$ $+\tau_A - 2\lambda_B]$

$E(d_{91}) = \frac{3}{2}E(Y_{31} - Y_{32} - Y_{33} + Y_{34} + Y_{35})] = \frac{3}{2}$ [μ + $(\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5)$ $+(\tau_B)$]

$$E(d_{92}) = \frac{3}{2}E(Y_{41} - Y_{42} - Y_{43} + Y_{44} + Y_{45})] = \frac{3}{2} \quad [\mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + (\tau_A)\ ]$$

Thus (3.1.5) is obtained by finding difference between the four contrasts,

$$\lambda_A - \lambda_B = (d_{90} - d_{89}) + (d_{91} - d_{92}) \quad (4.1.49)$$

4.1.28 Discussion

The method gave best linear unbiased estimates for both treatments and carry-over effects for a majority of the five period cross-over designs. However, $D_1, D_2, D_3, D_4, \& D_5$ were found not to have unbiased estimates for carry-over effects. This is because in all the five designs, the first four periods received a similar treatment while the remaining one period for the five designs received alternative treatments. This implies that as we moved from one period to the other, the carry-over effects diminishes if the same treatment is assigned in two or more subsequent periods. The fact that the carryover effects for $(D_1 - D_5)$ were not obtained implies that the designs can be effectively used to estimate the treatments effects even when the carryover effects are expected in the experiment. This is because the design by itself can eliminate the carry-over effects. For the rest of the designs $(D_6 - D_{27})$, the significance of carry-over effects difference needs to be evaluated and their contribution to treatment differences be established.

4.2. Optimality criteria for C (2×5)Ccross-Over Designs

4.2.1 Direct Treatments variance for C $(2\times 5\times 2)$

4.2.1.1 Design D_1

From (4.1.1),

$$\tau_A - \tau_B = E[Y_{11} + Y_{12} - Y_{13} + Y_{14} + Y_{15} - Y_{21} - Y_{22} + Y_{23} - Y_{24} - Y_{25}] \quad (4.2.1.1)$$

Applying (3.2.1) on (4.2.1.1) gives,

$$\text{var}(\tau_A - \tau_B) = 10\frac{\sigma^2}{n} \quad (4.2.1.2)$$

4.2.1.2 Design D_2

From (4.1.2),

$$\tau_A - \tau_B = E[Y_{11} + Y_{12} + Y_{13} - Y_{14} + Y_{15} - Y_{21} - Y_{22} - Y_{23} + Y_{24} - Y_{25}] \quad (4.2.1.3)$$

Applying (3.2.1) on (4.2.1.3) gives,

$$\text{var}(\tau_A - \tau_B) = 10\frac{\sigma^2}{n} \quad (4.2.1.4)$$

4.2.1.3 Design D_3

From (4.1.3),

$$\tau_A - \tau_B = E[Y_{11} - Y_{12} + Y_{13} + Y_{14} + Y_{15} - Y_{21} + Y_{22} - Y_{23} - Y_{24} - Y_{25}] \quad (4.2.1.5)$$

Applying (3.2.1) on (4.2.1.5) gives,

$$\text{var}(\tau_A - \tau_B) = 10\frac{\sigma^2}{n} \quad (4.2.1.6)$$

4.2.1.4 Design D_4

From (4.1.4),

$$\tau_A - \tau_B = E[Y_{11} - Y_{12} + Y_{13} + Y_{14} + Y_{15} - Y_{21} + Y_{22} - Y_{23} - Y_{24} - Y_{25}] \quad (4.2.1.7)$$

Applying (3.2.1) on (4.2.1.7) gives,

$$\text{var}(\tau_A - \tau_B) = 10\frac{\sigma^2}{n} \quad (4.2.1.8)$$

4.2.1.5 Design D_5

From (4.1.5),

$$\tau_A - \tau_B = E[-Y_{11} + Y_{12} - Y_{13} + Y_{14} - Y_{15} + Y_{21} - Y_{22} + Y_{23} - Y_{24} + Y_{25}] \quad (4.2.1.9)$$

Applying (3.2.1) on (4.2.1.9) gives,

$$\text{var}(\tau_A - \tau_B) = 10\frac{\sigma^2}{n} \quad (4.2.1.10)$$

4.2.1.6 Design D_6

From (4.1.6),

$$\tau_A - \tau_B = E[Y_{11} - Y_{12} + Y_{13} - Y_{14} + Y_{15} - Y_{21} + Y_{22} - Y_{23} + Y_{24} - Y_{25}] \quad (4.2.1.11)$$

Applying (3.2.1) on (4.2.1.11) gives,

$$\text{var}(\tau_A - \tau_B) = 10\frac{\sigma^2}{n} \quad (4.2.1.12)$$

4.2.1.7 Design D_7

From (4.1.8),

$$\tau_A - \tau_B = E[Y_{11} - Y_{12} - Y_{13} + Y_{14} + Y_{15} - Y_{21} + Y_{22} + Y_{23} - Y_{24} - Y_{25}] \quad (4.2.1.13)$$

Applying (3.2.1) on (4.2.1.13) gives,

$$\text{var}(\tau_A - \tau_B) = 10\frac{\sigma^2}{n} \quad (4.2.1.14)$$

4.2.1.8 Design D_8

From (4.1.10),

$$\tau_A - \tau_B = \frac{1}{3}E[Y_{11} - Y_{12} + Y_{13} - Y_{14} + Y_{15} - Y_{21} + Y_{22} - Y_{23} + Y_{24} - Y_{25}] \quad (4.2.1.15)$$

Applying (3.2.1) on (4.2.1.15) gives,

$$\text{var}(\tau_A - \tau_B) = 1.111\ \frac{\sigma^2}{n} \quad (4.2.1.16)$$

4.2.1.9 Design D_9

From (4.1.12),

$$\tau_A - \tau_B = E[-Y_{11} - Y_{12} - Y_{13} + Y_{14} - Y_{15} + Y_{21} + Y_{22} + Y_{23} - Y_{24} + Y_{25}] \quad (4.2.1.17)$$

Applying (3.2.1) on (4.2.1.17) gives,

$$\text{var}(\tau_A - \tau_B) = 10\ \frac{\sigma^2}{n} \quad (4.2.1.18)$$

4.2.1.10 Design D_{10}

From (4.1.14),

$$\tau_A - \tau_B = E[Y_{11} - Y_{12} + Y_{13} - Y_{14} + Y_{15} - Y_{21} + Y_{22} - Y_{23} + Y_{24} - Y_{25}] \quad (4.2.1.19)$$

Applying (3.2.1) on (4.2.1.19) gives,

$$\text{var}(\tau_A - \tau_B) = 10\ \frac{\sigma^2}{n} \quad (4.2.1.20)$$

4.2.1.11 Design D_{11}

From (4.1.16),

$$\tau_A - \tau_B = E[Y_{11} + Y_{12} + Y_{13} + Y_{14} + Y_{15} - Y_{21} - Y_{22} - Y_{23} - Y_{24} - Y_{25}] \quad (4.2.1.21)$$

Applying (3.2.1) on (4.2.1.21) gives,

$$\text{var}(\tau_A - \tau_B) = 10\ \frac{\sigma^2}{n} \quad (4.2.1.22)$$

4.2.1.12 Design D_{12}

From (4.1.18),

$$\tau_A - \tau_B = E[-Y_{11} - Y_{12} - Y_{13} + Y_{14} - Y_{15} + Y_{21} + Y_{22} + Y_{23} - Y_{24} + Y_{25}] \quad (4.2.1.23)$$

Applying (3.2.1) on (4.2.1.23) gives,

$$\text{var}(\tau_A - \tau_B) = 10\ \frac{\sigma^2}{n} \quad (4.2.1.24)$$

4.2.1.13 Design D_{13}

From (4.1.20),

$$\tau_A - \tau_B = E[Y_{11} - Y_{12} + Y_{13} - Y_{14} + Y_{15} - Y_{21} + Y_{22} - Y_{23} + Y_{24} - Y_{25}] \quad (4.2.1.25)$$

Applying (3.2.1) on (4.2.1.25) gives,

$$\text{var}(\tau_A - \tau_B) = 10\ \frac{\sigma^2}{n} \quad (4.2.1.26)$$

4.2.1.14 Design D_{14}

From (4.1.22),

$$\tau_A - \tau_B = E[-Y_{11} + Y_{12} - Y_{13} - Y_{14} - Y_{15} + Y_{21} - Y_{22} + Y_{23} + Y_{24} + Y_{25}] \quad (4.2.1.27)$$

Applying (3.2.1) on (4.2.1.27) gives,

$$\text{var}(\tau_A - \tau_B) = 10\ \frac{\sigma^2}{n} \quad (4.2.1.28)$$

4.2.1.15 Design D_{15}

From (4.1.24),

$$\tau_A - \tau_B = \frac{1}{3} E[Y_{11} + Y_{12} + Y_{13} - Y_{14} + Y_{15} - Y_{21} - Y_{22} - Y_{23} + Y_{24} - Y_{25}] \quad (4.2.1.29)$$

Applying (3.2.1) on (4.2.1.29) gives,

$$\text{var}(\tau_A - \tau_B) = 1.11\ \frac{\sigma^2}{n} \quad (4.2.1.30)$$

4.2.2 Residuals variance for C ($2\times 5\times 2$)

4.2.2.1 Design D_6

From (4.1.7),

$$\lambda_A-\lambda_B=\frac{1}{5}E[Y_{11}-Y_{12}-2Y_{13}+Y_{14}+Y_{15}-Y_{21}+Y_{22}+2Y_{23}-Y_{24}-Y_{25}] \quad (4.2.2.1)$$

Applying (3.2.2) on (4.2.2.1) gives,

$$\text{var}(\lambda_A-\lambda_B)=0.64\ \frac{\sigma^2}{n} \quad (4.2.2.2)$$

4.2.2.2 Design D_7

From (4.1.9),

$$\lambda_A-\lambda_B=E[Y_{11}-2Y_{12}-Y_{13}+Y_{14}+Y_{15}-Y_{21}+2Y_{22}+Y_{23}-Y_{24}-Y_{25}] \quad (4.2.2.3)$$

Applying (3.2.2) on (4.2.2.3) gives,

$$\text{var}(\lambda_A-\lambda_B)=16\ \frac{\sigma^2}{n} \quad (4.2.2.4)$$

4.2.2.3 Design D_8

From (4.1.11),

$$\lambda_A-\lambda_B=E[Y_{11}+Y_{12}+Y_{13}-Y_{14}-Y_{15}-Y_{21}-Y_{22}-Y_{23}+Y_{24}-Y_{25}] \quad (4.2.2.5)$$

Applying (3.2.2) on (4.2.2.5) gives,

$$\text{var}(\lambda_A-\lambda_B)=10\ \frac{\sigma^2}{n} \quad (4.2.2.6)$$

4.2.2.4 Design D_9

From (4.1.13),

$$\lambda_A-\lambda_B=\frac{1}{3}E[Y_{11}-2Y_{12}+Y_{13}+Y_{14}-Y_{15}-Y_{21}+2Y_{22}-Y_{23}-Y_{24}+Y_{25}] \quad (4.2.2.7)$$

Applying (3.2.2) on (4.2.2.7) gives,

$$\text{var}(\lambda_A - \lambda_B) = 1.78\ \frac{\sigma^2}{n} \quad (4.2.2.8)$$

4.2.2.5 Design D_{10}

From (4.1.15),

$$\lambda_A - \lambda_B = \frac{1}{3}E[Y_{11} + Y_{12} + Y_{13} - 2Y_{14} + Y_{15} - Y_{21} - Y_{22} - Y_{23} + 2Y_{24} - Y_{25}] \quad (4.2.2.9)$$

Applying (3.2.2) on (4.2.2.9) gives,

$$\text{var}(\lambda_A - \lambda_B) = 1.78\ \frac{\sigma^2}{n} \quad (4.2.2.10)$$

4.2.2.6 Design D_{11}

From (4.1.17),

$$\lambda_A - \lambda_B = E[Y_{11} + 2Y_{12} + Y_{13} + Y_{14} + Y_{15} - Y_{21} - 2Y_{22} - Y_{23} - Y_{24} - Y_{25}] \quad (4.2.2.11)$$

Applying (3.2.2) on (4.2.2.11) gives,

$$\text{var}(\lambda_A - \lambda_B) = 16\ \frac{\sigma^2}{n} \quad (4.2.2.12)$$

4.2.2.7 Design D_{12}

From (4.1.19),

$$\lambda_A - \lambda_B = \frac{1}{3}E[-Y_{11} + Y_{12} - Y_{13} + 2Y_{14} - Y_{15} + Y_{21} - Y_{22} + Y_{23} - 2Y_{24} + Y_{25}] \quad (4.2.2.13)$$

Applying (3.2.2) on (4.2.2.13) gives,

$$\text{var}(\lambda_A - \lambda_B) = 1.78\ \frac{\sigma^2}{n} \quad (4.2.2.14)$$

4.2.2.8 Design D_{13}

From (4.1.21),

$$\lambda_A - \lambda_B = E[-Y_{11} + Y_{12} - Y_{13} + Y_{14} - Y_{15} + Y_{21} - Y_{22} + Y_{23} - Y_{24} + Y_{25}] \quad (4.2.2.15)$$

Applying (3.2.2) on (4.2.2.15) gives,

$$\text{var}(\lambda_A - \lambda_B) = 16\ \frac{\sigma^2}{n} \quad (4.2.2.16)$$

4.2.2.9 Design D_{14}

From (4.1.23),

$$\lambda_A - \lambda_B = \frac{1}{3}E[-Y_{11} + 2Y_{12} + Y_{13} - Y_{14} - Y_{15} + Y_{21} - 2Y_{22} - Y_{23} + Y_{24} + Y_{25}] \quad (4.2.2.17)$$

Applying (3.2.2) on (4.2.2.17) gives,

$$\text{var}(\lambda_A - \lambda_B) = 1.78\ \frac{\sigma^2}{n} \quad (4.2.2.18)$$

4.2.2.10 Design D_{15}

From (4.1.25),

$$\lambda_A - \lambda_B = \frac{1}{3}E[-Y_{11} - Y_{12} + 2Y_{13} + Y_{14} - Y_{15} + Y_{21} + Y_{22} - 2Y_{23} - Y_{24} + Y_{25}] \quad (4.2.2.19)$$

Applying (3.2.2) on (4.2.2.19) gives,

$$\text{var}(\lambda_A - \lambda_B) = 1.78\ \frac{\sigma^2}{n} \quad (4.2.2.20)$$

4.2.3 Treatments and Residuals Covariance for C $(2\times 5\times 2)$ Cross-Over Designs

4.2.3.1 Design D_6

Summing (4.2.1.11) and (4.2.2.1) gives,

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{5}\,E(6y_{11} - 6y_{12} + 3y_{13} - 4y_{14} + 6y_{15}) - \frac{1}{5}\,E(6y_{21} - 6y_{22} + 3y_{23} - 4y_{24} + 6y_{25}) \quad (4.2.3.1)$$

Applying (3.2.1) and (3.2.2) on (4.2.3.1) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 10.64\frac{\sigma^2}{n} \quad (4.2.3.2)$$

Substituting (4.2.1.12), (4.2.2.2) and (4.2.3.2) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 5.32\,\frac{\sigma^2}{n}$$

4.2.3.2 Design D_7

Summing (4.2.1.13) and (4.2.2.3)

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \text{E}(2y_{11} - 3y_{12} - 2y_{13} + 2y_{14} + 2y_{15}) - \text{E}(2y_{21} - 3y_{22} - 2y_{23} + 2y_{24} + 2y_{25}) \quad (4.2.3.3)$$

Applying (3.2.1) and (3.2.2) on (4.2.3.3) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 50\,\frac{\sigma^2}{n} \quad (4.2.3.4)$$

Substituting (4.2.1.14), (4.2.2.4) and (4.2.3.4) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 1\,\frac{\sigma^2}{n} \quad (4.2.3.5)$$

4.2.3.3 Design D_8

Summing (4.2.1.15) and (4.2.2.5)

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{3}\,\text{E}(4y_{11} + 2y_{12} + 4y_{13} - 4y_{14} - 2y_{15}) - \frac{1}{3}\,\text{E}(4y_{21} + 2y_{22} + 4y_{23} - 4y_{24} - 2y_{25}) \quad (4.2.3.6)$$

Applying (3.2.1) and (3.2.2) on (4.2.3.6) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 12.44\,\frac{\sigma^2}{n} \quad (4.2.3.7)$$

Substituting (4.2.1.16), (4.2.2.6 and (4.2.3.7) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 4.89\,\frac{\sigma^2}{n} \quad (4.2.3.8)$$

4.2.3.4 Design D_9

Summing (4.2.1.17) and (4.2.2.7) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{3}E\,(-2y_{11} - 5y_{12} - 2y_{13} + 4y_{14} - 4y_{15}) - \frac{1}{3}E\,(-2y_{21} - 5y_{22} - 2y_{23} + 4y_{24} - 4y_{25}) \quad (4.2.3.9)$$

Applying (3.2.1) and (3.2.2) on (4.2.3.9) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 14.44\ \frac{\sigma^2}{n} \quad (4.2.3.10)$$

Substituting (4.2.1.18), (4.2.2.8) and (4.2.3.10) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 4.56\ \frac{\sigma^2}{n} \quad (4.2.3.11)$$

4.2.3.5 Design D_{10}

Summing (4.2.1.19) and (4.2.2.9) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{3}\,E(4y_{11} - 2y_{12} + 4y_{13} - 5y_{14} + 4y_{15}) - \frac{1}{3}\,E(4y_{21} - 2y_{22} + 4y_{23} - 5y_{24} + 4y_{25}) \quad (4.2.3.12)$$

Applying (3.2.1) and (3.2.2) on (4.2.3.12) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 17.11\ \frac{\sigma^2}{n} \quad (4.2.3.13)$$

Substituting (4.2.1.20), (4.2.2.10) and (4.2.3.13) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 3.22\ \frac{\sigma^2}{n} \quad (4.2.3.14)$$

4.2.3.6 Design D_{11}

Summing (4.2.1.21) and (4.2.2.11) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = E(2y_{11} + 3y_{12} + 2y_{13} + 2y_{14} + 2y_{15}) - E(2y_{21} + 3y_{22} + 2y_{23} + 2y_{24} + 2y_{25}) \quad (4.2.3.15)$$

Applying (3.2.1) and (3.2.2) on (4.2.3.15) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 50\ \frac{\sigma^2}{n} \quad (4.2.3.16)$$

Substituting (4.2.1.22), (4.2.2.12) and (4.2.3.16) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 1\ \frac{\sigma^2}{n} \quad (4.2.3.17)$$

4.2.3.7 Design D_{12}

Summing (4.2.1.23) and (4.2.2.13) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{3}E(-4y_{11} - 2y_{12} - 4y_{13} + 5y_{14} - 4y_{15}) - \frac{1}{3}E(-4y_{21} - 2y_{22} - 4y_{23} + 5y_{24} - 4y_{25}) \quad (4.2.3.18)$$

Applying (3.2.1) and (3.2.2) on (4.2.3.18) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 17.11\ \frac{\sigma^2}{n} \quad (4.2.3.19)$$

Substituting (4.2.1.24), (4.2.2.14) and (4.2.3.19) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 3.22\ \frac{\sigma^2}{n} \quad (4.2.3.20)$$

4.2.3.8 Design D_{13}

Summing (4.2.1.25) and (4.2.2.15) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = E(y_{12} + y_{22}) \quad (4.2.3.21)$$

Applying (3.2.1) and (3.2.2) on (4.2.3.21) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 2\ \frac{\sigma^2}{n} \quad (4.2.3.22)$$

Substituting (4.2.1.26), (4.2.2.16) and (4.2.3.22) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 25\ \frac{\sigma^2}{n} \quad (4.2.3.23)$$

4.2.3.9 Design D_{14}

Summing (4.2.1.27) and (4.2.2.17) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{3}\ E(-4y_{11} + 5y_{12} - 2y_{13} - 4y_{14} - 4y_{15}) - \frac{1}{3}\ E(-4y_{21} + 5y_{22} - 2y_{23} - 4y_{24} - 4y_{25}) \quad (4.2.3.24)$$

Applying (3.2.1) and (3.2.2) on (4.2.3.24) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 17.11\ \frac{\sigma^2}{n} \quad (4.2.3.25)$$

Substituting (4.2.1.28), (4.2.2.18) and (4.2.3.25) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 3.22\ \frac{\sigma^2}{n} \quad (4.2.3.26)$$

4.2.2.10 Design D_{15}

Summing (4.2.1.29) and (4.2.2.19) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = E(y_{13} + y_{23}) \quad (4.2.3.27)$$

Applying (3.2.1) and (3.2.2) on (4.2.3.27) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 2\ \frac{\sigma^2}{n} \quad (4.2.3.28)$$

Substituting (4.2.1.30), (4.2.2.20) and (4.2.3.28) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 1.89\ \frac{\sigma^2}{n} \quad (4.2.3.29)$$

4.2.4 Treatments effects variance for C ($2\times 5\times 4$) Cross-Over Designs

4.2.4.1 Design D_{16}

From (4.1.26),

$$\tau_A-\tau_B=\frac{1}{2}E([Y_{11}-Y_{12}-Y_{13}+Y_{14}+Y_{15}]+[Y_{21}-Y_{22}-Y_{23}+Y_{24}+Y_{25}]+$$

$$[Y_{31}+Y_{32}-Y_{33}+Y_{34}-Y_{35}]+[Y_{41}+Y_{42}-Y_{43}+Y_{44}-Y_{45}]) \quad (4.2.4.1)$$

Applying (3.2.1) on (4.2.4.1) gives,

$$\text{var}(\tau_A-\tau_B)=5\frac{\sigma^2}{n} \quad (4.2.4.2)$$

4.2.4.2 Design D_{17}

From (4.1.28),

$$\tau_A-\tau_B=\frac{1}{2}E([Y_{11}+Y_{12}-Y_{13}+Y_{14}+Y_{15}]-[Y_{21}+Y_{22}-Y_{23}+Y_{24}+Y_{25}]+$$

$$[Y_{31}-Y_{32}+Y_{33}+Y_{34}+Y_{35}]-[Y_{41}-Y_{42}+Y_{43}+Y_{44}+Y_{45}]) \quad (4.2.4.3)$$

Applying (3.2.1) on (4.2.4.3) gives,

$$\text{var}(\tau_A-\tau_B)=5\frac{\sigma^2}{n} \quad (4.2.4.4)$$

4.2.4.3 Design D_{18}

From (4.1.30),

$$\tau_A-\tau_B=\frac{1}{2}E([Y_{11}+Y_{12}-Y_{13}+Y_{14}+Y_{15}]-[Y_{21}+Y_{22}-Y_{23}+Y_{24}+Y_{25}]+$$

$$[Y_{31}-Y_{32}+Y_{33}+Y_{34}+Y_{35}]-[Y_{41}-Y_{42}+Y_{43}+Y_{44}+Y_{45}]) \quad (4.2.4.5)$$

Applying (3.2.1) on (4.2.4.5) gives,

$$\text{var}(\tau_A-\tau_B)=5\frac{\sigma^2}{n} \quad (4.2.4.6)$$

4.2.4.4 Design $\mathbf{D_{19}}$

From (4.1.32),

$$\tau_A - \tau_B = \frac{1}{2}E([Y_{11} - Y_{12} + Y_{13} + Y_{14} + Y_{15}] - [Y_{21} - Y_{22} + Y_{23} + Y_{24} + Y_{25}] + [Y_{31} - Y_{32} + Y_{33} + Y_{34} + Y_{35}] - [Y_{41} - Y_{42} + Y_{43} + Y_{44} + Y_{45}]) \quad (4.2.4.7)$$

Applying (3.2.1) on (4.2.4.7) gives,

$$\text{var}(\tau_A - \tau_B) = 5\frac{\sigma^2}{n} \quad (4.2.4.8)$$

4.2.4.5 Design $\mathbf{D_{20}}$

From (4.1.34),

$$\tau_A - \tau_B = \frac{1}{2}E([-Y_{11} + Y_{12} - Y_{13} + Y_{14} - Y_{15}] - [-Y_{21} + Y_{22} - Y_{23} + Y_{24} - Y_{25}] + [Y_{31} - Y_{32} + Y_{33} - Y_{34} + Y_{35}] - [Y_{41} - Y_{42} + Y_{43} - Y_{44} + Y_{45}]) \quad (4.2.4.9)$$

Applying (3.2.1) on (4.2.4.9) gives,

$$\text{var}(\tau_A - \tau_B) = 5\frac{\sigma^2}{n} \quad (4.2.4.10)$$

4.2.4.6 Design $\mathbf{D_{21}}$

From (4.1.36),

$$\tau_A - \tau_B = \frac{1}{4}E[Y_{11} - Y_{12} - Y_{13} + Y_{14} + Y_{15}] - \frac{1}{4}E[Y_{21} - Y_{22} - Y_{23} + Y_{24} + Y_{25}] + \frac{1}{12}E[Y_{31} - Y_{32} + Y_{33} - Y_{34} + Y_{35}] - \frac{1}{12}E[Y_{41} - Y_{42} + Y_{43} - Y_{44} + Y_{45}] \quad (4.2.4.11)$$

Applying (3.2.1) on (4.2.4.11) gives,

$$\text{var}(\tau_A - \tau_B) = 0.6944\frac{\sigma^2}{n} \quad (4.2.4.12)$$

4.2.4.7 Design D_{22}

From (4.1.38),

$$\tau_A - \tau_B = \frac{1}{2}E[-Y_{11} - Y_{12} - Y_{13} + Y_{14} - Y_{15}] - \frac{1}{2}E[-Y_{21} - Y_{22} - Y_{23} + Y_{24} - Y_{25}] + \frac{1}{2}E[Y_{31} - Y_{32} + Y_{33} - Y_{34} + Y_{35}] - \frac{1}{2}E[Y_{41} - Y_{42} + Y_{43} - Y_{44} + Y_{45}] \quad (4.2.4.13)$$

Applying (3.2.1) on (4.2.4.13) gives,

$$\text{var}(\tau_A - \tau_B) = 5\frac{\sigma^2}{n} \quad (4.2.4.14)$$

4.2.4.8 Design D_{23}

From (4.1.40),

$$\tau_A - \tau_B = \frac{1}{2}E[Y_{11} + Y_{12} + Y_{13} + Y_{14} + Y_{15}] - \frac{1}{2}E[Y_{21} + Y_{22} + Y_{23} + Y_{24} + Y_{25}] + \frac{1}{2}E[-Y_{31} - Y_{32} - Y_{33} + Y_{34} - Y_{35}] - \frac{1}{2}E[-Y_{41} - Y_{42} - Y_{43} + Y_{44} - Y_{45}] \quad (4.2.4.15)$$

Applying (3.2.1) on (4.2.4.15) gives,

$$\text{var}(\tau_A - \tau_B) = 5\frac{\sigma^2}{n} \quad (4.2.4.16)$$

4.2.4.9 Design D_{24}

From (4.1.42),

$$\tau_A - \tau_B = \frac{1}{2}E[-Y_{11} + 2Y_{12} - Y_{13} + Y_{14} - Y_{15}] - \frac{1}{2}E[-Y_{21} + 2Y_{22} + Y_{23} - Y_{24} + Y_{25}] + \frac{1}{2}E[-Y_{31} + Y_{32} - Y_{33} - Y_{34} - Y_{35}] - \frac{1}{2}E[-Y_{41} + Y_{42} - Y_{43} - Y_{44} - Y_{45}] \quad (4.2.4.17)$$

Applying (3.2.1) on (4.2.4.17) gives,

$$\text{var}(\tau_A - \tau_B) = 5\frac{\sigma^2}{n} \quad (4.2.4.18)$$

4.2.4.10 Design D_{25}

From (4.1.44),

$$\tau_A - \tau_B = \frac{1}{2}E[-Y_{11} + Y_{12} - Y_{13} - Y_{14} - Y_{15}] - \frac{1}{2}E[-Y_{21} + Y_{22} - Y_{23} - Y_{24} - Y_{25}] +$$

$$\frac{1}{6}E[Y_{31} + Y_{32} + Y_{33} - Y_{34} + Y_{35}] - \frac{1}{6}E[Y_{41} + Y_{42} + Y_{43} - Y_{44} + Y_{45}] \quad (4.2.4.19)$$

Applying (3.2.1) on (4.2.4.19) gives,

$$\text{var}(\tau_A - \tau_B) = 2.78\ \frac{\sigma^2}{n} \quad (4.2.4.20)$$

4.2.4.11 Design D_{26}

From (4.1.46),

$$\tau_A - \tau_B = E[Y_{11} - Y_{12} + Y_{13} + Y_{14} - Y_{15}] - E[Y_{21} - Y_{22} + Y_{23} + Y_{24} - Y_{25}] +$$

$$3E[Y_{31} + Y_{32} - 2Y_{33} + Y_{34} + Y_{35}] - 3E[Y_{41} + Y_{42} - 2Y_{43} + Y_{44} + Y_{45}] \quad (4.2.4.21)$$

Applying (3.2.1) on (4.2.4.21) gives,

$$\text{var}(\tau_A - \tau_B) = 154\ \frac{\sigma^2}{n} \quad (4.2.4.22)$$

4.2.4.12 Design D_{27}

From (4.1.48),

$$\tau_A - \tau_B = \frac{1}{3}E[Y_{11} + Y_{12} - 2Y_{13} + Y_{14} - 2Y_{15}] - \frac{1}{3}E(Y_{21} + Y_{22} - 2Y_{23} + Y_{24} - 2Y_{25}) =$$

$$+\frac{2}{3}E(Y_{31} + Y_{32} - 2Y_{33} + Y_{34} + Y_{35}) - \frac{2}{3}E(Y_{41} + Y_{42} - 2Y_{43} + Y_{44} + Y_{45}) \quad (4.2.4.23)$$

Applying (3.2.1) on (4.2.4.23) gives,

$$\text{var}(\tau_A - \tau_B) = 9.6\ \frac{\sigma^2}{n} \quad (4.2.4.24)$$

4.2.5 Carryover variance for C ($2\times 5\times 4$)

4.2.4.1 Design D_{16}

From (4.1.27),

$$\lambda_A - \lambda_B = \frac{1}{4}(E[Y_{11} - Y_{12} - Y_{13} + Y_{14} + Y_{15}] + [Y_{21} - Y_{22} - Y_{23} + Y_{24} + Y_{25}] +$$

$$[Y_{31} + Y_{32} + Y_{33} - Y_{34} - Y_{35}] + [Y_{41} + Y_{42} + Y_{43} - Y_{44} - Y_{45}]) \quad (4.2.5.1)$$

Applying (3.2.2) on (4.2.5.1) gives,

$$\text{var}(\lambda_A - \lambda_B) = 1.25\frac{\sigma^2}{n} \quad (4.2.5.2)$$

4.2.4.2 Design D_{17}

From (4.1.29),

$$\lambda_A - \lambda_B = \frac{1}{4}(E[Y_{11} - Y_{12} - Y_{13} - Y_{14} + Y_{15}] - [Y_{21} - Y_{22} - Y_{23} - Y_{24} + Y_{25}] +$$

$$[Y_{31} + Y_{32} - Y_{33} - Y_{34} - Y_{35}] - [Y_{41} + Y_{42} - Y_{43} - Y_{44} - Y_{45}]) \quad (4.2.5.3)$$

Applying (3.2.2) on (4.2.5.2) gives,

$$\text{var}(\lambda_A - \lambda_B) = 1.25\frac{\sigma^2}{n} \quad (4.2.5.4)$$

4.2.4.3 Design D_{18}

From (4.1.31),

$$\lambda_A - \lambda_B = \frac{1}{4}(E[Y_{11} - Y_{12} - Y_{13} - Y_{14} + Y_{15}] - [Y_{21} - Y_{22} - Y_{23} - Y_{24} + Y_{25}] +$$

$$[Y_{31} + Y_{32} - Y_{33} - Y_{34} - Y_{35}] - [Y_{41} + Y_{42} - Y_{43} - Y_{44} - Y_{45}]) \quad (4.2.5.5)$$

Applying (3.2.2) on (4.2.5.5) gives,

$$\text{var}(\lambda_A - \lambda_B) = 1.25\frac{\sigma^2}{n} \quad (4.2.5.6)$$

4.2.4.4 Design D_{19}

From (4.1.33),

$$\lambda_A - \lambda_B = \frac{1}{4}(E[Y_{11} - Y_{12} + Y_{13} + Y_{14} - Y_{15}] - [Y_{21} - Y_{22} + Y_{23} + Y_{24} - Y_{25}] +$$

$$[Y_{31} - Y_{32} + Y_{33} + Y_{34} - Y_{35}] - [Y_{41} - Y_{42} + Y_{43} + Y_{44} - Y_{45}]) \quad (4.2.5.7)$$

Applying (3.2.2) on (4.2.5.7) gives,

$$\text{var}(\lambda_A - \lambda_B) = 1.25\,\frac{\sigma^2}{n} \tag{4.2.5.8}$$

4.2.4.5 Design D_{20}

From (4.1.35),

$$\lambda_A - \lambda_B = \tfrac{1}{4}(E[Y_{11} - Y_{12} + Y_{13} + Y_{14} - Y_{15}] - [Y_{21} - Y_{22} + Y_{23} + Y_{24} - Y_{25}] + [Y_{31} + Y_{32} - Y_{33} + Y_{34} + Y_{35}] - [Y_{41} + Y_{42} - Y_{43} + Y_{44} + Y_{45}]) \tag{4.2.5.9}$$

Applying (3.2.2) on (4.2.5.9) gives,

$$\text{var}(\lambda_A - \lambda_B) = 1.25\,\frac{\sigma^2}{n} \tag{4.2.5.10}$$

4.2.4.6 Design D_{21}

From (4.1.37),

$$\lambda_A - \lambda_B = \tfrac{1}{2}(E[Y_{11} - 2Y_{12} - Y_{13} + Y_{14} + Y_{15}] - \tfrac{1}{2}E[Y_{21} - 2Y_{22} - Y_{23} + Y_{24} + Y_{25}] + \tfrac{1}{2}E[Y_{31} + Y_{32} + Y_{33} - Y_{34} - Y_{35}] - \tfrac{1}{2}E[Y_{41} + Y_{42} + Y_{43} - Y_{44} - Y_{45}]) \tag{4.2.5.11}$$

Applying (3.2.2) on (4.2.5.11) gives,

$$\text{var}(\lambda_A - \lambda_B) = 6.5\,\frac{\sigma^2}{n} \tag{4.2.5.12}$$

4.2.4.7 Design D_{22}

From (4.1.39),

$$\lambda_A - \lambda_B = \tfrac{1}{6}(E[Y_{11} - 2Y_{12} + Y_{13} + Y_{14} - Y_{15}] - \tfrac{1}{6}E[Y_{21} - 2Y_{22} + Y_{23} + Y_{24} - Y_{25}] + \tfrac{1}{6}E[Y_{31} + Y_{32} + Y_{33} - 2Y_{34} + Y_{35}] - \tfrac{1}{6}E[Y_{41} + Y_{42} + Y_{43} - 2Y_{44} + Y_{45}]) \tag{4.2.5.13}$$

Applying (3.2.2) on (4.2.5.13) gives,

$$\text{var}(\lambda_A - \lambda_B) = 0.89\,\frac{\sigma^2}{n} \qquad (4.2.5.14)$$

4.2.4.8 Design D_{23}

From (4.1.41),

$$\lambda_A - \lambda_B = \frac{1}{2}E[Y_{11} + 2Y_{12} + Y_{13} + Y_{14} + Y_{15}] - \frac{1}{2}E[Y_{21} + 2Y_{22} + Y_{23} + Y_{24} + Y_{25}] + \frac{1}{2}E[-Y_{31} + Y_{32} - Y_{33} + 2Y_{34} - Y_{35}] - \frac{1}{2}E[-Y_{41} + Y_{42} - Y_{43} + 2Y_{44} - Y_{45}] \qquad (4.2.5.15)$$

Applying (3.2.2) on (4.2.5.15) gives,

$$\text{var}(\lambda_A - \lambda_B) = 4.44\ \frac{\sigma^2}{n} \qquad (4.2.5.16)$$

4.2.4.9 Design D_{24}

From (4.1.43),

$$\lambda_A - \lambda_B = \frac{1}{2}E[-Y_{11} + 2Y_{12} - Y_{13} + Y_{14} - Y_{15}] - \frac{1}{2}E[-Y_{21} + 2Y_{22} - Y_{23} + Y_{24} - Y_{25}] + \frac{1}{6}E[-Y_{31} + 2Y_{32} + Y_{33} - Y_{34} - Y_{35}] - \frac{1}{6}E[-Y_{41} + 2Y_{42} + Y_{43} - Y_{44} - Y_{45}]$$

(4.2.5.17)

Applying (3.2.2) on (4.2.5.17) gives,

$$\text{var}(\lambda_A - \lambda_B) = 1.56\,\frac{\sigma^2}{n} \qquad (4.2.5.18)$$

4.2.4.10 Design D_{25}

From (4.1.45),

$$\lambda_A - \lambda_B = \frac{1}{6}\,E[-Y_{11} + 2Y_{12} + Y_{13} - Y_{14} - Y_{15}] - \frac{1}{6}E[-Y_{21} + 2Y_{22} + Y_{23} - Y_{24} - Y_{25}] + \frac{1}{6}E[-Y_{31} - Y_{32} + 2Y_{33} + Y_{34} - Y_{35}] - \frac{1}{6}E[-Y_{41} - Y_{42} + 2Y_{43} + Y_{44} - Y_{45}] \qquad (4.2.5.19)$$

Applying (3.2.2) on (4.2.5.19) gives,

$$\text{var}(\lambda_A - \lambda_B) = 0.87\ \frac{\sigma^2}{n} \quad (4.2.5.20)$$

4.2.4.11 Design D_{26}

From (4.1.47),

$$\lambda_A - \lambda_B = \frac{1}{4}E[Y_{11} - Y_{12} - Y_{13} - Y_{14} + Y_{15}] + \frac{1}{4}E(Y_{21} - Y_{22} - Y_{23} - Y_{24} + Y_{25}) -$$

$$\frac{1}{4}E(Y_{31} - Y_{32} - Y_{33} + Y_{34} + Y_{35}) - \frac{1}{4}E(Y_{41} - Y_{42} - Y_{43} + Y_{44} + Y_{45})] \quad (4.2.5.21)$$

Applying (3.2.2) on (4.2.5.21) gives,

$$\text{var}(\lambda_A - \lambda_B) = 1.25\ \frac{\sigma^2}{n} \quad (4.2.5.22)$$

4.2.4.12 Design D_{27}

From (4.1.49),

$$\lambda_A - \lambda_B = \frac{1}{2}E(Y_{11} - Y_{12} - Y_{13} - Y_{14} + Y_{15}) - \frac{1}{2}E(Y_{21} - Y_{22} - Y_{23} - Y_{24} + Y_{25}) +$$

$$\frac{3}{2}E(Y_{31} - Y_{32} - Y_{33} + Y_{34} + Y_{35}) - \frac{3}{2}E(Y_{41} - Y_{42} - Y_{43} + Y_{44} + Y_{45}) \quad (4.2.5.23)$$

Applying (3.2.2) on (4.2.5.23) gives,

$$\text{var}(\lambda_A - \lambda_B) = 25\ \frac{\sigma^2}{n} \quad (4.2.5.24)$$

4.2.6 Treatments and Residuals Covariance for C ($2\times 5\times 4$)

4.2.6.1 Design D_{16}

Summing (4.2.4.1) and (4.2.5.1) gives,

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{4}E(3y_{11} - 3y_{12} - 3y_{13} + 3y_{14} + 3y_{15})$$

$$+\frac{1}{4}E(y_{21} - y_{22} - y_{23} + y_{24} + y_{25}) + \frac{1}{4}E(y_{31} - y_{32} - 3y_{33} + 3y_{24} - y_{25}) +$$

$$\frac{1}{4}E(3y_{41} + 3y_{42} - y_{43} + y_{44} - 3y_{45}) \quad (4.2.6.1)$$

Applying (3.2.1) and (3.2.2) on (4.2.6.1) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 6.25\,\frac{\sigma^2}{n} \qquad (4.2.6.2)$$

Substituting (4.2.4.2), (4.2.5.2) and (4.2.6.2) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 3.125\,\frac{\sigma^2}{n}$$

4.2.6.2 Design D_{17}

Summing (4.2.4.3) and (4.2.5.3)

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{4}\,E(3y_{11} + y_{12} - 3y_{13} + y_{14} + 3y_{15})$$

$$+\frac{1}{4}\,E(-3y_{21} - y_{22} + 3y_{23} - y_{24} - 3y_{25}) + \frac{1}{4}\,E(-y_{31} - 5y_{32} + 5y_{33} + 5y_{34} +$$

$$5y_{25}) + \frac{1}{4}\,E(y_{41} + 5y_{42} - 5y_{43} - 5y_{44} - 5y_{45}) \qquad (4.2.6.3)$$

Applying (3.2.1) and (3.2.2) on (4.2.6.3) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 16.25\,\frac{\sigma^2}{n} \qquad (4.2.6.4)$$

Substituting (4.2.4.4), (4.2.5.4) and (4.2.6.4) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 1.875\,\frac{\sigma^2}{n} \qquad (4.2.6.5)$$

4.2.6.3 Design D_{18}

Summing (4.2.4.5) and (4.2.5.5)

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{4}\,E(3y_{11} + y_{12} - 3y_{13} + y_{14} + 3y_{15})$$

$$+\frac{1}{4}\,E(-3y_{21} - y_{22} + 3y_{23} - y_{24} - 3y_{25}) + \frac{1}{4}\,E(-y_{31} - 5y_{32} + 5y_{33} + 5y_{34} +$$

$$5y_{35}) + \frac{1}{4}\,E(y_{41} + 5y_{42} - 5y_{43} - 5y_{44} - 5y_{45}) \qquad (4.2.6.6)$$

Applying (3.2.1) and (3.2.2) on (4.2.6.6) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 16.25\ \frac{\sigma^2}{n} \quad (4.2.6.7)$$

Substituting (4.2.4.6), (4.2.5.6 and (4.2.6.7) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 1.875\ \frac{\sigma^2}{n} \quad (4.2.6.8)$$

4.2.6.4 Design D_{19}

Summing (4.2.4.7) and (4.2.5.7) gives,

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{4}\,E(3y_{11} - 3y_{12} + 3y_{13} + 3y_{14} + y_{15})$$

$$+\frac{1}{4}\,E(-3y_{21} + 3y_{22} - 3y_{23} - 3y_{24} - y_{25}) + \frac{1}{4}\,E(3y_{31} - 3y_{32} + 3y_{33} + 3y_{24} +$$

$$y_{25}) + \frac{1}{4}\,E(-3y_{41} + 3y_{42} - 3y_{43} - 3y_{44} - y_{45}) \quad (4.2.6.9)$$

Applying (3.2.1) and (3.2.2) on (4.2.6.9) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 9.25\ \frac{\sigma^2}{n} \quad (4.2.6.10)$$

Substituting (4.2.4.8), (4.2.5.8) and (4.2.6.10) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 1.625\ \frac{\sigma^2}{n} \quad (4.2.6.11)$$

4.2.6.5 Design D_{20}

Summing (4.2.4.9) and (4.2.5.9) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{4}\,E(-y_{11} + y_{12} - y_{13} + 3y_{14} - 3y_{15})$$

$$+\frac{1}{4}\,E(y_{21} - y_{22} + y_{23} - 3y_{24} + 3y_{25}) + \frac{1}{4}\,E(y_{31} - 3y_{32} + 3y_{33} - 3y_{34} + y_{35}) +$$

$$\frac{1}{4}\,E(-3y_{41} + y_{42} - y_{43} + y_{44} - 3y_{45}) \quad (4.2.6.12)$$

Applying (3.2.1) and (3.2.2) on (4.2.6.12) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 5.75\ \frac{\sigma^2}{n} \quad (4.2.6.13)$$

Substituting (4.2.4.10), (4.2.5.10) and (4.2.6.13) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 3.375\ \frac{\sigma^2}{n} \quad (4.2.6.14)$$

4.2.6.6 Design D_{21}

Summing (4.2.4.11) and (4.2.5.11) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{4}\,E(3y_{11} - 5y_{12} - 3y_{13} + 3y_{14} + 3y_{15})$$

$$+\frac{1}{4}\,E(-3y_{21} + 5y_{22} + 3y_{23} - 3y_{24} - 3y_{25}) + \frac{1}{12}\,E(7y_{31} + 5y_{32} + 7y_{33} - 7y_{34} -$$

$$5y_{35}) + \frac{1}{12}\,E(-7y_{41} - 5y_{42} - 7y_{43} + 7y_{44} + 5y_{45}) \quad (4.2.6.15)$$

Applying (3.2.1) and (3.2.2) on (4.2.6.15) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 10.36\ \frac{\sigma^2}{n} \quad (4.2.6.16)$$

Substituting (4.2.4.12), (4.2.5.12) and (4.2.6.16) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 2.0138\ \frac{\sigma^2}{n} \quad (4.2.6.17)$$

4.2.6.7 Design D_{22}

Summing (4.2.4.13) and (4.2.5.13) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{6}\,E(-2y_{11} - 5y_{12} - 2y_{13} + 4y_{14} - 4y_{15})$$

$$+\frac{1}{6}\,E(2y_{21} + 5y_{22} - 2y_{23} - 4y_{24} + 5y_{25}) + \frac{1}{6}\,E(4y_{31} - 2y_{32} + 4y_{33} - 5y_{34} +$$

$$4y_{35}) + \frac{1}{6}\,E(-4y_{41} + 2y_{42} - 4y_{43} + 5y_{44} - 4y_{45}) \quad (4.2.6.18)$$

Applying (3.2.1) and (3.2.2) on (4.2.6.18) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 8.139\ \frac{\sigma^2}{n} \quad (4.2.6.19)$$

Substituting (4.2.4.14), (4.2.5.14) and (4.2.6.19) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 1.821\ \frac{\sigma^2}{n} \quad (4.2.6.20)$$

4.2.6.8 Design D_{23}

Summing (4.2.4.15) and (4.2.5.15) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{2}\,E(2y_{11} + 3y_{12} + 2y_{13} + 2y_{14} + 2y_{15})$$

$$+\frac{1}{2}\,E(-2y_{21} - 3y_{22} - 2y_{23} - 2y_{24} - 2y_{25}) + \frac{1}{6}\,E(-2y_{32}) + \frac{1}{6}\,E(-4y_{41} + 2y_{42} -$$

$$4y_{43} + 5y_{44} - 4y_{45}) \quad (4.2.6.21)$$

Applying (3.2.1) and (3.2.2) on (4.2.6.21) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 3.638\ \frac{\sigma^2}{n} \quad (4.2.6.22)$$

Substituting (4.2.4.16), (4.2.5.16) and (4.2.6.22) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 7.62\ \frac{\sigma^2}{n} \quad (4.2.6.23)$$

4.2.6.9 Design D_{24}

Summing (4.2.4.17) and (4.2.5.17) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{2}\,E(y_{12}) - \frac{1}{2}\,E(y_2) + \frac{1}{6}\,E(-4y_{31} + 5y_{32} - 2y_{33} -$$

$$4y_{34} - 4y_{35}) + \frac{1}{6}\,E(4y_{41} - 5y_{42} + 2y_{43} + 4y_{44} + 4y_{45}) \quad (4.2.6.24)$$

Applying (3.2.1) and (3.2.2) on (4.2.6.24) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 4.77\ \frac{\sigma^2}{n} \quad (4.2.6.25)$$

Substituting (4.2.4.18), (4.2.5.18) and (4.2.6.25) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 4.1712\ \frac{\sigma^2}{n} \quad . \quad (4.2.6.26)$$

4.2.6.10 Design D_{25}

Summing (4.2.4.19) and (4.2.5.19) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{6}\,E(-4y_{11} + 5y_{12} - y_{13} - 4y_{14} - 4y_{15})$$

$$+\frac{1}{6}\,E(4y_{21} - 5y_{22} + 2y_{23} + 4y_{24} + 4y_{25}) + \frac{1}{6}\,E(3y_{33}) - \frac{1}{6}\,E(3y_{43}) \quad (4.2.6.27)$$

Applying (3.2.1) and (3.2.2) on (4.2.6.27) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 4.694\ \frac{\sigma^2}{n} \quad (4.2.6.28)$$

Substituting (4.2.4.20), (4.2.5.20) and (4.2.6.28) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 1.30\ \frac{\sigma^2}{n} \quad (4.2.6.29)$$

4.2.6.11 Design D_{26}

Summing (4.2.4.21) and (4.2.5.21) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{4}\,E(5y_{11} - 5y_{12} + 3y_{13} + 3y_{14} - 3y_{15})$$

$$+\frac{1}{4}\,E(-3y_{21} + 3y_{22} - 5y_{23} - 5y_{24} + 5y_{25}) + \frac{1}{4}\,E(11y_{31} + 13y_{32} - 23y_{33} +$$

$$11y_{34} + 11y_{35}) + \frac{1}{4}\,E(-13y_{41} - 11y_{42} + 25y_{43} - 13y_{44} - 13y_{45}) \quad (4.2.6.30)$$

Applying (3.2.1) and (3.2.2) on (4.2.6.30) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 155.25\ \frac{\sigma^2}{n} \quad (4.2.6.31)$$

Substituting (4.2.4.22), (4.2.5.22) and (4.2.6.31) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 77.625\ \frac{\sigma^2}{n} \quad (4.2.6.32)$$

4.2.6.12 Design D_{27}

Summing (4.2.4.23) and (4.2.5.23) gives

$$(\tau_A - \tau_B) + (\lambda_A - \lambda_B) = \frac{1}{6}\,E(5y_{11} - y_{12} - 7y_{13} - y_{14} - y_{15})$$

$$+\frac{1}{6}\,E(-5y_{21} + y_{22} + 7y_{23} + y_{24} + y_{25}) + \frac{1}{6}\,E(13y_{31} - 5y_{32} - 17y_{33} + 13y_{34} +$$

$$13y_{35}) + \frac{1}{6}\,E(-13y_{41} + 5y_{42} + 17y_{43} - 13y_{44} - 13y_{45}) \qquad (4.2.6.33)$$

Applying (3.2.1) and (3.2.2) on (4.2.6.33) gives,

$$\text{var}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 49.89\ \frac{\sigma^2}{n} \qquad (4.2.6.34)$$

Substituting (4.2.4.24), (4.2.5.24) and (4.2.6.34) to (3.2.6) gives,

$$\text{covar}[(\tau_A - \tau_B) + (\lambda_A - \lambda_B)] = 9.66\ \frac{\sigma^2}{n} \qquad (4.2.6.35)$$

Table 4.2.1: Summary of Variances and Covariance of C (2× 5 × 2) Designs in Multiples of $\frac{\sigma^2}{n}$

Design	Treatment effects variance	Carry-over effects variance	Covariance of treatment and carry-over effects
D_1	10.00	–	–
D_2	10.00	–	–
D_3	10.00	–	–
D_4	10.00	–	–
D_5	10.00	–	–
D_6	10.00	0.64	5.32
D_7	10.00	16.00	1.00
D_8	1.11	10.00	4.89
D_9	10.00	1.78	4.56
D_{10}	10.00	0.64	3.22
D_{11}	10.00	16.00	1.00
D_{12}	10.00	1.78	3.22
D_{13}	10.00	16.00	25.00
D_{14}	10.00	1.78	3.22
D_{15}	1.11	1.78	1.89

Table 4.2.2: Summary of Variances and Covariance of C (2× 5 × 4) Designs in Multiples of $\frac{\sigma^2}{n}$

Design	Treatment effects variance	Carry-over effects variance	Covariance of treatment and carry-over effects
D_{16}	5.000	1.250	3.125
D_{17}	5.000	1.250	1.875
D_{18}	5.000	1.250	1.875
D_{19}	5.000	1.250	1.625
D_{20}	5.000	1.250	3.375
D_{21}	0.690	6.500	2.014
D_{22}	5.000	0.890	1.821
D_{23}	5.000	4.440	7.620
D_{24}	5.000	1.560	4.171
D_{25}	2.780	0.870	1.300
D_{26}	154.000	1.250	77.625
D_{27}	9.600	25.000	9.660

4.2.7 Discussion

In this section, the optimality criteria of the five period cross-over designs were evaluated. The significance of this section is to enable experimenters who would like to obtain efficient designs in estimating effects of interest make informed decisions when two or more competing designs are involved. In their book on design and analysis of cross-over designs, Jones and Kenward in the year 2015 asserts that the optimality for two treatments cross-over designs can be evaluated using their variances. In this regard, the C (2× 5× 2) designs were categorized into three groups depending on the estimates required. In estimating carry-over effects,D_6& D_{10} were the most optimum since they gave the least variance of 0.64 $\frac{\sigma^2}{n}$ whereas D_7, D_{11}& D_{13} were the least optimum with variance of 16$\frac{\sigma^2}{n}$. D_9, D_{12}, D_{14}&D_{15} Were found to be equally optimum with a variance of 1.78$\frac{\sigma^2}{n}$ while D_8 had a variance of 10$\frac{\sigma^2}{n}$. Additionally, the estimation of treatment effects prefers D_8 & D_{15} due to the fact that they give minimum variance of 1.11$\frac{\sigma^2}{n}$. All the other designs are equally optimum with a variance of 10$\frac{\sigma^2}{n}$. Moreover,

the estimation of treatment effects in the presence of carry-over effects requires the use of covariance to assess their optimality. In this regard, D_7 & D_{11} were the most optimum with variance of $\frac{\sigma^2}{n}$ whereas D_{13} was the least optimum with variance of $25\frac{\sigma^2}{n}$. $D_{10}, D_{12}, \& D_{14}$ were equally optimal with variance of $3.22\frac{\sigma^2}{n}$ while $D_6, D_8, D_9 \& D_{15}$, had variances of $5.32\frac{\sigma^2}{n}$, $4.89\frac{\sigma^2}{n}$, $4.56\frac{\sigma^2}{n}$ &$1.89\frac{\sigma^2}{n}$ respectively. For the C ($2\times 5 \times 4$), D_{21} was optimum for estimating treatment effects with a variance of $0.69\frac{\sigma^2}{n}$ while D_{26} was the least optimal with a variance of $154\frac{\sigma^2}{n}$. all the other designs were found to be equally optimal with a variance of $5\frac{\sigma^2}{n}$ except D_{25} & D_{27} whose variance was $2.7\frac{\sigma^2}{n}$ and, $9.6\frac{\sigma^2}{n}$ respectively. With regards to carry-over effects, D_{25} & D_{22} were the most optimal with variances $0.87\frac{\sigma^2}{n}$ and $0.89\frac{\sigma^2}{n}$ respectively while D_{27} was the least optimal with variance of $25\frac{\sigma^2}{n}$. $D_{16}, D_{17}, D_{18}, D_{19}, D_{20}, \& D_{26}$, were found to be equally optimal with variance of $1.25\frac{\sigma^2}{n}$ whereas $D_{21}, D_{23}, \& D_{24}$ had optimal values of $6.5\frac{\sigma^2}{n}$, $4.44\frac{\sigma^2}{n}$ and $1.56\frac{\sigma^2}{n}$ respectively. For estimating treatments effects in the presence of carry-over effects, D_{25} was the most optimal with $1.3\frac{\sigma^2}{n}$ while D_{26} was the least optimal with $77.625\frac{\sigma^2}{n}$. D_{17} and D_{18} were found to be equally optimal with $1.875\frac{\sigma^2}{n}$ whereas $D_{16}, D_{19}, D_{20}, D_{21}, D_{22}, D_{23}, D_{24} \& D_{27}$ had optimal values of $3.125\frac{\sigma^2}{n}$,$1.625\frac{\sigma^2}{n}$,$3.375\frac{\sigma^2}{n}$,$2.014\frac{\sigma^2}{n}$,$1.821\frac{\sigma^2}{n}$,$7.620\frac{\sigma^2}{n}$,$4.171\frac{\sigma^2}{n}$ &$9.66\frac{\sigma^2}{n}$ respectively.

4.3 Assessment of Robustness For The (2× 5) Cross-Over Designs Against Missing Data.

4.3.1 Robustness for Missing Data for D_{16}

Table 4.3.1: Expected values for Design D_{16} with only two complete periods for all subjects

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	*	*	*
ABBBB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	*	*	*
ABAAA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	*	*	*
BABBB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	*	*	*

4.3.1.1 Robustness for Missing Data in Carry-over Effects for D_{16}

The contrasts a_1, a_2, a_3 and a_4 , identified from Table 4.3.1 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(a_1) = \frac{1}{2}E(Y_{11} + Y_{12}) = \frac{1}{2}[2\,\mu + (\pi_1 + \pi_2)] + (\tau_A + \tau_B) + \lambda_B]$$

$$E(a_2) = \frac{1}{2}E(Y_{21} + Y_{22}) = \frac{1}{2}[2\mu + (\pi_1 + \pi_2) + (\tau_B + \tau_A) + \lambda_A]$$

$$E(a_3) = \frac{1}{2}E(Y_{31} + Y_{32}) = \frac{1}{2}[2\,\mu + (\pi_1 + \pi_2) + (\tau_A + \tau_B) + \lambda_A]$$

$$E(a_4) = \frac{1}{2}E(Y_{41} + Y_{42}) = \frac{1}{2}[2\mu + (\pi_1 + \pi_2) + (\tau_B + \tau_A) + \lambda_B]$$

A linear combination of $(a_2 - a_1) + (a_3 - a_4)$ forms unbiased estimate of carry-over effects,

$$\text{Thus, } [\lambda_A - \lambda_B] = (a_2 - a_1) + (a_3 - a_4) \qquad (4.3.1)$$

From (4.2.1), the design remains connected for the first two periods in all sequences, whence the design is said to be perpetually connected for carry-over effects.

4.3.1.2 Robustness for Missing Data in Treatment Effects for D_{16}

The contrasts a_5, a_6, a_7 and a_8 , identified from Table 4.3.1 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(a_5) = \frac{1}{2}E(Y_{11} - Y_{12}) = \frac{1}{2}[\ (\pi_1 - \pi_2)] + (\ \tau_A - \tau_B) - \lambda_B]$$

$$E(a_6) = \frac{1}{2}E(Y_{21} - Y_{22}) = \frac{1}{2}[\ (\pi_1 - \pi_2) + (\ \tau_B - \tau_A) - \lambda_A]$$

$$E(a_7) = \frac{1}{2}E(Y_{31} - Y_{32}) = \frac{1}{2}[\ (\pi_1 - \pi_2) + (\ \tau_A - \tau_B) - \lambda_A]$$

$$E(a_8) = \frac{1}{2}E(Y_{41} - Y_{42}) = \frac{1}{2}[\ (\pi_1 - \pi_2) + (\ \tau_B - \tau_A) - \lambda_B]$$

A linear combination of $(a_5 - a_6) + (a_7 - a_8)$ forms unbiased estimate for treatment effects,

Thus,

$$[\ \tau_A - \tau_B] = (a_5 - a_6) + (a_7 - a_8)\ . \qquad (4.3.2)$$

From (4.2.2), the design remains connected for the first two periods in all sequences, whence the design is said to be perpetually connected for Treatment effects.

4.3.2 Robustness for Missing Data for D_{17}

Table 4.3.2: Expected values of design D_{17} with only two complete periods for all subjects

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	*	*	*
ABBBB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	*	*	*
A ABAA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	*	*	*
BBABB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	*	*	*

4.3.2.1 Robustness for Missing Data in Carry-over Effects for D_{17}

The contrasts d_1, d_2, d_3 and d_4 , identified from Table 4.3.2 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_1) = \frac{1}{2}E(Y_{11} + Y_{12}) = \frac{1}{2}[2\,\mu + (\pi_1 + \pi_2) + (\,\tau_A + \tau_B) + \lambda_B]$$

$$E(d_2) = \frac{1}{2}E(Y_{21} + Y_{22}) = \frac{1}{2}[2\mu + (\pi_1 + \pi_2) + \ (\tau_B + \tau_A) + \lambda_A]$$

$$E(d_3) = \frac{1}{2}E(-Y_{31} + Y_{32}) = \frac{1}{2}[-(\pi_1 + \pi_2) + \lambda_A]$$

$$E(d_4) = \frac{1}{2}E(-Y_{41} + Y_{42}) = \frac{1}{2}[(-\pi_1 + \pi_2) + \ \lambda_B]$$

A linear combination of $(d_2 - d_1) + (d_3 - d_4)$ forms unbiased estimate of carry-over effects,

$$\text{Thus,}[\lambda_A - \lambda_B] = (d_2 - d_1) + (d_3 - d_4) \qquad (4.3.3)$$

From (4.3.3), the design remains connected for the first two periods in all sequences, whence the design is said to be perpetually connected for carry-over effects.

4.3.2.2 Robustness for Missing Data in Treatment Effects for D_{17}

The contrasts $d_5, d_6, d_7$and d_8 , identified from Table 4.3.2 in such a way that (3.1.6), and (3.1.8)are satisfied are given by;

$$E(d_5) = \frac{1}{2}E(Y_{11} + Y_{12}) = \frac{1}{2}[2\,\mu + (\pi_1 + \pi_2) + (\,\tau_A + \tau_B) + \lambda_B]$$

$$E(d_6) = \frac{1}{2}E(Y_{21} + Y_{22}) = \frac{1}{2}[2\mu + (\pi_1 + \pi_2) + \ (\tau_B + \tau_A) + \lambda_A]$$

$$E(d_7) = \frac{1}{2}E(Y_{31} + Y_{32}) = \frac{1}{2}[\,(\pi_1 + \pi_2) + 2\tau_A + \lambda_A]$$

$$E(d_8) = \frac{1}{2}E(Y_{41} + Y_{42}) = \frac{1}{2}[(\pi_1 + \pi_2) + 2\tau_B + \ \lambda_B]$$

A linear combination of $(d_5 - d_6) + (d_7 - d_8)$ forms unbiased estimate of treatment effects,

$$\text{Thus, } [\tau_A - \tau_B] = (d_5 - d_6) + (d_7 - d_8) \qquad (4.3.4)$$

From (4.3.4), the design remains connected for the first two periods in all sequences, whence the design is said to be perpetually connected for treatment effects.

4.3.3 Robustness for Missing Data for D_{18}

Table 4.3.3: Expected values for Design D_{18} with only two complete periods for all subjects

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	*	*	*
ABBBB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	*	*	*
A AABA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	*	*	*
BBBAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	*	*	*

4.3.3.1 Robustness for Missing Data in Carry-over Effects for D_{18}

The contrasts d_9, d_{10}, d_{11} and d_{12} , identified from Table 4.3.3 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_9) = \frac{1}{2}E(Y_{11} + Y_{12}) = \frac{1}{2}[2\mu + (\pi_1 + \pi_2) + (\tau_A + \tau_B) + \lambda_B]$$

$$E(d_{10}) = \frac{1}{2}E(Y_{21} + Y_{22}) = \frac{1}{2}[2\mu + (\pi_1 + \pi_2) + (\tau_B + \tau_A) + \lambda_A]$$

$$E(d_{11}) = \frac{1}{2}E(-Y_{31} + Y_{32}) = \frac{1}{2}[(-\pi_1 + \pi_2) + \lambda_A]$$

$$E(d_{12}) = \frac{1}{2}E(-Y_{41} + Y_{42}) = \frac{1}{2}[(-\pi_1 + \pi_2) + \lambda_B]$$

A linear combination of $(d_{10} - d_9) + (d_{11} - d_{12})$ forms unbiased estimate of carry-over effects,

$$\text{Thus, } [\lambda_A - \lambda_B] = (d_{10} - d_9) + (d_{11} - d_{12}) \qquad (4.3.5)$$

From (4.3.5), the design remains connected for the first two periods in all sequences, whence the design is said to be perpetually connected for carry-over effects.

4.3.3.2 Robustness for Missing Data in Treatment Effects for D_{18}

The contrasts d_{13}, d_{14}, d_{15} and d_{16} , identified from Table 4.3.4 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(d_{13}) = \frac{1}{2}E(Y_{11} - Y_{12}) = \frac{1}{2}[\,(\pi_1 - \pi_2) + (\,\tau_A - \tau_B) - \lambda_B]$$

$$E(d_{14}) = \frac{1}{2}E(-Y_{21} + Y_{22}) = \frac{1}{2}[(-\pi_1 + \pi_2) + \ (-\tau_B + \tau_A) + \lambda_A]$$

$$E(d_{15}) = \frac{1}{2}E(Y_{31} - Y_{32}) = \frac{1}{2}[\,(\pi_1 - \pi_2) - \lambda_A]$$

$$E(d_{16}) = \frac{1}{2}E(Y_{41} - Y_{42}) = \frac{1}{2}[(\pi_1 - \pi_2) - \lambda_B]$$

A linear combination of $(d_{13} + d_{14} + d_{15} - d_{16})$ forms unbiased estimate for treatment effects,

Thus, $[\,\tau_A - \tau_B] = (d_{13} + d_{14} + d_{15} - d_{16})$. (4.3.6)

From (4.3.6), the design remains connected for the first two periods in all subjects, whence the design is said to be perpetually connected for Treatment effects.

4.3.4 Robustness for Missing Data for D_{19}

Table 4.3.4: Expected values for Design D_{19} with only two complete periods for all subjects

SEQ	p_1	p_2	p_3	p_4	p_5
AABAA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	*	*	*
BBABB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	*	*	*
A AABA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	*	*	*
BBBAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	*	*	*

4.3.4.1 Robustness for Missing Data in Carry-over Effects for D_{19}

The contrasts d_{17}, d_{18}, d_{19} and d_{20} , identified from Table 4.3.4 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_{17}) = \frac{1}{2}E(-Y_{11} + Y_{12}) = \frac{1}{2}[(-\pi_1 + \pi_2) + \lambda_A]$$

$$E(d_{18}) = \frac{1}{2}E(-Y_{21} + Y_{22}) = \frac{1}{2}[(-\pi_1 + \pi_2) + \lambda_B]$$

$$E(d_{19}) = \frac{1}{2}E(-Y_{31} + Y_{32}) = \frac{1}{2}[(-\pi_1 + \pi_2) + \lambda_A]$$

$$E(d_{20}) = \frac{1}{2}E(-Y_{41} + Y_{42}) = \frac{1}{2}[(-\pi_1 + \pi_2) + \lambda_B]$$

A linear combination of $(d_{17} + d_{19} - d_{18} - d_{20})$. forms unbiased estimate of carry-over effects,

Thus, $[\lambda_A - \lambda_B] = (d_{17} + d_{19} - d_{18} - d_{20})$. (4.3.7)

From (4.3.7), the design remains connected for the first two periods in all subjects, whence the design is said to be perpetually connected for carry-over effects.

Table 4.3.5: Expected values for Design D_{19} with 10 Observations missing

SEQ	p_1	p_2	p_3	p_4	p_5
AABAA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	*	*
BBABB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	*	*
A AABA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	*	*	*
BBBAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	*	*	*

4.3.4.2 Robustness for Missing Data in Treatment Effects for D_{19}

The contrasts d_{21}, d_{22}, d_{23} and d_{24} , identified from Table 4.3.5 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(d_{21}) = \frac{1}{4}E(Y_{11} + Y_{12} - 2Y_{13}) = \frac{1}{4}[(\pi_1 + \pi_2 - 2\pi_3) + 2\tau_A - 2\tau_B - \lambda_A]$$

$$E(d_{22}) = \frac{1}{4}E(-Y_{21} - Y_{22} + 2Y_{23}) = \frac{1}{4}[(-\pi_1 - \pi_2 + 2\pi_3) - 2\tau_B + 2\tau_A + \lambda_B]$$

$$E(d_{23}) = \frac{1}{4}E(Y_{31} - Y_{32}) = \frac{1}{4}[(\pi_1 - \pi_2) - \lambda_A]$$

$$E(d_{24}) = \frac{1}{4}E(Y_{41} - Y_{42}) = \frac{1}{4}[(\pi_1 - \pi_2) - \lambda_B]$$

A linear combination of $(d_{21} + d_{22} + d_{24} - d_{23})$. forms unbiased estimate of treatment effects,

Thus, $[\tau_A - \tau_B] = (d_{21} + d_{22} + d_{24} - d_{23})$ (4.2.8)

From (4.3.8), the maximum number of subjects that can be lost and the design remains connected is 10, whence the break down number DM=10.

4.3.5 Robustness for Missing Data for D_{20}

Table 4.3.6: Expected values for Design D_{20} with only two complete periods for all subjects

SEQ	p_1	p_2	p_3	p_4	p_5
AAAAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	*	*	*
BBBBA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	*	*	*
BBAAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	*	*	*
AABBB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	*	*	*

4.3.5.1 Robustness for Missing Data in Carry-over Effects for D_{20}

The contrasts d_{25}, d_{26}, d_{27} and d_{28} , identified from Table 4.3.6 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_{25}) = \frac{1}{2}E(-Y_{11} + Y_{12}) = \frac{1}{2}[(\pi_1 + \pi_2) + \lambda_A]$$

$$E(d_{26}) = \frac{1}{2}E(-Y_{21} + Y_{22}) = \frac{1}{2}[(\pi_1 + \pi_2) + \lambda_B]$$

$$E(d_{27}) = \frac{1}{2}E(-Y_{31} + Y_{32}) = \frac{1}{2}[(\pi_1 + \pi_2) + \lambda_A]$$

$$E(d_{28}) = \frac{1}{2}E(-Y_{41} + Y_{42}) = \frac{1}{2}[(\pi_1 + \pi_2) + \lambda_B]$$

A linear combination of $(d_{25} + d_{27} - d_{26} - d_{28})$. forms unbiased estimate of carry-over effects,

Thus,$\lambda_A - \lambda_B = d_{25} + d_{27} - d_{26} - d_{28}$ (4.3.9)

From (4.3.9), the design remains connected for the first two periods in all subjects, whence the design is said to be perpetually connected for carry-over effects.

Table 4.3.7: Expected values for Design D_{20} with 10 Observations missing.

SEQ	p_1	p_2	p_3	p_4	p_5
AAAAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$*$	$*$	$*$
BBBBA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$*$	$*$	$*$
BBAAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$*$	$*$
AABBB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$*$	$*$

4.3.5.2 Robustness for Missing Data in treatment Effects for D_{20}

The contrasts d_{29}, d_{30}, d_{31} and d_{32} , identified from Table 4.3.7 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(d_{29}) = \frac{1}{4}E(Y_{11} - Y_{12}) = \frac{1}{4}[\,(\pi_1 - \pi_2) - \lambda_A]$$

$$E(d_{30}) = \frac{1}{4}E(Y_{21} - Y_{22}) = \frac{1}{4}[(\pi_1 - \pi_2) - \lambda_B]$$

$$E(d_{31}) = \frac{1}{4}E(-Y_{31} - Y_{32} + 2Y_{33}) = \frac{1}{4}[\,(-\pi_1 - \pi_2 + 2\pi_3) - 2\tau_B + 2\tau_A + \lambda_B]$$

$$E(d_{32}) = \frac{1}{4}E(Y_{41} + Y_{42} - 2Y_{43}) = \frac{1}{4}[(\pi_1 + \pi_2 - 2\pi_3) + 2\tau_A - 2\tau_B - \lambda_A]$$

A linear combination of $(d_{32} + d_{31} + d_{30} - d_{29})$ forms unbiased estimate of treatment effects,

Thus,$\tau_A - \tau_B = d_{32} + d_{31} + d_{30} - d_{29}$. (4.3.10)

From (4.3.10), the maximum number of subjects that can be lost and the design remains connected is 10, whence the break down number DM=10.

4.3.6 Robustness for Missing Data for $\mathbf{D_{21}}$

Table 4.3.8: Expectation for Design D_{21} with only two complete periods for all subjects

SEQ	p_1	p_2	p_3	p_4	p_5
BABAA	$\mu+\pi_1+\tau_B$	$\mu+\pi_2+\tau_A+\lambda_B$	*	*	*
ABABB	$\mu+\pi_1+\tau_A$	$\mu+\pi_2+\tau_B+\lambda_A$	*	*	*
BA ABA	$\mu+\pi_1+\tau_B$	$\mu+\pi_2+\tau_A+\lambda_B$	*	*	*
ABBAB	$\mu+\pi_1+\tau_A$	$\mu+\pi_2+\tau_B+\lambda_A$	*	*	*

4.3.6.1 Robustness for Missing Data in Carry-over Effects for D_{21}

The contrasts d_{33}, d_{34}, d_{35} and d_{36} , identified from Table 4.3.8 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_{33}) = \frac{1}{2}E(Y_{11}+Y_{12}) = \frac{1}{2}[2\,\mu + (\pi_1+\pi_2) + \tau_B+\tau_A + \lambda_B]$$

$$E(d_{34}) = \frac{1}{2}E(Y_{21}+Y_{22}) = \frac{1}{2}[2\mu + (\pi_1+\pi_2)+\tau_A+\tau_B + \lambda_A]$$

$$E(d_{35}) = \frac{1}{2}E(Y_{31}+Y_{32}) = \frac{1}{2}[2\,\mu + (\pi_1+\pi_2)+\tau_B+\tau_A + \lambda_B]$$

$$E(d_{36}) = \frac{1}{2}E(Y_{41}+Y_{42}) = \frac{1}{2}[2\,\mu + (\pi_1+\pi_2) + \tau_A+\tau_B + \lambda_A]$$

A linear combination of $(d_{36} + d_{34} - d_{35} - d_{31})$ forms unbiased estimate for carry-over effects,

Thus, $\lambda_A - \lambda_B = d_{36} + d_{34} - d_{35} - d_{31}$ (4.3.11)

From (4.3.11), the design remains connected for the first two periods in all subjects, whence the design is said to be perpetually connected for carry-over effects.

4.3.6.2 Robustness for Missing Data in Treatment Effects for D_{21}

The contrasts $d_{45}, d_{46}, d_{47}$and d_{48} , identified from Table 4.3.9 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$d_{45} = \frac{1}{2}(-Y_{11}-Y_{12}) = \frac{1}{2}[\,(-\pi_1-\pi_2) - \tau_B-\tau_A - \lambda_B]$$

$d_{46} = \frac{1}{2}(-Y_{21} - Y_{22}) = \frac{1}{2}[(-\pi_1 - \pi_2) - \tau_A - \tau_B \ - \lambda_A]$

$d_{47} = \frac{1}{2}(-Y_{31} + Y_{32}) = \frac{1}{2}[(-\pi_1 + \pi_2) - \tau_B + \tau_A \ + \lambda_B]$

$d_{48} = \frac{1}{2}(Y_{41} - Y_{42}) = \frac{1}{2}[\ (\pi_1 - \pi_2) \ + \tau_A - \tau_B - \lambda_A]$

A linear combination of $(d_{45} + d_{47} + d_{48} - d_{46})$. forms unbiased estimate of treatment effects,

Thus, $\tau_A - \tau_B = d_{45} + d_{47} + \ d_{48} - d_{46}$ (4.3.12)

From (4.3.12), the design remains connected for the first two periods in all subjects, whence the design is said to be perpetually connected for treatment effects.

4.3.7 Robustness for Missing Data for D_{22}

Table 4.3.9: Expectation for Design D_{22} with only two complete periods for all subjects

SEQ	p_1	p_2	p_3	p_4	p_5
BAAAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$*$	$*$	$*$
ABBBA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$*$	$*$	$*$
ABBAA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$*$	$*$	$*$
BAABB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$*$	$*$	$*$

4.3.7.1 Robustness for Missing Data in Carry-over Effects for D_{22}

The contrasts d_{49}, d_{50}, d_{51} and d_{52} , identified from Table 4.3.9 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$E(d_{49}) = \frac{1}{2}E(Y_{11} + Y_{12}) = \frac{1}{2}[2\ \mu + (\pi_1 + \pi_2) + \tau_B + \tau_A \ + \lambda_B]$

$E(d_{50}) = \frac{1}{2}E(Y_{21} + Y_{22}) = \frac{1}{2}[2\mu + (\pi_1 + \pi_2) + \tau_A + \tau_B + \ \ \lambda_A]$

$E(d_{51}) = \frac{1}{2}E(Y_{31} + Y_{32}) = \frac{1}{2}[2\ \mu + (\pi_1 + \pi_2) + \tau_A + \tau_B \ + \lambda_A]$

$E(d_{52}) = \frac{1}{2}E(Y_{41} + Y_{42}) = \frac{1}{2}[2\ \mu + (\pi_1 + \pi_2) \ + \tau_B + \tau_A + \lambda_B]$

A linear combination of $(d_{50} + d_{51} + d_{49} - d_{52})$ forms unbiased estimate of carry-over effects,

Thus, $\lambda_A - \lambda_B = d_{50} + d_{51} - d_{49} - d_{52}$. (4.3.13)

From (4.3.13), the design remains connected for the first two periods in all subjects, whence the design is said to be perpetually connected for carry-over effects.

4.3.7.2 Robustness for Missing Data in Treatment Effects for D_{22}

The contrasts d_{53}, d_{54}, d_{55} and d_{56} , identified from Table 4.3.10 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(d_{53}) = \frac{1}{2}E(-Y_{11} + Y_{12}) = \frac{1}{2}[\,(-\pi_1 + \pi_2) - \tau_B + \tau_A + \lambda_B]$$

$$E(d_{54}) = \frac{1}{2}E(Y_{21} - Y_{22}) = \frac{1}{2}[(\pi_1 - \pi_2) + \tau_A - \tau_B - \lambda_A]$$

$$E(d_{55}) = \frac{1}{2}E(Y_{31} + Y_{32}) = \frac{1}{2}[\,(\pi_1 + \pi_2) + \tau_A + \tau_B + \lambda_A]$$

$$E(d_{56}) = \frac{1}{2}E(-Y_{41} - Y_{42}) = \frac{1}{2}[(-\pi_1 - \pi_2) - \tau_B - \tau_A - \lambda_B]$$

A linear combination of $(d_{53} + d_{54} + d_{55} + d_{56})$ forms unbiased estimate of treatment effects,

Thus, $\tau_A - \tau_B = d_{53} + d_{54} + d_{55} + d_{56}$. (4.3.14)

From (4.3.14), the design remains connected for the first two periods in all subjects, whence the design is said to be perpetually connected for treatment effects.

4.3.8 Robustness for Missing Data for D_{23}

Table 4.3.10: Expected values for Design D_{23} with only two complete periods for all subjects

SEQ	p_1	p_2	p_3	p_4	p_5
ABABA	$\mu+\pi_1+\tau_A$	$\mu+\pi_2+\tau_B+\lambda_A$	*	*	*
BABAB	$\mu+\pi_1+\tau_B$	$\mu+\pi_2+\tau_A+\lambda_B$	*	*	*
ABAAB	$\mu+\pi_1+\tau_A$	$\mu+\pi_2+\tau_B+\lambda_A$	*	*	*
BABBA	$\mu+\pi_1+\tau_B$	$\mu+\pi_2+\tau_A+\lambda_B$	*	*	*

4.3.8.1 Robustness for Missing Data in Carry-over Effects for D_{23}

The contrasts d_{57}, d_{58}, d_{59} and d_{60} , identified from Table 4.3.10 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_{57}) = \frac{1}{2}E(Y_{11}+Y_{12}) = \frac{1}{2}[2\,\mu + (\pi_1+\pi_2) + \tau_A+\tau_B\ +\lambda_A]$$

$$E(d_{58}) = \frac{1}{2}E(Y_{21}+Y_{22}) = \frac{1}{2}[2\mu + (\pi_1+\pi_2) + \tau_B+\tau_A+\ \ \lambda_B]$$

$$E(d_{59}) = \frac{1}{2}E(Y_{31}+Y_{32}) = \frac{1}{2}[2\,\mu + (\pi_1+\pi_2) + \tau_A+\tau_B\ +\lambda_A]$$

$$E(d_{60}) = \frac{1}{2}E(Y_{41}+Y_{42}) = \frac{1}{2}[2\,\mu + (\pi_1+\pi_2)\ + \tau_B+\tau_A+\lambda_B]$$

A linear combination of $(d_{57} + d_{59} - d_{58} - d_{60})$. forms unbiased estimate of carry-over effects,

Thus, $\lambda_A - \lambda_B = d_{57} + d_{59} - \ d_{58} - d_{60}$. (4.3.15)

From (4.3.15), the design remains connected for the first two periods in all subjects, whence the design is said to be perpetually connected for carry-over effects.

4.3.8.2 Robustness for Missing Data in Treatment Effects for D_{23}

The contrasts d_{61}, d_{62}, d_{63} and d_{64} , identified from Table 4.3.11 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$E(d_{61}) = \frac{1}{2}E(-Y_{11} + Y_{12}) = \frac{1}{2}[\ (-\pi_1 + \pi_2) - \tau_A + \tau_B\ + \lambda_A]$

$E(d_{62}) = \frac{1}{2}E(Y_{21} - Y_{22}) = \frac{1}{2}[(\pi_1 - \pi_2) + \tau_B - \tau_A - \ \lambda_B]$

$E(d_{63}) = \frac{1}{2}E(-Y_{31} - Y_{32}) = \frac{1}{2}[\ (-\pi_1 - \pi_2) - \tau_A - \tau_B\ - \lambda_A]$

$E(d_{64}) = \frac{1}{2}E(Y_{41} + Y_{42}) = \frac{1}{2}[(\pi_1 + \pi_2)\ + \tau_B + \tau_A + \lambda_B]$

A linear combination of $(d_{64} + d_{63} - d_{62} - d_{61})$ forms unbiased estimate of treatment effects,

Thus, $\tau_A - \tau_B = d_{59} - d_{60} - \ d_{58} - d_{57}$. (4.3.16)

From (4.3.9), the design remains connected for the first two periods in all subjects, whence the design is said to be perpetually connected for Treatment effects.

4.3.9 Robustness for Missing Data for D_{24}

Table 4.3.11: Expected values for Design D_{24} with only two complete periods for all subjects

SEQ	p_1	p_2	p_3	p_4	p_5
AABBA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$*$	$*$	$*$
BBAAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$*$	$*$	$*$
AABAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$*$	$*$	$*$
BBABA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$*$	$*$	$*$

4.3.9.1 Robustness for Missing Data in Carry-over Effects for D_{24}

The contrasts d_{65}, d_{66}, d_{67} and d_{68} , identified from Table 4.3.11 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$E(d_{65}) = \frac{1}{2}E(-Y_{11} + Y_{12}) = \frac{1}{2}[2\ \mu + (-\pi_1 + \pi_2)\ \ \ + \lambda_A]$

$E(d_{66}) = \frac{1}{2}E(-Y_{21} + Y_{22}) = \frac{1}{2}[2\mu + (-\pi_1 + \pi_2) + \ \ \lambda_B]$

$E(d_{67}) = \frac{1}{2}E(-Y_{31} + Y_{32}) = \frac{1}{2}[2\ \mu + (-\pi_1 + \pi_2) + \lambda_A]$

$E(d_{68}) = \frac{1}{2}E(-Y_{41} + Y_{42}) = \frac{1}{2}[2\ \mu + (-\pi_1 + \pi_2) + \lambda_B]$

A linear combination of $(d_{65} + d_{67} - d_{66} - d_{68})$ forms unbiased estimate of carry-over effects,

Thus, $\lambda_A - \lambda_B = d_{65} + d_{67} - d_{66} - d_{68}$. (4.3.17)

From (4.3.17), the design remains connected for the first two periods in all subjects, whence the design is said to be perpetually connected for carry-over effects.

Table 4.3.12: Expected values of Design D_{24} with 10 Missing Observations.

SEQ	P1	P2	P3	P4	P5
AABBA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	*	*	*
BBAAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	*	*
AABAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	*	*
BBABA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	*	*	*

4.3.9.2 Robustness for Missing Data in Treatment Effects for D_{24}

The contrasts d_{69}, d_{70}, d_{71} and d_{72} , identified from Table 4.3.12 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$E(d_{69}) = E(Y_{11} - Y_{12}) = [\ (\pi_1 - \pi_2)\ \ -\lambda_A]$

$E(d_{70}) = E(-Y_{21} - Y_{22} + 2Y_{23}) = [3\mu + (-\pi_1 - \pi_2 + 2\pi_3) - 2\tau_B + 2\tau_A + \ \ \lambda_B]$

$E(d_{71}) = E(Y_{31} + Y_{32} - 2Y_{33}) = [3\mu + (\pi_1 + \pi_2 - 2\pi_3) + 2\tau_A - 2\tau_B - \lambda_A]$

$E(d_{72}) = E(Y_{41} - Y_{42}) = [(\pi_1 - \pi_2) - \lambda_B]$

A linear combination of $(d_{72} + d_{71} + d_{70} - d_{69})$. forms unbiased estimate of treatment effects,

Thus, $\tau_A - \tau_B = d_{72} + d_{71} + d_{70} - d_{69}$. (4.3.18)

From (4.3.18), the maximum number of subjects that can be lost and the design remains connected is 10, whence the break down number, DM=10.

4.3.10 Robustness for Missing Data for D_{25}

Table 4.3.13: Expected values for Design D_{25} with only two complete periods for all subjects

SEQ	p_1	p_2	p_3	p_4	p_5
AABAB	$\mu+\pi_1+\tau_A$	$\mu+\pi_2+\tau_A+\lambda_A$	*	*	*
BBABA	$\mu+\pi_1+\tau_B$	$\mu+\pi_2+\tau_B+\lambda_B$	*	*	*
AAABB	$\mu+\pi_1+\tau_A$	$\mu+\pi_2+\tau_A+\lambda_A$	*	*	*
BBBAA	$\mu+\pi_1+\tau_B$	$\mu+\pi_2+\tau_B+\lambda_B$	*	*	*

4.3.10.1 Robustness for Missing Data in Carry-over Effects for D_{25}

The contrasts d_{73}, d_{74}, d_{75} and d_{76} , identified from Table 4.3.13 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_{73}) = \frac{1}{2}E(-Y_{11}+Y_{12}) = \frac{1}{2}[2\,\mu + (-\pi_1+\pi_2) \quad +\lambda_A]$$

$$E(d_{74}) = \frac{1}{2}E(-Y_{21}+Y_{22}) = \frac{1}{2}[2\mu + (-\pi_1+\pi_2) + \quad \lambda_B]$$

$$E(d_{75}) = \frac{1}{2}E(-Y_{31}+Y_{32}) = \frac{1}{2}[2\,\mu + (-\pi_1+\pi_2) + \lambda_A]$$

$$E(d_{76}) = \frac{1}{2}E(-Y_{41}+Y_{42}) = \frac{1}{2}[2\,\mu + (-\pi_1+\pi_2) + \lambda_B]$$

A linear combination of $(d_{73} + d_{75} - d_{74} - d_{76})$ forms unbiased estimate of carry-over effects,

Thus, $\lambda_A - \lambda_B = d_{73} + d_{75} - d_{74} - d_{76}$. (4.3.19)

From (4.3.19), the design remains connected for the first two periods in all subjects, whence the design is said to be perpetually connected for carry-over effects.

4.3.10.2 Robustness for Missing Data in Treatment Effects for D_{25}

Table 4.3.14: Expected values for Design D_{25} with 10 observations missing

SEQ	p_1	p_1	p_1	p_1	p_1
AABAB	$\mu+\pi_1+\tau_A$	$\mu+\pi_2+\tau_A+\lambda_A$	$\mu+\pi_3+\tau_B+\lambda_A$	*	*
BBABA	$\mu+\pi_1+\tau_B$	$\mu+\pi_2+\tau_B+\lambda_B$	$\mu+\pi_3+\tau_A+\lambda_B$	*	*
AAABB	$\mu+\pi_1+\tau_A$	$\mu+\pi_2+\tau_A+\lambda_A$	*	*	*
BBBAA	$\mu+\pi_1+\tau_B$	$\mu+\pi_2+\tau_B+\lambda_B$	*	*	*

4.3.10.3 Robustness for Missing Data in Treatment Effects for D_{25}

The contrasts d_{77}, d_{78}, d_{79} and d_{80} , identified from Table 4.3.14 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$E(d_{77}) = \frac{1}{4}E(Y_{11} + Y_{12} - 2Y_{13}) = \frac{1}{4}[\ (\pi_1 + \pi_2 - 2\pi_3)\ + 2\tau_A - 2\tau_B\ \ - \lambda_A]$$

$$E(d_{78}) = \frac{1}{4}E(-Y_{21} - Y_{22} + 2Y_{23}) = \frac{1}{4}\ [(-\pi_1 - \pi_2 + 2\pi_3) - 2\tau_B + 2\tau_A - \ \lambda_B]$$

$$E(d_{79}) = \frac{1}{4}E(Y_{31} - Y_{32}) = \frac{1}{4}\ [\ (\pi_1 - \pi_2) - \lambda_A]$$

$$E(d_{80}) = \frac{1}{4}E(Y_{41} - Y_{42}) = \frac{1}{4}[(\pi_1 - \pi_2) - \lambda_B]\ .$$

A linear combination of $(d_{77} + d_{78} - d_{79} - d_{70})$ forms unbiased estimate of treatment effects,

Thus, $\tau_A - \tau_B = d_{77} + d_{78} - \ d_{79} - d_{80}$ (4.3.20)

From (4.3.20), the maximum number of observations that can be lost and the design remains connected is 10, whence the break down number DM=10.

4.3.11 Robustness for Missing Data for D_{26}

Table 4.3.15: Expected values for Design D_{26} with only two complete periods for all subjects

SEQ	P_1	P_2	P_3	P_4	P_5
AAABA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	*	*	*
BBBAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	*	*	*
AAAAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	*	*	*
BBBBA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	*	*	*

4.3.11.1 Robustness for Missing Data in in carry-over Effects for D_{26}

The contrasts d_{81}, d_{82}, d_{83} and d_{84} , identified from Table 4.3.15 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$$E(d_{81}) = \frac{1}{2}E(Y_{11} - Y_{12}) = \frac{1}{2}[\ (\pi_1 - \pi_2)\ -\lambda_A\ ]$$

$$E(d_{82}) = \frac{1}{2}E(Y_{21} - Y_{22}) = \frac{1}{2}[\ (\pi_1 - \pi_2)\ -\lambda_B\ ]$$

$$E(d_{83}) = \frac{1}{2}E(Y_{31} - Y_{32}) = \frac{1}{2}[\ (\pi_1 - \pi_2) - \lambda_A\ ]$$

$$E(d_{84}) = \frac{1}{2}E(Y_{41} - Y_{42}) = \frac{1}{2}[\ (\pi_1 - \pi_2) - \lambda_B\ ]$$

A linear combination of $(d_{82} + d_{84} - d_{81} - d_{83})$ forms unbiased estimate of carry-over effects,

Thus, $\lambda_A - \lambda_B = (d_{82} + d_{84} - d_{81} - d_{83})$ (4.3.21)

From (4.3.21), the design remains connected for the first two periods in all subjects, whence the design is said to be perpetually connected for carry-over effects.

Table 4.3.16: Design D_{26} with 8 Missing Observations.

SEQ	P_1	P_2	P_3	P_4	P_5
AAABA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_A$	*
BBBAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$	*
AAAAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	*	*	*
BBBBA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	*	*	*

4.3.11.2 Robustness for Missing Data in Treatment Effects for D_{26}

The contrasts d_{85}, d_{86}, d_{87} and d_{88} , identified from Table 4.3.16 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$$d_{85} = \frac{1}{4}(Y_{11} + Y_{12} + Y_{13} - Y_{14}) = \frac{1}{4}[\ 2\mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4)\ + 3\tau_A - \tau_B + \lambda_A\ ]$$

$$d_{86} = \frac{1}{4}(Y_{21} + Y_{22} + Y_{23} - Y_{24}) = \frac{1}{4}[\ 2\mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4)\ + 3\tau_B - \tau_A + \lambda_B\ ]$$

$$d_{87} = \frac{1}{4}(Y_{31} - Y_{32}) = \frac{1}{4}[\ (\pi_1 - \pi_2) - \lambda_A\ ]$$

$d_{88} = \frac{1}{4}(Y_{41} - Y_{42}) = \frac{1}{4}[\,(\pi_1 - \pi_2) - \lambda_B\,]$

A linear combination of $(d_{85} - d_{86}) + (d_{87} - d_{88})$ forms unbiased estimate of treatment effects,

Thus, $\tau_A - \tau_B = (d_{85} - d_{86}) + (d_{87} - d_{88})$ (4.3.22)

From (4.3.22), the maximum number of subjects that can be lost and the design remains connected is 8, whence the break down number DM=8.

4.3.12 Robustness for Missing Data for $\mathbf{D_{27}}$

Table 4.3.17: Expected values for Design D_{27} with only two complete periods for all subjects

SEQ	P_1	P_2	P_3	P_4	P_5
AAAAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	*	*	*
BBBBA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	*	*	*
AAAAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	*	*	*
BBBBA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	*	*	*

4.3.12.1 Robustness for Missing Data in in carry-over Effects for D_{27}

The contrasts d_{89}, d_{90}, d_{91} and d_{92} , identified from Table 4.3.17 in such a way that (3.1.7), and (3.1.9) are satisfied are given by;

$E(d_{89}) = \frac{1}{2}E(Y_{11} - Y_{12}) = \frac{1}{2}[\,(\pi_1 - \pi_2) - \lambda_A\,]$

$E(d_{90}) = \frac{1}{2}E(Y_{21} - Y_{22}) = \frac{1}{2}[\,(\pi_1 - \pi_2) - \lambda_B\,]$

$E(d_{91}) = \frac{1}{2}E(Y_{31} - Y_{32}) = \frac{1}{2}[\,(\pi_1 - \pi_2) - \lambda_A\,]$

$E(d_{92}) = \frac{1}{2}E(Y_{41} - Y_{42}) = \frac{1}{2}[\,(\pi_1 - \pi_2) - \lambda_B\,]$

A linear combination of $(d_{92} + d_{90} - d_{89} - d_{91})$ forms unbiased estimate of treatment effects,

Thus, $\lambda_A - \lambda_B = (d_{92} + d_{90} - d_{89} - d_{91})$ (4.3.23)

From (4.3.23), the design remains connected for the first two periods in all subjects, whence the design is said to be perpetually connected for carry-over effects.

Table 4.3.18: Expected values for Design D_{27} with 6 observations missing

SEQ	P_1	P_2	P_3	P_4	P_5
AAAAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_A$
BBBBA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$
AAAAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$	*	*	*
BBBBA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$	*	*	*

4.3.12.2 Robustness for Missing Data in Treatment Effects for D_{27}

The contrasts; d_{93}, d_{94}, d_{95} and d_{96} , identified from Table 4.3.18 in such a way that (3.1.6), and (3.1.8) are satisfied are given by;

$E(d_{93}) = \frac{1}{3}E(Y_{11} + Y_{12} + Y_{13} + Y_{14} + Y_{15}) = \frac{1}{3}[\quad 5\mu + (\pi_1 + \pi_2 + \pi_3 + \pi_4 + \pi_5) + 4\tau_A + \tau_B + 4\lambda_A]$

$E(d_{94}) = \frac{1}{3}E(Y_{21} + Y_{22} + Y_{23} + Y_{24} + Y_{25}) = \frac{1}{3}[\quad 5\mu + (\pi_1 + \pi_2 + \pi_3 + \pi_4 + \pi_5) + 4\tau_B + \tau_A + 4\lambda_B\ ]$

$E(d_{95}) = \frac{4}{3}E(Y_{31} - Y_{32}) = \frac{4}{3}[\ (\pi_1 - \pi_2) - \lambda_A\ ]$

$E(d_{96}) = \frac{4}{3}E(Y_{41} - Y_{42}) = \frac{4}{3}[\ (\pi_1 - \pi_2) - \lambda_{\mathrm{B}}\ ]$

A linear combination of $(d_{93} - d_{94}) + (d_{95} - d_{96})$ forms unbiased estimate of treatment effects,

Thus, $\tau_A - \tau_B = (d_{93} - d_{94}) + (d_{95} - d_{96})]$ (4.3.24)

From (4.3.24), the maximum number of subjects that can be lost and the design remains connected is 6, whence the break down number DM=6.

Table 4.3.19: Summary for Robustness against Missing Data for the Four Sequence C ($2\times 5\times 2$) Cross-Over Designs.

Design	Carry-over estimates variance in $\frac{\sigma^2}{n}$	Treatments estimates variance in $\frac{\sigma^2}{n}$	Break down numbers for carry-over effects	Breakdown numbers for treatment effects
D_{16}	1.25	5	∞	∞
D_{17}	1.25	5	∞	∞
D_{18}	1.25	5	∞	∞
D_{19}	1.25	5	∞	10
D_{20}	1.25	5	∞	10
D_{21}	6.5	0.7	∞	∞
D_{22}	0.9	5	∞	∞
D_{23}	4.4	5	∞	∞
D_{24}	1.5	5	∞	10
D_{25}	0.9	2.7	∞	10
D_{26}	1.25	154	∞	8
D_{27}	25	9.6	∞	6

4.3.13 Discussion

From table (4.2.1), it is evident that all the C ($2\times 5\times 2$) designs were perpetually connected in estimating carry-over effects. In this case, the variances of the carry-over effects were used to measure Robustness for missing data where the design with the minimum variance was highly recommended. In this regard, D_{22} and D_{25} were the most Robust, followed by $D_{16}, D_{17}, D_{18}, D_{19}$, and$D_{20}$ respectively which were equally robust. Designs; D_{24} , D_{21},and D_{27} respectively were the least desirable in this category due to their relatively higher variances for estimating carry-over effects.

In treatment effects estimation; $D_{16}, D_{17}, D_{18}, D_{21}, D_{22}$ and D_{23} were perpetually robust against missing data while $D_{19}, D_{20}, D_{24}, D_{25}, D_{26}$ and D_{27} , had breakdown

numbers of; 10, 10, 10, 10, 6, and 8 respectively. For the perpetually connected designs, D_{21} with variance of $0.7\frac{\sigma^2}{n}$ was the most robust in that category and was highly recommended for use in estimating treatment effects. However, it is interesting to note that D_{21} which was the most robust for missing data in estimating treatment effects was relatively lowly ranked in robustness for missing data in estimating carry-over effects.

It is also important to note that both D_{26} and D_{27} have the lowest breakdown numbers and both of them have relatively higher variances for treatment and carry-over effects. Hence the two designs are not desirable in cross-over experiments and are not recommended for use.

4.4 Data Analysis Based On the Bayesian Method

Table 4.4.1: Hypothetical experimental data for two treatments (A, B).

Sequence	Period	Treatment	1	2	3	4	5	6	7	8	Mean(μ_i)	σ^2
1	1	B	2.4	7.1	8.0	2.3	2.9	6.4	7.0	2.9	4.8750	
1	2	A	4.1	7.6	9.7	1.8	2.7	5.6	5.5	2.4	4.9250	
1	3	B	1.9	0.5	0.6	8.7	15.7	5.3	3.7	9.8	5.7750	
1	4	A	6.4	0.5	2.8	3.8	9.5	5.4	4.6	5.8	4.8500	
1	5	A	0.1	5.2	6.2	4.4	2.4	7.5	2.1	4.2	4.0125	10.1057
2	1	A	1.0	3.0	6.9	7.0	5.9	5.1	4.9	2.4	4.5250	
2	2	B	1.6	0.8	1.5	7.8	13.1	2.4	2.2	8.6	4.7500	
2	3	A	1.5	0.7	1.5	7.8	13.2	2.5	2.2	8.7	4.7625	
2	4	B	2.9	3.3	2.0	7.5	8.2	2.5	5.1	9.4	5.1125	
2	5	B	1.4	3.4	0.6	0.7	0.2	3.4	3.0	0.9	1.7000	11.6447
3	1	B	0.5	2.1	1.1	0.5	0.6	1.9	4.2	0.9	1.4750	
3	2	A	3.7	1.2	2.1	4.1	3.6	3.9	2.8	7.5	3.6125	
3	3	A	7.2	3.7	4.8	6.8	6.3	5.8	3.9	13.4	6.4875	
3	4	B	2.3	5.1	7.2	2.7	5.3	6.7	3.6	1.2	4.2625	
3	5	A	5.7	6.6	8.1	5.2	6.7	8.4	7.4	1.9	6.2500	7.6876
4	1	A	3.6	4.3	6.0	12.3	10.7	2.7	5.9	3.8	6.1625	
4	2	B	13.3	3.6	2.64	8.6	9.2	1.5	4.7	3.8	5.9125	
4	3	B	2.0	4.5	3.8	1.8	1.3	1.5	3.6	1.5	2.5000	
4	4	A	2.0	5.3	5.4	1.3	2.2	2.5	5.3	2.2	3.2750	
4	5	B	4.7	1.4	2.9	2.0	3.2	2.4	1.5	3.4	2.6875	8.7971

In this section, data from a hypothetical example was used for data analysis. The Bayesian analysis method was used and for validation purpose, the t-test was used.

Table 4.4.2: Expected values for design D_{21}

Sequence	p_1	p_2	p_3	p_4	p_5
BABAA	$E(Y_{11})$ =4.875	$E(Y_{12})$ =4.925	$E(Y_{13})$ =5.775	$E(Y_{14})$ =4.850	$E(Y_{15})$ =4.0125
ABABB	$E(Y_{21})$ =4.525	$E(Y_{22})$ =4.750	$E(Y_{23})$ =4.763	$E(Y_{24})$ =5.113	$E(Y_{25})$ =1.700
BAABA	$E(Y_{31})$ =1.475	$E(Y_{32})$ =3.613	$E(Y_{33})$ =6.488	$E(Y_{34})$ =4.263	$E(Y_{35})$ =6.250
ABBAB	$E(Y_{41})$ =6.163	$E(Y_{42})$ =5.913	$E(Y_{43})$ =2.500	$E(Y_{44})$ =3.275	$E(Y_{45})$ =2.688

The variances of the four groups from Table (4.4.1) are given by;

Substituting the variances s_{11}^2= 10.1057 s_{21}^2= 11.6447 s_{31}^2= 7.6876 s_{41}^2= 8.7971in table (4.4.1) to (3.4.1) and (3.4.2) gives,

s_1^2= 10.8752 (4.3.1.1)

And

s_2^2= 8.24235 (4.3.1.2)

4.4.1 Bayesian Method for Treatment Effects test for Design D_{21}

The hypothesis to be tested is;

H_O: $[\tau_A - \tau_B]_W = 0$

H_1: $[\tau_A - \tau_B]_W \neq 0$

Substituting (4.3.1.1) and (4.3.1.2) on (3.4.5) and (3.4.6) using the contrasts given in 4.1.72 gives,

$V(\tau_A - \tau_B)_1 = \frac{s_1^2}{k^2}\left[\frac{1}{n_{11}} + \frac{1}{n_{21}}\right]$ = 0.033985 (4.3.1.3)

$V(\tau_A - \tau_B)_2 = \frac{s_2^2}{m^2}\left[\frac{1}{n_{31}} + \frac{1}{n_{41}}\right]$ = 0.00286 (4.3.1.4)

From (4.1.72),

$$[\tau_A - \tau_B]_1 = \frac{1}{2}(d_{37} - d_{38}) \quad (4.3.1.5)$$

$$[\tau_A - \tau_B]_2 = \frac{1}{12}(d_{39} - d_{40}) \quad (4.3.1.6)$$

Substituting the values of Table 4.1.43 on the contrasts given in (4.1.36) gives

d_{37}=8.8125 & d_{38}=1.55 (4.3.1.7)

$d_{39} = 6.337$ d_{37}=2.163 (4.3.1.8)

Substituting (4.3.1.7) & (4.3.1.8) on (4.3.1.5) and (4.3.1.6) respectively gives,

$(\tau_A - \tau_B)_1$= 3.63125 (4.3.1.9)

$(\tau_A - \tau_B)_2$= 0.34783 (4.3.1.10)

Substituting (4.3.1.3) and (4.3.1.4) on (3.4.7) and (3.4.8) gives,

$W_1 = 29.42474621$ (4.3.1.11)

$W_2 = 349.6503497$ (4.3.1.12)

Substituting (4.3.1.9), (4.3.1.10), (4.3.1.11), & (4.3.1.12) on (3.4.9) and (3.4.10) respectively gives,

$(\tau_A - \tau_B)_w$= 0.602697235 (4.3.1.13)

$V(\tau_A - \tau_B)_w$= 0.002637999729 (4.3.1.14)

Substituting (4.3.1.3) and (4.3.1.4) on (3.4.17) gives

$cos_\theta^2 = 0.922377527$ (4.3.1.15)

Substituting (4.3.15) on (3.4.18) gives

$sin_{\theta}^{2} = 0.077622472$ (4.3.1.16)

Substituting (4.3.1.15) and (4.3.1.16) on (3.4.1.15) gives,

$f_1 = 1.0128205$ (4.3.1.17)

Substituting (4.3.1.15) and (4.3.1.16) on (3.4.1.16) gives,

$f_2 = 0.01156468$ (4.3.1.18)

Substituting (4.3.1.17) and (4.3.1.18) on (3.4.1.14) gives,

$b = 92.701$ (4.3.1.19)

Substituting (4.3.1.17) and (4.3.1.19) to (3.4.13) gives

a=0.995474339 (4.3.1.20)

Substituting (4.3.1.3), (4.3.1.4), (4.3.1.13), (4.3.1.19) & (4.3.1.20) on (3.4.20) gives the interval

(0.5607, 0.6453) (4.3.1.21)

The interval in (4.3.1.21) is represented in HPD graph as,

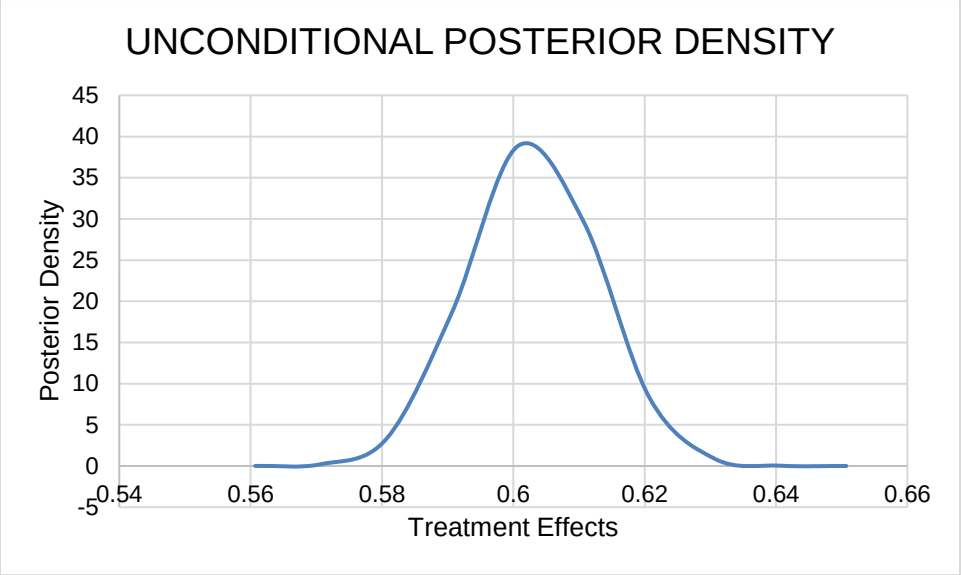

Figure 4.1: HPD for treatment effects when carry-over effects are absent

Discussion: The null hypothesis of no significant difference in the treatment effects was tested. From Figure 4.1, the $p((\tau_A - \tau_B)/y) > 0 = 1$. This implies that the treatment effects were significant, thus, the null hypothesis was rejected and the alternative hypothesis upheld.

4.4.2 Bayesian Method for Carry-over Effects test for Design D_{21}

The hypothesis to be tested is;

H_O: $[\lambda_A - \lambda_B]_W = 0$

H_1: $[\lambda_A - \lambda_B]_W \neq 0$

Substituting (4.3.1.1) and (4.3.1.2) on (3.4.5) and (3.4.6) using the contrasts given in (4.1.74) gives,

$$V(\lambda_A - \lambda_B)_1 = \frac{s_1^2}{k^2}\left[\frac{1}{n_{11}} + \frac{1}{n_{21}}\right] = 0.13594 \quad (4.3.2.3)$$

$$V(\lambda_A - \lambda_B)_2 = \frac{s_2^2}{m^2}\left[\frac{1}{n_{31}} + \frac{1}{n_{41}}\right] = 0.103029375 \quad (4.3.2.4)$$

From (4.1.74),

$$[\lambda_A - \lambda_B]_1 = \frac{1}{2}(d_{41} - d_{42}) \quad (4.3.2.5)$$

$[\lambda_A - \lambda_B]_2 = \frac{1}{2}(d_{43} - d_{44})$ (4.3.2.6)

Substituting the values of table 4.1.43 on the contrasts given in (4.1.37) gives

$d_{41} = -0.94375$ & $d_{38} = -1.4625$ (4.3.2.7)

$d_{39} = 0.528083$ $d_{37} = 0.18025$ (4.3.2.8)

Substituting (4.3.2.7) & (4.3.2.8) on (4.3.2.5) and (4.3.2.6) respectively gives,

$[\lambda_A - \lambda_B]_1 = 0.259375$ (4.3.2.9)

$[\lambda_A - \lambda_B]_2 = 0.17392$ (4.3.2.10)

Substituting (4.3.2.3) and (4.3.2.4) on (3.4.7) and (3.4.8) gives,

$W_1 = 7.356186553$ (4.3.2.11)

$W_2 = 9.705969778$ (4.3.2.12)

Substituting (4.3.2.9), (4.3.2.10), (4.3.2.11), & (4.3.2.12) on (3.4.9) and (3.4.10) respectively gives,

$(\lambda_A - \lambda_B)_w = 0.098936044$ (4.3.2.13)

$V(\lambda_A - \lambda_B)_w = 0.03334042$ (4.3.2.14)

Substituting (4.3.2.3) and (4.3.2.4) on (3.4.17) gives

$cos_\theta^2 = 0.431140496$ (4.3.2.15)

Substituting (4.3.2.15) on (3.4.18) gives,

$sin_\theta^2 = 0.568859504$ (4.3.2.16)

Substituting (4.3.2.15) and (4.3.2.16) on (3.4.15) gives,

$f_1 = 1.0128205$ (4.3.2.17)

Substituting (4.3.2.15) and (4.3.2.16) on (3.4.2.16) gives,

f_2= 0.00725204 (4.3.2.18)

Substituting (4.3.2.17) and (4.3.2.18) on (3.4.14) gives,

$b = 145.450$ (4.3.2.19)

Substituting (4.3.2.17) and (4.3.2.19) on (3.4.13) gives

a=0.99945 (4.3.2.20)

Substituting (4.3.2.3), (4.3.2.4), (4.3.2.13), (4.3.2.19) & (4.3.2.20) on (3.4.20) gives the interval,

(-0.008, 0.21) (4.3.2.21)

The interval in (4.3.2.21) is represented in HPD graph as,

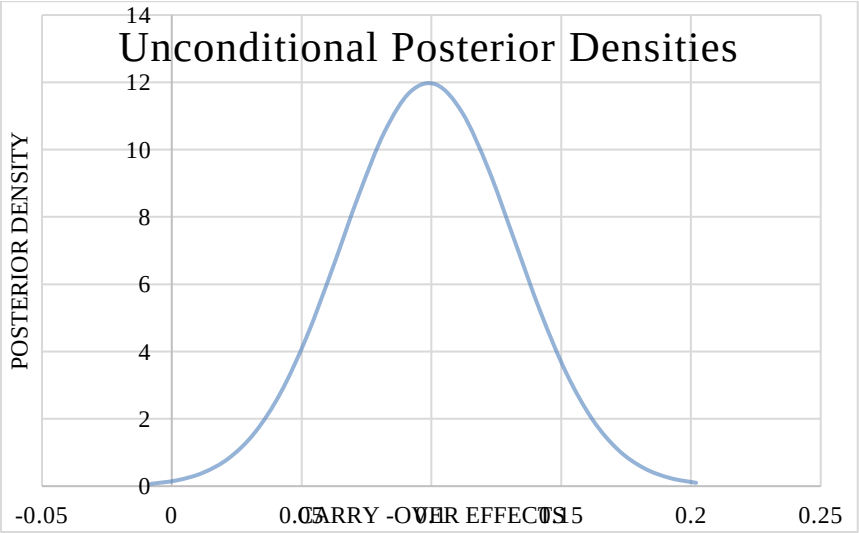

Figure 4.2: HPD for carry-over effects

Discussion: The null hypothesis of no significant difference in the carry-over effects was tested. From Figure 4.2, the range of the carry-over effects included a zero value. This implies that there was a likelihood for absence of carry-over effects. However, p $((\lambda_A - \lambda_B)/y) > 0 = 0.9633$ implied that the carry-over effects

difference was significant, thus, the null hypothesis was rejected. This implies that the carryover effects were present.

4.4.3 Bayesian Method for treatment effects given Carry-over Effects test for Design D_{21}

The hypothesis to be tested was;

H_O: $(\tau_A - \tau_B)_W/(\lambda_A - \lambda_B)_W = 0$

H_1: $(\tau_A - \tau_B)_W/(\lambda_A - \lambda_B)_W \neq 0$

Substituting (4.3.1) and (4.3.2) on (3.4.5) and (3.4.6) using the sum of the contrasts given in (4.1.72) and (4.1.74) gives,

$$V((\tau_A - \tau_B)/(\lambda_A - \lambda_B))_1 = \frac{s_1^2}{k^2}\left[\frac{1}{n_{11}} + \frac{1}{n_{21}}\right] = 0.0169625 \quad (4.3.3.3)$$

$$V((\tau_A - \tau_B)/(\lambda_A - \lambda_B))_2 = \frac{s_2^2}{m^2}\left[\frac{1}{n_{31}} + \frac{1}{n_{41}}\right] = 0.00143096 \quad (4.3.3.4)$$

From (4.1.74),

$$(\tau_A - \tau_B)/(\lambda_A - \lambda_B)_1 = \frac{1}{2}(d_{37} - d_{38}) + \frac{1}{2}(d_{41} - d_{42}) \quad (4.3.3.5)$$

$$(\tau_A - \tau_B)/(\lambda_A - \lambda_B)_2 = \frac{1}{12}(d_{39} - d_{40}) + \frac{1}{2}(d_{43} - d_{44}) \quad (4.3.3.6)$$

Substituting the values of table 4.1.43 on the contrasts given in (4.1.36) and (4.1.37) gives

$$d_{41} = -0.94375 \ \& \ d_{38} = -1.4625 \quad (4.3.3.7)$$

$$d_{39} = 0.528083 \ d_{37} = 0.18025 \quad (4.3.3.8)$$

Substituting (4.3.3.7) & (4.3.3.8) on (4.3.3.5) and (4.3.3.6) respectively gives,

$(\tau_A - \tau_B)/(\lambda_A - \lambda_B)_1$= -1.190625 (4.3.3.9)

$(\tau_A - \tau_B)/(\lambda_A - \lambda_B)_2$= 12.99500 (4.3.3.10)

Substituting (4.3.3.3) and (4.3.3.4) on (3.4.7) and (3.4.8) gives,

$W_1 = 58.95357406$ (4.3.3.11)

$W_2 = 698.8315536$ (4.3.3.12)

Substituting (4.3.3.9), (4.3.3.10), (4.3.3.11), & (4.3.3.12) on (3.4.9) and (3.4.10) respectively gives,

$((\tau_A - \tau_B)/(\lambda_A - \lambda_B))_w$=11.89139785 (4.3.3.13)

$V((\tau_A - \tau_B)/(\lambda_A - \lambda_B))_w$= 0.001319635294 (4.3.3.14)

Substituting (4.3.3.3) and (4.3.3.4) on (3.4.17) gives

$cos^2_\theta = 0.077797$ (4.3.3.15)

Substituting (4.3.3.15) on (3.4.18) gives

$sin^2_\theta = 0.922203$ (4.3.3.16)

Substituting (4.3.3.15) and (4.3.3.16) on (3.4.3.15) gives,

f_1= 1.026315789 (4.3.3.17)

Substituting (4.3.3.15) and (4.3.3.16) on (3.4.3.16) gives,

f_2= 0.012191667 (4.3.3.18)

Substituting (4.3.3.17) and (4.3.3.18) on (3.4.3.14) gives,

$b = 90.4$ (4.3.3.19)

Substituting (4.3.3.17) and (4.3.3.19) on (3.4.13) gives

a=1.00180321 (4.3.3.20)

Substituting (4.3.3.3), (4.3.3.4), (4.3.3.13), (4.3.3.19) & (4.3.3.20) on (3.4.20) gives the interval,

(11.86, 11.92) (4.3.3.21)

The interval in (4.3.3.21) is represented in HPD graph as,

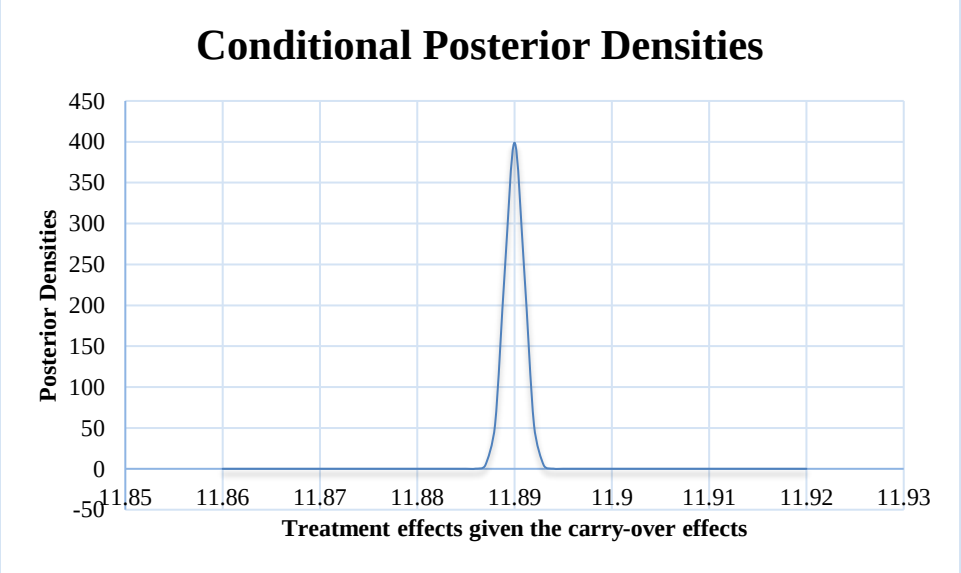

Figure 4.3: HPD for Treatment effects in the presence of Carry-over effects.

Discussion: The null hypothesis of no significant difference in the treatment effects given carry-over effects was tested. From Figure 4.3, $p((\tau_A - \tau_B)/y) > 0 = 1$. This implies that the treatment effects were significant, thus, the null hypothesis was rejected.

4.4.4 *t*-test for treatment effects

The hypothesis to be tested was,

H_O: $[\tau_A - \tau_B]_W = 0$

H_1: $[\tau_A - \tau_B]_W \neq 0$

Substituting (4.3.1.13) and (4.3.1.14) on (3.4.5.1) gives

t_{C_1} = 11.73442533 (4.4.4.1)

4.4.4.1 Degrees of Freedom for treatment effects

Let,

$a_1 = \frac{W_1}{W_1+W_2}$ (4.4.4.2)

$a_2 = \frac{W_2}{W_1+W_2}$ (4.4.4.3)

Substituting (4.3.1.11) and (4.3.1.12) on (4.4.4.2) and (4.4.4.3) respectively gives

a_1 =0.077622472 (4.4.4.4)

And

$a_2 = 0.922377527$ (4.4.4.5)

Substituting (4.4.4.4), (4.4.4.5), (4.3.1.3), and (4.3.1.4) on (3.4.5.8) with $f_1 = f_2 = 78$ degrees of freedom gives.

Then $f_w = 156$ (4.4.4.6)

Discussion: The null hypothesis of no significant difference in treatment effects was tested, comparison of the tabulated value at 156 degrees of freedom in (4.4.4.6) with the calculated value from (4.4.4.1), the calculated value is greater than the tabulated value at 95% level of significance, hence the null hypothesis is rejected.

4.4.5 t-test for carry-over effects

The hypothesis to be tested was,

H_O: $(\lambda_A - \lambda_B)_W = 0$

H_1: $(\lambda_A - \lambda_B)_W \neq 0$

Substituting (4.3.2.13) and (4.3.2.14) on (3.4.5.2) gives

$t_{C_2} = 0.541837436$ (4.4.5.1)

4.4.5.1 Degrees of Freedom for carry-over effects

Let,

$a_1 = \frac{W_1}{W_1+W_2}$ (4.4.5.2)

$a_2 = \frac{W_2}{W_1+W_2}$ (4.4.5.3)

Substituting (4.3.2.11) and (4.3.2.12) on (4.4.5.2) and (4.4.5.3) respectively gives

$a_1 = 0.431140496$ (4.4.5.4)

And

$a_2 = 0.568859503$ (4.4.5.5)

Substituting (4.4.5.4), (4.4.5.5), (4.3.2.3), and (4.3.2.4) on (3.4.5.8) with $f_1 = f_2 = 78$ degrees of freedom gives

Then $f_w = 155.4$ (4.4.5.6)

Discussion: By comparing the tabulated value at 155.4 degrees of freedom in (4.4.5.6) with the calculated value from (4.4.5.1), the calculated value is less than the tabulated value at 95% confidence level hence the null hypothesis is not rejected.4.4.6

4.4.6 Discussion

In this section, the Bayesian method was used to test the null hypothesis of; H_0: $\tau_A - \tau_B = 0,\ \lambda_A - \lambda_B = 0$, and ($\tau_A - \tau_B / \lambda_A - \lambda_B$) = 0. The t −test was used to validate the Bayesian method. The results indicate that the two methods gave similar conclusions.

4.4.7 Plotting Graphs

4.4.7.1 Subject Profiles Plots

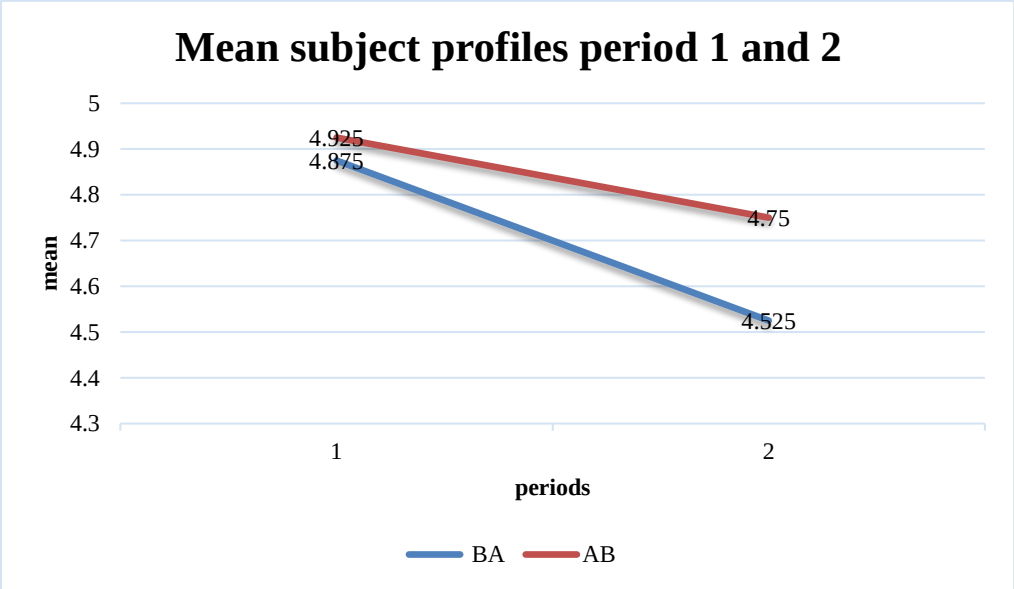

Figure 4.4: Mean subject profiles for periods 1 and 2 of the first two sequences

Discussion: From Figure 4.4 above, in the first group of sequence BA indicates that treatment B is more effective compared to treatment A whereas in the second group of sequence AB indicates that treatment A is more effective compared to treatment B. Since each group favors a different treatment, periods 2 and 3 do not give conclusive results.

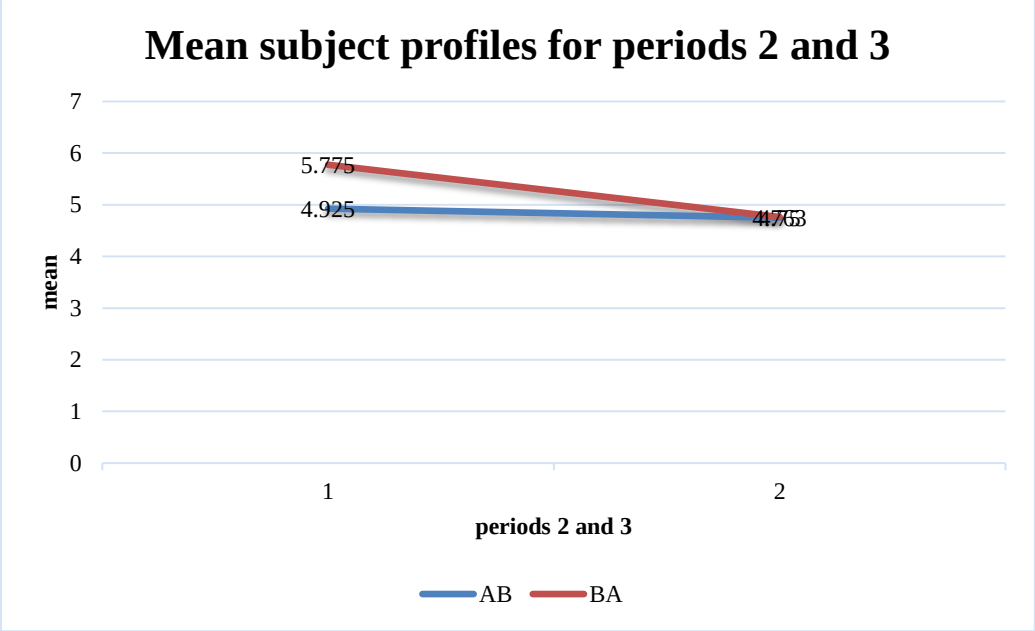

Figure 4.5: Mean subject profiles for periods 2 and 3 of the first two sequences

Discussion: From Figure 4.5 above, in the first group of sequence AB indicates that treatment A and B are almost equally effective whereas in the second group of sequence BA indicates that treatment B is more effective compared to treatment A. from this figure, it can be concluded that treatment B is more effective than treatment A in the first two sequences of period 2 and 3.

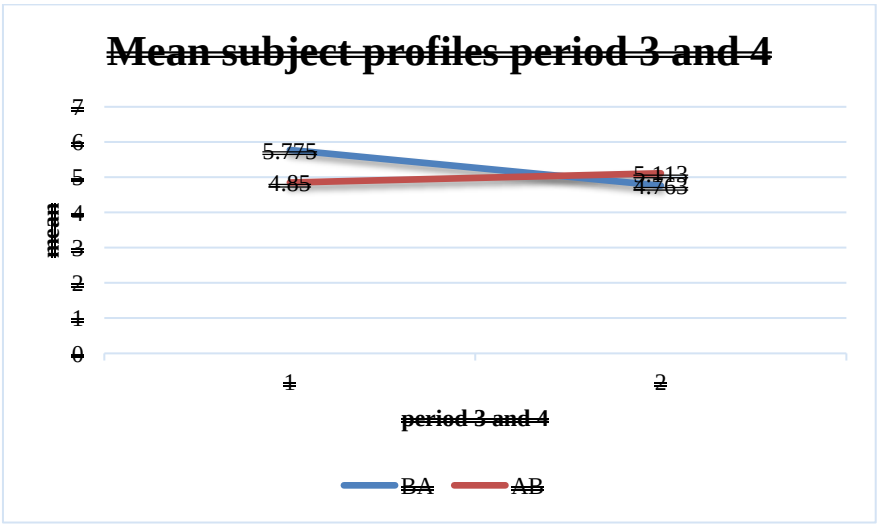

Figure 4.6: Mean subject profiles for periods 3 and 4 of the first two sequences

Discussion: From Figure 4.6 above, the first group of sequence BA indicates that treatment B is more effective than treatment A whereas the second group of sequence AB indicates that treatment B is more effective compared to treatment A. from this figure, it can be concluded that treatment B is more effective than treatment A in the first two sequences of period 3 and 4 since treatment B is favored in both groups.

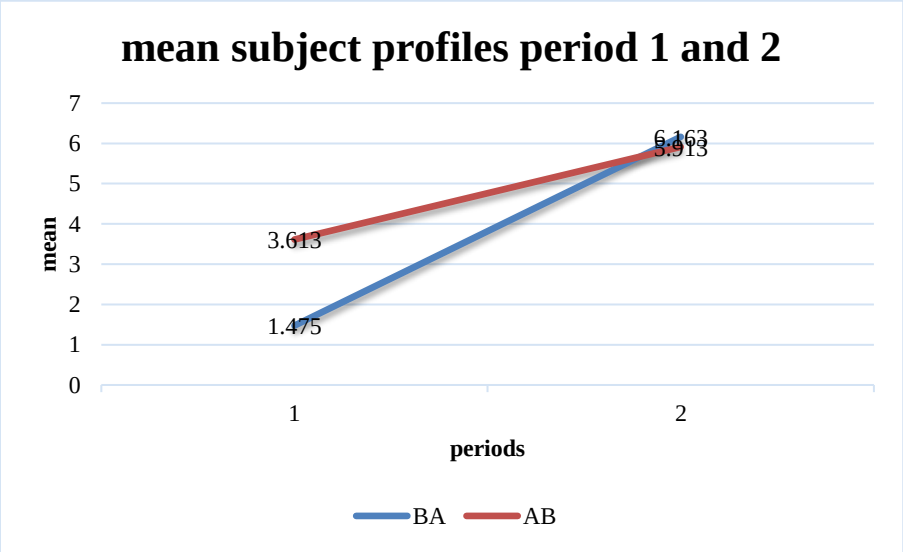

Figure 4.7: Mean subject profiles for periods 1 and 2 of the last two sequences

Discussion*:* From figure 4.7 above, in the first group of sequence BA indicates that treatment A is more effective compared to treatment B whereas in the second group of sequence AB indicates that treatment B is more effective compared to treatment A. Since each group favors a different treatment, periods 1 and 2 of the last two sequences do not give conclusive results.

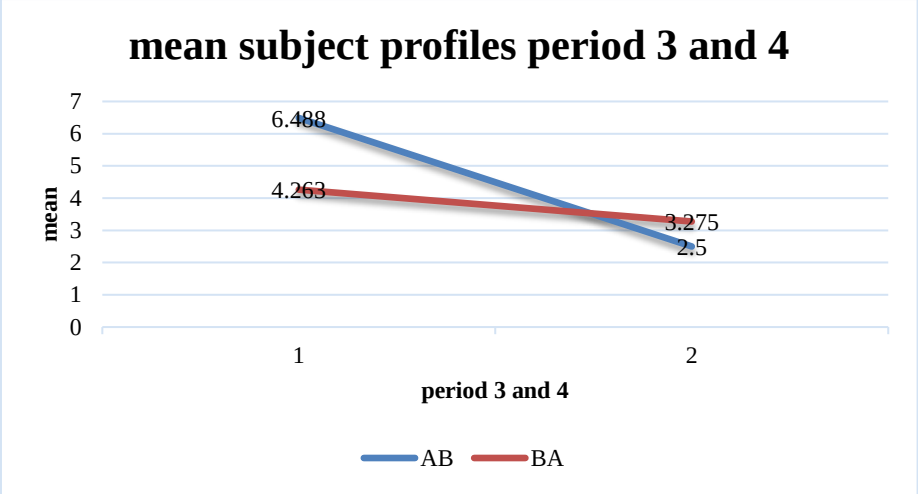

Figure 4.8: Mean subject profiles for periods 3 and 4 of the last two sequences

Discussion: From Figure 4.8 above, the first group of sequence AB indicates that treatment A is more effective compared to treatment B whereas in the second group of sequence BA indicates that treatment B is more effective compared to treatment A. Since each group favors a different treatment, periods 3 and 4 of the last two sequences do not give conclusive results.

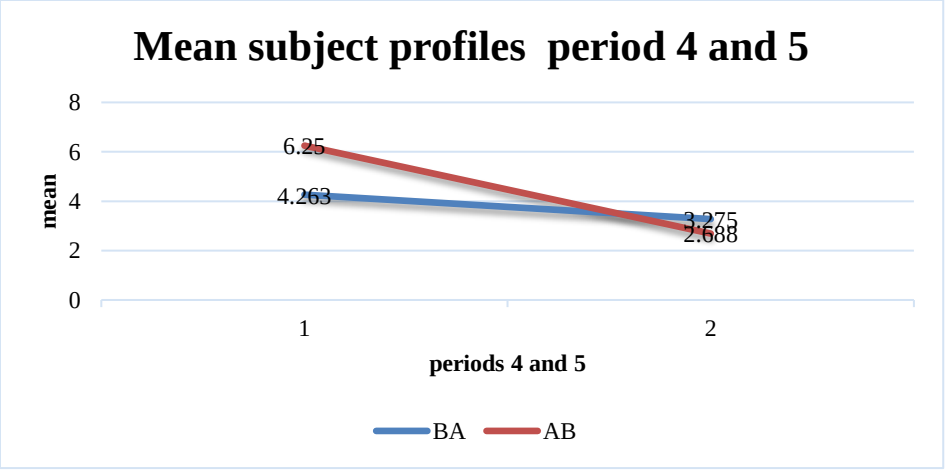

Figure 4.9: Mean subject profiles for periods 4 and 5 of the last two sequences

Discussion: From Figure 4.9 above, the first group of sequence BA indicates that treatment B is more effective compared to treatment A whereas in the second group of sequence AB indicates that treatment A is more effective compared to treatment B.

Since each group favors a different treatment, periods 4 and 5 of the last two sequences do not give conclusive results.

4.4.7.1.1 Discussion

High between individual variability is evident as are the low mean values of some individuals in group 3. However, from figures 4.4, 4.5, 4.6, 4.7, 4.8, and 4.9 the general trend implies a direct treatment effect in favor of treatment B.

4.4.7.2 Group by periods plots

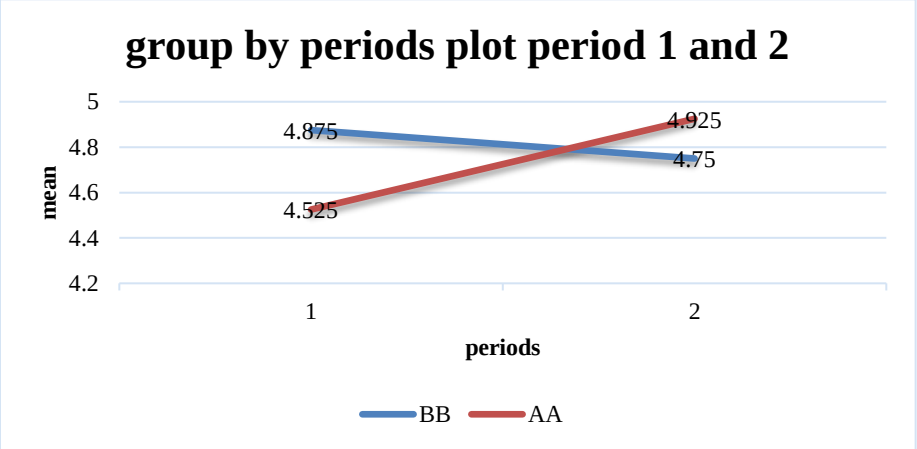

Figure 4.10: Group by periods plot for periods 1 and 2 of the first two sequences

Discussion: From Figure 4.10, it is evident that the BB and AA intersects. This implies that there are interaction effects.

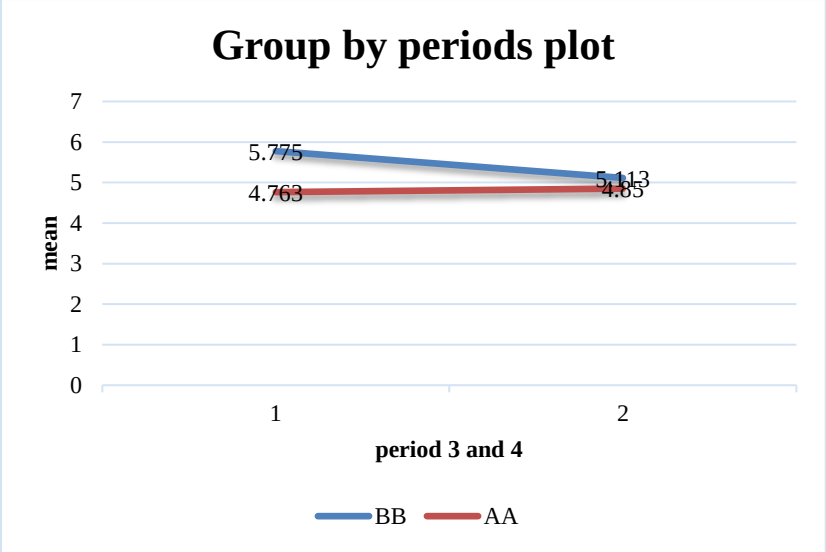

Figure 4.11: Group by periods plot for periods 3 and 4 of the first two sequences

Discussion*:* From Figure 4.11, it is evident that the BB and AA do not intersect. This implies that there are no interaction effects.

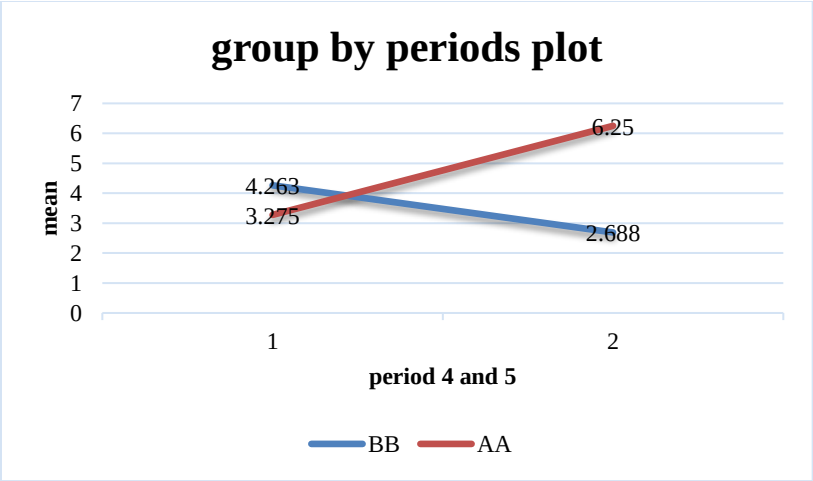

Figure 4.12: Group by periods plot for periods 4 and 5 of the first two sequences

Discussion: From Figure 4.12, it is evident that the BB and AA intersects. This implies that there are interaction effects.

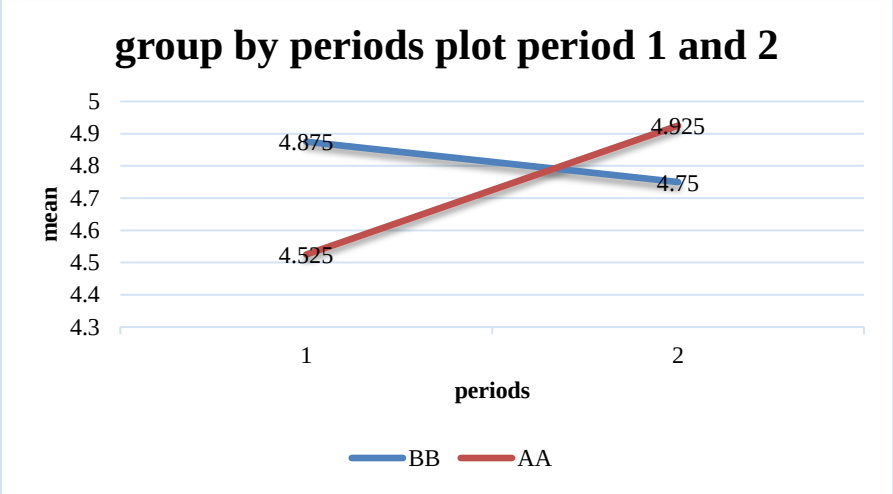

Figure 4.13: Group by periods plot for periods 1 and 2 of the last two sequences

Discussion: From Figure 4.13, it is evident that the BB and AA intersects. This implies that there are interaction effects.

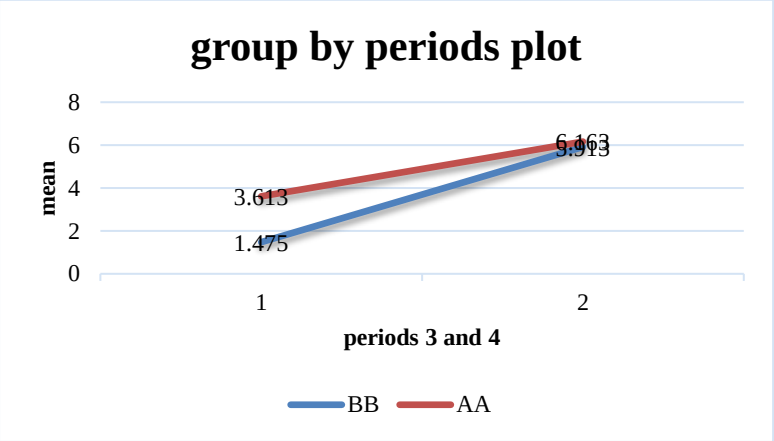

Figure 4.14: Group by periods plot for periods 3 and 4 of the last two sequences

Discussion: From Figure 4.14, it is evident that the BB and AA intersects. This implies that there are interaction effects.

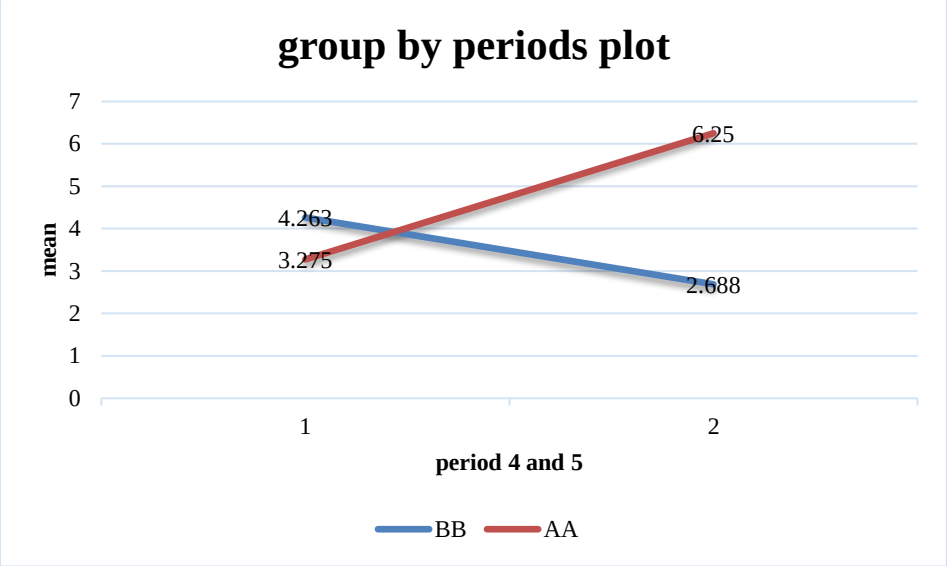

Figure 4.15: Group by periods plot for periods 4 and 5 of the last two sequences

Discussion: From Figure 4.15, it is evident that the BB and AA intersects. This implies that there are interaction effects.

4.4.7.2.1 Discussion

A majority of the figures; 4.10, 4.12, 4.13, 4.14, and 4.15, indicate presence of treatment by period interaction effects. It can therefore be concluded that the periods interact with the treatment effects and should be taken into consideration when assessing the efficacy of treatments.

CHAPTER FIVE: CONCLUSIONS AND RECOMMENDATIONS

5.0 Introduction

This chapter presents the conclusion and recommendations of the study.

5.1 Conclusions

In this thesis, C (2×5) cross-over designs were designed and analyzed. The objectives of the study were to: Estimate the direct treatments and carryover effects using BLUE method; evaluate the optimality criteria for the designs; evaluate the robustness for missing data for the designs and compare the Bayesian and the t −test analysis methods on the treatments and carry-over effects.

With regard to estimation of direct treatments and carry-over effects, the study established that the BLUE method gives both treatments and carry-over effects estimates for all the five period designs in two and four sequences except $\mathrm{D}_1, \mathrm{D}_2, \mathrm{D}_3, \mathrm{D}_4 \& \mathrm{D}_5$ whose carry-over effects were inestimable. BLUE method is normally associated with unbiased estimates for both treatments and carryover effects. The fact that the carryover effects estimates for $(D_1 - D_5)$ were not obtained implies the designs can be effectively used to estimate treatment effects even when the carryover effects are expected in the experiment.

With regard to optimality criteria, for the C $(2\times 5 \times 2)$ designs, it was shown that; $\mathrm{D}_6$and D_{10} are optimum for estimating carry-over effects, D_8 and D_{15} are optimum for estimating treatment effects and D_7 &D_{11} are optimum in estimating treatment effects when the carry-over effects are present. For the C $(2\times 5 \times 4)$ designs, D_{21} is optimum for estimating treatment effects while D_{22} and D_{25} are optimum for estimating carry-over effects. In estimating treatment effects when the carry-over effects are present, D_{25} is the most optimal and preferable. It is interesting to note that the optimum design

(D_{21}) was relatively strongly variance balanced with respect to the other designs. This implies that variance balance plays a role in determining the optimality criteria and by extension the efficiency of the designs.

The assessment of C ($2\times 5\times 4$) robustness for missing data gave D_{21} as the most Robust since it is perpetually connected and has minimum variance in estimating treatment effects. The result from this design and other C (2, 5) crossover designs with different breakdown numbers improve upon previous contributions in the literature that have been largely confined to cases in which dropout occurs only in the final periods of the study. The fact that the optimal design (D_{21}) is also most robust for missing data implies that there could be a positive relationship in the design's optimality criteria and robustness for missing data.

The results from the Bayesian analysis were similar to those from the t-test. This implies that the Bayesian method is equally as good as the other classical methods. This confirms the assertion by Jones and Kenward in the year 2014 that the Bayesian analysis is equally or more accurate when compared to other classical methods of analysis.

5.2 Recommendations

This study recommends that the most optimum and robust design in C (2, 5, 4) be applied in Bioequivalence experiments to assess the efficacy of new treatments against the existing standard treatments. For further research, the BLUE method should be used in estimation of direct and treatment effects for designs with three or more treatments.

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