

ANALYSIS OF A WILLIAMS SQUARE SEQUENCE STRUCTURE

by

Joyce E. Little

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Approved by:



George A. Milliken

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1. Introduction

A traditional experimental design is to compare treatments in a one-way treatment structure with a completely randomized design structure where each experimental unit is subjected to one treatment. Since each experimental unit is subjected to only one treatment, direct treatment effects, the effect a treatment has on the subject's response, is measured through among-subjects comparisons. In an experiment involving t treatments, N experimental units are randomly assigned to t groups with n_i experimental units in group i , $i = 1, 2, \dots, t$ and $N =$

$\sum_{i=1}^t n_i$. The classical model for analyzing a one-way treatment structure

in a completely randomized design structure is

$$Y_{ij} = \mu + \tau_i + \epsilon_{ij}, \quad (1.1)$$

where μ = overall mean,

τ_i = mean effect of treatment i , and

ϵ_{ij} = random error.

For inference purposes, it is assumed that $\epsilon_{ij} \sim \text{i.i.d. } N(0, \sigma_\epsilon^2)$. The estimate of the error variance is obtained from the variation among subjects, within treatment groups. Often, there is a relatively large variation among subjects within a treatment group, which can inhibit the chance of detecting treatment differences.

An alternative experimental design, is to allow each subject to go through a sequence of treatments, where each subject is its own "control". Such a design is called a crossover design. This experimental design can be used in a wide variety of applications in experimental research, from agriculture to testing biological assays to

marketing and sociological experimentation. A crossover design incorporates a repeated measures design structure, where treatments are administered in a sequence over time to each subject. Thus, comparisons of treatments are based on within-subject comparisons. The inherent variation among responses within a subject is often smaller than the variation among subjects, making this class of designs more appealing to researchers. When this is the case, the crossover design provides more precise estimates of treatment effects than those from a one-way treatment structure in a completely randomized design. Due to the smaller variation fewer experimental units are required to detect treatment differences of a fixed size with a crossover design compared to a one-way design. However, when different treatments are applied in succession to the same experimental unit, carryover, or residual effects from the preceding treatment can affect the present treatment's response. A carryover treatment effect is the effect of a treatment which carries over beyond the period of application which can bias subsequent estimates of direct treatment effects. The main focus of discussion is on one-period carryover effects, i.e., where the effect of a treatment can extend one more time period. Other residual effects will be discussed briefly.

2. Crossover Designs

Crossover designs involve constructing s sequences of t treatments in which subjects are randomly assigned to one of the sequences of treatments. Treatments are applied to the subjects in a specific sequence over periods of time. Each period should be of sufficient length to allow expression of the treatment effects and also long enough

so that the effect of treatment does not go beyond the period. When there is a risk of carryover effects, it is possible, in some situations, to separate the time intervals in which treatments are applied by enough time for carryover effects to die out, typically called washout periods. This extends the length of the experiment and is impractical in many situations. Treatment carryover effects may affect future treatment responses in one of two ways. If the carryover effects are equal, then the average treatment response will increase or decrease by a fixed amount, resulting in the same power for detecting treatment differences as if there were no carryover. If differential carryover effects occur, adjusting treatment means for carryover effects can be accomplished by using a set of sequences balanced for specified types of carryover effects. One-period carryover, or first order carryover, is a residual treatment effect which affects only the next treatment's response in the sequence. A set of sequences is balanced for a one-period carryover, if each treatment is preceded equally often by each other treatment and each treatment occurs equally often in each period. Similarly, second, third, ..., k^{th} order carryover effects may occur lasting for two, three, and k periods, respectively, beyond the period of application. Unless carryover effects are equal, direct treatment effects are biased if the analysis does not incorporate an adjustment for the differing carryover effects.

In the simplest case, two treatments in a two-period crossover design, involves two sequences of treatments, treatment A followed by B and treatment B followed by A with possibly a washout between periods. Subjects are assigned completely at random to sequences of treatments such that one-half of the experimental units receive treatment A and the

other one-half receive treatment B in the first period. The experimental unit receiving treatment A (or B) in period one then receives treatment B (or A) in period two, thus the name crossover design. One response is obtained per subject per period in a standard crossover experiment, although this response could be an average of several measurements taken during the period.

Table 1 is a layout of the data for a two-period crossover design using notation from Grizzle (1965), where S_{ij} denotes subject j in sequence i and Y_{ijk} denotes the observed response of subject j in sequence i to the treatment administered during period k .

Table 1. Layout of the Data for a Two-Period Crossover Design

<u>PERIOD</u>	<u>SEQUENCE</u>	<u>SUBJECT</u>	<u>SEQUENCE</u>	<u>SUBJECT</u>
		S_{11}, \dots, S_{1n_1}		S_{21}, \dots, S_{2n_2}
1	A	$Y_{111}, \dots, Y_{1n_1 1}$	B	$Y_{211}, \dots, Y_{2n_2 1}$
2	B	$Y_{112}, \dots, Y_{1n_2 2}$	A	$Y_{212}, \dots, Y_{2n_2 2}$

Since each treatment is observed on the same subject, a repeated measures design with two sizes of experimental units is generated. Each subject, the larger experimental unit, is assigned to a treatment sequence completely at random. The experimental design for period, the smaller experimental unit, is a one-way treatment structure with levels A and B in a randomized complete block design structure where the subjects are the blocks. The appropriate model for a two-period crossover design is,

$$Y_{ijkt} = \mu_{ikt} + \xi_{j(i)} + \epsilon_{ijkt} \quad (2.1)$$

where μ_{ikt} = mean effect of treatment t within sequence i at time k ,

$\xi_{j(i)}$ = random error of subject j within sequence i , and

ϵ_{ijkt} = random error associated with the period within the subject.

For inference purposes, assume $\xi_{j(i)} \sim$ i.i.d. $N(0, \sigma_\xi^2)$, $\epsilon_{ijkt} \sim$ i.i.d. $N(0, \sigma_\epsilon^2)$, when $\xi_{j(i)}$ and ϵ_{ijkt} are independent.

Since there are two sizes of experimental units, the subjects and the periods, there are two types of comparisons, between-subject comparisons and within-subject comparisons. The sequence effect, the residual effect, and the treatment by period interaction effect are equivalent for the two-period crossover design, each comparing the carryover effects for the two treatments. The treatment effect, a within-subject comparison, is equivalent to the period by sequence interaction effect, and the period effect, also a within-subject comparison, is equivalent to the treatment by sequence interaction effect.

A reparameterized model with carryover effects is,

$$Y_{ijkt} = \mu + \xi_{j(i)} + \pi_k + \tau_t + \lambda_A^X X_{i(k-1)A} + \lambda_B^X X_{i(k-1)B} + \epsilon_{ijkt} \quad (2.2)$$

where μ = overall mean,

$\xi_{j(i)}$ = random effect of subject j within sequence i ,

π_k = mean effect of period k ,

τ_t - mean direct effect of treatment t,

λ_t - mean carryover effect of treatment t,

$$X_{i(k-1)t} = \begin{cases} 1 & \text{if } k=2 \text{ and treatment } t \text{ occurs in period one} \\ & \text{of sequence } i, \\ 0 & \text{otherwise, and} \end{cases}$$

ϵ_{ijkt} = random error associated with the period within the subject,

where $j = 1, 2, \dots, n_1$; $i, k = 1, 2$; $t = A, B$; $\xi_{j(i)} \sim \text{i.i.d. } N(0, \sigma_\xi^2)$,

$\epsilon_{ijkt} \sim \text{i.i.d. } N(0, \sigma_\epsilon^2)$, and the $\xi_{j(i)}$ are independent of the ϵ_{ijkt} .

Based on the above distributional properties and assumptions, the sources of variation, associated degrees of freedom, and quantities proportional to the noncentrality parameters are given in Table 2.

Table 2. ANOVA Table for the Two-Treatment Two-Period Crossover Design

<u>Source of Variation</u>	<u>df</u>	<u>Noncentrality Parameter</u>
Between Subject Analysis		
Carryover or Sequence	1	$(\lambda_A - \lambda_B)^2$
Subject(Sequence)	$\sum_{i=1}^2 (n_i - 1)$	
Within Subject Analysis		
Period	1	$[\pi_1 - \pi_2 - 1/2(\lambda_A + \lambda_B)]^2$
Treatment	1	$[\tau_A - \tau_B + 1/2(\lambda_B - \lambda_A)]^2$
Error	$\sum_{i=1}^2 (n_i - 1)$	
Total	$2 \sum_{i=1}^2 n_i - 1$	

The tests for direct treatment effects assumes no period by treatment interaction. No period by treatment interaction, equivalent to carryover effects and sequence effects, implies that the effectiveness of one treatment does not change relative to the other as subjects go from period one to period two. Direct treatment effects are estimated by averaging the corresponding treatment responses of period one and period two. If the assumption of no period by treatment interaction is not satisfied, then there is a difference in the reliability of the results in the different periods. Each treatment in a two-period crossover design appears equally often in both periods and both sequences, but each treatment does not appear in every possible treatment-period pairing. Treatment A is in period two only in the second sequence, so it is possible only to observe how treatment A responds in period two when it is preceded by treatment B. If A reacts differently in period two, it could be due to the order of testing (sequence) or to the time of testing (period). It is impossible to determine how much, if any, of the overall difference between the two treatments is due to the treatments or to the treatment interaction with period and sequence effects. In period one, the responses for treatments A and B can be compared, even if differential carryover exists, because of the random assignment of subjects to the two sequences. In period two, if there is differential carryover, the subjects in each sequence start in a dissimilar state due to the different experience that occurred in period one. There is no way to adjust the treatments means for the differential carryover effects from the within-subject analysis since the carryover effects are estimated from the between-subject analysis. In this case, an appropriate

analysis is a two sample t-test performed on data in period one only, assuming normality. In this case, the expected treatment response is assumed to be the same, except for a random component, for all subjects. In addition, the expected treatment response is assumed to be the same regardless of which period the treatment is administered in. As an alternative, treatment comparisons can be made using a combined estimate of between-subject and within-treatment comparisons as shown by Milliken and Johnson (1984). The response to treatment in period one in the two sequence groups may be compared by a Wilcoxon two sample test if non-normality is a concern.

Crossover designs with more than two periods are similar to two period designs in that there are two sizes of experimental units, two error terms, and two levels of the analysis. In the following sections, concentration is focused on designs in which three periods are used. A model to describe a three-period crossover is,

$$\begin{aligned}
 Y_{ijkt} = & \mu + \kappa_i + \xi_{j(1)} + \pi_k + r_t + \lambda_A X_{i(k-1)A} \\
 & + \lambda_B X_{i(k-1)B} + \lambda_C X_{i(k-1)C} + \epsilon_{ijkt}, \quad (2.3)
 \end{aligned}$$

where μ - overall mean,

κ_i - mean effect of sequence i ,

$\xi_{j(1)}$ - random error of subject j within sequence i ,

π_k - mean effect of period k ,

r_t - effect of treatment t ,

λ_t - mean residual effect of treatment t ,

$$X_{i(k-1)t} = \begin{cases} 1 & \text{if treatment } t \text{ occurs in period } (k-1) \text{ of} \\ & \text{sequence } i, k = 2, 3, \\ 0 & \text{otherwise, and} \end{cases}$$

ϵ_{ijk} = random error associated with the period within the subject.

3. Latin Square

The two sequences in the two-period two-treatment crossover design form a Latin square. The traditional Latin square design structure can be employed in constructing crossover designs in which three or more treatments are to be studied. For crossover designs, the row blocks of the Latin square are the sequences and the column blocks are the treatment periods. Treatments are then assigned to periods for each sequence such that each treatment occurs once in each period and once in each sequence. A standard Latin square, defined by Federer (1955), is one in which the first row and the first column are ordered alphabetically or numerically. The procedure to construct a standard Latin square is as follows:

1. Number the treatments, $i = 1, \dots, t$.
2. The first row of the square consists of a sequential ordering of the treatments, i.e., 1 2 3 ... t.
3. A one step cyclic permutation of a sequence of treatments is one which moves the first treatment in the sequence to the extreme right, simultaneously moving all other treatments one

position to the left. i.e., Row two of the Latin square is
 2 3 4, ..., t 1.

The analysis of variance model for a Latin square sequence structure where subjects are assigned to sequences in a completely randomized design structure is the same as that defined in model (2.3). It is assumed that the effects of all three factors are additive and that treatment effects do not interact with sequence and period effects. The sources of variation and the associated degrees of freedom for the Latin square model are given in Table 3.

Table 3. ANOVA Table for the Latin Square Design

<u>Source of Variation</u>	<u>df</u>
<u>Between Subject Analysis</u>	
Sequence	t - 1
Subject(Sequence)	$\sum_{i=1}^t (n_i - 1)$
<u>Within Subject Analysis</u>	
Period	t - 1
Treatment	t - 1
Carryover	t - 1
Error	$\sum_{i=1}^t n_i (t-1) - 3(t-1)$
Total	$t \sum_{i=1}^t n_i - 1$

4. Williams Square

Crossover designs balanced for one-period carryover effects were developed by E. J. Williams (1949). These designs were devised in order

to measure both direct treatment and carryover effects from the within-subject comparisons for three or more treatments over three or more periods of time. Williams defines a crossover design to be balanced for one-period carryover effects when two conditions are satisfied. First, each treatment is preceded equally often by each other treatment. Second, each treatment must occur equally often in each period, in order of application to the subjects. These conditions for balancing require the number of sequences to be a multiple of the number of treatments. When there are t treatments, there are $t(t-1)$ ordered pairs of treatments. Since there are $(t-1)$ adjacent pairs in each sequence, the first condition requires a multiple of t sequences for all ordered pairs to occur equally often. The second condition is also satisfied by a multiple of t sequences.

Williams shows that when the number of treatments is even, a design balanced for one-period carryover effects can be achieved with a minimum of t sequences. When the number of treatments is odd, a minimum of $2t$ sequences is needed to balance the design. Balanced designs can be constructed from the cyclic Latin square of size t in which the rows represent the sequences, the columns the periods, and the symbols the treatments. One square is required when the number of treatments is even and two squares are required when the number of treatments is odd. Williams presents methods of balancing designs for one-period and two-period carryover effects. Two-period carryover effects occur when the effect of a treatment carries two periods beyond the application. The original construction of these balanced designs is fairly complicated. A more simple method of construction for designs balanced for one-period carryover is given in Bradley (1958) for an even number of treatments.

Sheehe and Bross (1961) present the following extension of Bradley's results in which construction of designs balanced for one-period carryover can be created for both even and odd numbers of treatments.

1. Number the treatments, $i = 1 \dots t$.
2. Start with a cyclic $t \times t$ Latin square in which the sequence of treatments in the i^{th} row is $i, i+1, \dots, t, 1, 2, \dots, i-1$.
3. Interlace each row of the cyclic Latin square with its own reverse order sequence (its mirror image). For example, if $t=3$ the first row of the cyclic Latin square is 1,2,3. Its mirror image is 3,2,1. When this is interlaced with the first row of the original square, the structure is 1,3,2,2,3,1.
4. Form two $t \times t$ Latin squares by vertically cutting this $t \times 2t$ rectangle down the middle. The columns of each square represent the order of application from left to right, the rows represent the sequences, and the treatments are the elements within each square.

For Williams square sequence structures, the treatments are assigned numbers at random, and the sequences are randomized. For $t=3$, the following two squares form a design balanced for one-period carryover effects.

Sequence 1: 1 3 2		Sequence 4: 2 3 1
Sequence 2: 2 1 3	and	Sequence 5: 3 1 2
Sequence 3: 3 2 1		Sequence 6: 1 2 3

For $t=4$, the following squares are formed:

Sequence 1: 1	4	2	3	Sequence 1: 3	2	4	1
Sequence 2: 2	1	3	4	Sequence 2: 4	3	1	2
Sequence 3: 3	2	4	1	Sequence 3: 1	4	2	3
Sequence 4: 4	3	1	2	Sequence 4: 2	1	3	4

Since the number of treatments is even, either one of the two squares formed creates a design balanced for one-period carryover effects.

In addition to designs balanced for one-period carryover, Williams also considers designs balanced for two-period carryover effects. This condition of balance requires all ordered triplets of treatments to occur equally often in the design. Williams describes a construction method based on sets of $t-1$ mutually orthogonal Latin squares where t is an odd prime number or a power of a prime.

A model for analyzing a Williams square sequence structure without adjustment for carryover effects incorporates sources of variation for sequence, subjects within a sequence, period, treatment, and an error term. A model is,

$$y_{ijkt} = \mu + \kappa_i + \xi_{j(1)} + \kappa_k + \tau_t + \epsilon_{ijkt}, \quad (4.1)$$

where the effects are defined as in model (2.3), excluding the carryover terms.

The sources of variation with their respective degrees of freedom for the analysis unadjusted for the carryover effects are in Table 4.

Table 4. ANOVA Table for Williams Square Model with Unadjusted Treatment

<u>Source of Variation</u>	<u>df</u>
Between Subject Analysis	
Sequence	$s - 1$
Subject(Sequence)	$\sum_{i=1}^s (n_i - 1)$
Within Subject Analysis	
Period	$t - 1$
Treatment	$t - 1$
Error	$\sum_{i=1}^s (n_i - 1) (t - 1) - (t - 1)$
Total	$\sum_{i=1}^s (n_i) t - 1$

This analysis does not take advantage of the balanced treatment sequence structure of the Williams square design that is valuable in measuring the effects due to carryover.

A model for analyzing a Williams square sequence structure in which an adjustment for carryover effects is incorporated includes a sequence by treatment interaction term. The sequence by treatment interaction can be partitioned into $(t-1)$ degrees of freedom period and $(t-1)$ degrees of freedom for one-period carryover with the remaining degrees of freedom associated with other residual effects. The model with carryover effects is,

$$\begin{aligned}
 y_{ijklm} = & \mu + \kappa_i + \xi_j(i) + \pi_k + \tau_m + \sum_{m=1}^t \lambda_m X_{i(k-1)m} \\
 & + \sum_{m=1}^t \lambda_m^* X_{ikm}^* + \epsilon_{ijklm}
 \end{aligned}
 \tag{4.2}$$

where μ = overall mean,

κ_i = effect of sequence i,

$\xi_{j(i)}$ = effect of subject j within sequence i,

π_k = effect of period k,

τ_t = effect of treatment t,

λ_m = carryover effect of the treatment m occurring in the
previous period,

λ_{mki}^* = residual effect (excluding one period carryover) from
period k in sequence i,

$$X_{i(k-1)m} = \begin{cases} 1 & \text{if treatment m occurs in period (k-1) of} \\ & \text{sequence i,} \\ 0 & \text{otherwise,} \end{cases}$$

$$X_{i(k-2)m}^* = \begin{cases} 1 & \text{if treatment m occurs in period (k-2) of} \\ & \text{sequence i,} \\ 0 & \text{otherwise, and} \end{cases}$$

ϵ_{ijkt} = random error of time period within an experimental unit.

The sources of variation and the associated degrees of freedom for the analysis adjusted for carryover are given in Table 5.

Table 5. ANOVA Table for Williams Square Model with Carryover Effects

Source of Variation	df
Between Subject Analysis	
Sequence	$s - 1$
Subject(Sequence)	$\sum_{i=1}^s (n_i - 1)$
Within Subject Analysis	
Period	$t - 1$
Treatment	$t - 1$
Sequence * Treatment	
One-Period Carryover	$t - 1$
Other Carryover	$(s-2)(t-1) - (t-1)$
Error	$[(\sum_{i=1}^s n_i) - 1] (t-1) - (s-1)(t-1)$
Total	$(\sum_{i=1}^s n_i) t - 1$

5. Sequence by Treatment Interaction

The Williams square sequence structure was designed specifically to address the problem of possible differential carryover effects for experiments with three or more treatments. The sequence by treatment interaction term in the two-period crossover design is equivalent to the period effect. In a William square sequence structure with more than two periods, the period effect is a partition of the sequence by treatment interaction term. An experimenter choosing to use this sequence structure would expect the effects of treatment to extend beyond the period of application. Therefore, there are $t-1$ independent a priori comparisons involving one-period carryover effects. The sum of squares associated with these $t-1$ comparisons is also a partition of the

sequence by treatment sums of squares. The remainder of the sequence by treatment interaction is a lack of fit sum of squares associated with residual effects that have not been accounted for with a design balanced for only one-period carryover effects.

For each treatment in a three-treatment three-period crossover design, there are six possible types of carryover effects. The carryover effects associated with treatment A are,

- i) $\lambda_{A(B)}$: the carryover of treatment A from period one affecting treatment B in period two,
- ii) $\lambda_{A(C)}$: the carryover of treatment A from period one affecting treatment C in period two,
- iii) $\lambda_{A(BC)}$: the carryover of treatment A from period one affecting treatment C in period three with treatment B in period two,
- iv) $\lambda_{A(CB)}$: the carryover of treatment A from period one affecting treatment B in period three with treatment C in period two,
- v) $\lambda_{(B)A(C)}$: the carryover of treatment A from period two affecting treatment C in period three with treatment B in period one, and
- vi) $\lambda_{(C)A(B)}$: the carryover of treatment A from period two affecting treatment B in period three with treatment C in period one.

Incorporating a one-period carryover effect into a model assumes that, for treatment A, $\lambda_A - \lambda_{A(B)} - \lambda_{A(C)} - \lambda_{(B)A(C)} - \lambda_{(C)A(B)}$.

Similarly for treatments B and C, $\lambda_B - \lambda_{B(A)} - \lambda_{B(C)} - \lambda_{(A)B(C)} -$

$\lambda_{(C)B(A)}$ and $\lambda_C - \lambda_{C(B)} - \lambda_{C(A)} - \lambda_{(A)C(B)} - \lambda_{(B)C(A)}$, respectively.

Including a two-period carryover effect into a model assumes that, for treatment A, $\lambda_{A(BC)} = \lambda_{A(CB)}$. Similarly for treatments B and C, $\lambda_{B(AC)} = \lambda_{B(CA)}$ and $\lambda_{C(AB)} = \lambda_{C(BA)}$, respectively. The sums of squares associated with the sequence by treatment interaction, after partitioning out the sums of squares due to period and one-period carryover, is a lack of fit measure of the deviation from the one-period carryover model in (2.3).

In a Williams square sequence structure with six sequences, three treatments, and five subjects per sequence, the sources of variation and the degrees of freedom are given in Table 6.

Table 6. ANOVA Table for a Three-Period Williams Square Model

<u>Source of Variation</u>	<u>df</u>
Between Subject Analysis	
Sequence	5
Subject(Sequence)	24
Within Subject Analysis	
Period	2
Treatment	2
Carryover	2
Sequence*Treatment	6
Error	48

In this example, the sequence by treatment interaction term has only six degrees of freedom, instead of the expected ten degrees of freedom. Two degrees of freedom correspond to the period effects and two degrees of freedom to the one-period carryover effects. Six degrees of freedom remain as a lack of fit test for the proposed model with one-period carryover. If this test is insignificant, it implies that a model for one-period carryover effects is adequate in describing the data. If this term is significant, other carryover effects, such as two-period

carryover, bias the test for and the estimates of direct treatment effects.

6. Computer Analysis

In the preceding sections, a Williams square sequence structure with an associated model and analysis of variance table was described in which possible carryover effects were accounted for. In this section, a computer code is presented for use with the SAS computer package to conduct the analysis.

Tests of hypotheses for the main effects of sequence, period, and treatment and the sequence by treatment interaction are obtained directly from an application of the GLM procedure. However, a test for differential one-period carryover effects cannot be obtained directly since the appropriate partition of the design matrix cannot be constructed through the CLASSES and MODEL statement. The condition of no carryover effects in period one cannot be conveyed. A partition of the design matrix for differential carryover is constructed outside the GLM procedure and then passed in with the data.

Model (2.3) has more parameters than can be uniquely estimated. One method of solving the normal equations for an overspecified model is to constrain the parameters of the model. Three approaches for restricting the carryover effect parameters are discussed. Each results in the same overall test for carryover. The first method employs the traditional sum-to-zero constraints. The second alternative is based on set-to-zero constraints. Finally, the overparameterized model is analyzed through contrasts. It is shown that information obtained through the sum-to-zero and set-to-zero constraints can also be obtained

through the overparameterized model. A Williams square sequence structure with three treatments is used as an example throughout the discussions. With three treatments, there are two degrees of freedom associated with carryover.

Sum-to-zero, the traditional constraint, requires the sum of the carryover parameters to equal zero, i.e., $\sum_{i=1}^t \lambda_i = 0$. The source code to construct the design matrix for carryover employing the sum-to-zero restrictions is as follows, where the observed data are in a data set called RAW_DATA.

```
DATA DESIGN_1; SET RAW_DATA;
RETAIN LAST_TRT;
SUM_1=0; SUM_2=0;
IF PERIOD NE 1 THEN DO;
  IF LAST_TRT=1 THEN SUM_1=1;
  IF LAST_TRT=2 THEN SUM_2=1;
  IF LAST_TRT=3 THEN DO; SUM_1=-1; SUM_2=-1; END;
END;
LAST_TRT=TRT;
```

For three treatments and three periods, there is a possibility of carryover affecting treatment responses in periods two and three. The indicator variables, SUM_1 and SUM_2, are created to indicate the treatment causing the carryover. SUM_1 equals 1 if the carryover is due to treatment 1, SUM_2 equals 1 if the carryover is due to treatment 2, and the sum-to-zero restriction forces both SUM_1 and SUM_2 to be -1 if the carryover is caused by treatment 3. The GLM procedure is then used, calling the DESIGN_1 data set. Since the design matrix for carryover has been constructed in the previous data step, SUM_1 and SUM_2 are not specified as classification variables in the CLASSES statement in GLM. The source code is as follows.

```

PROC GLM DATA=DESIGN_1;
CLASSES SEQUENCE SUBJECT PERIOD TRT;
MODEL RESPONSE = SEQUENCE SUBJECT(SEQUENCE) PERIOD TRT SUM_1 SUM_2;

```

The sum of squares corresponding to SUM_1 tests the hypothesis that the carryover from treatment 1 is equal to the average of all the carryover effects and the sum of squares corresponding to SUM_2 tests the hypothesis that the carryover from treatment 2 is equal to the average of all the carryover effects, i.e., $H_0: \lambda_1 - \bar{\lambda}$ or $H_0: \lambda_1 = 1/2(\lambda_2 + \lambda_3)$ and $H_0: \lambda_2 - \bar{\lambda}$ or $H_0: \lambda_2 = 1/2(\lambda_1 + \lambda_3)$, respectively. A contrast statement is generated to test for equal carryover effects for all treatments, i.e., $H_0: \lambda_1 = \lambda_2 = \lambda_3$. For the sum-to-zero restriction, the contrast is as follows.

```

CONTRAST 'CARRYOVER' SUM_1 1 SUM_2 0,
                SUM_1 0 SUM_2 1;

```

Set-to-zero constraints use restrictions that equate the last parameter in each group equal to zero. The source code to construct the design matrix for the carryover effects with the set-to-zero restriction is as follows, where the observed data are in the data set RAW_DATA.

```

DATA DESIGN_2; SET RAW_DATA;
RETAIN LAST_TRT;
SET_1=0; SET_2=0;
IF PERIOD NE 1 THEN DO;
    IF LAST_TRT=1 THEN SET_1=1;
    IF LAST_TRT=2 THEN SET_2=1;
END;
LAST_TRT=TRT;

```

Similar to the sum-to-zero restrictions, SET_1 equals 1 if carryover is due to treatment 1, SET_2 equals 1 if carryover is due to treatment 2,

but the set-to-zero restriction forces both SET_1 and SET_2 to be zero if carryover is caused by treatment 3.

The CLM procedure is then used calling, the DESIGN_2 data set. Since the design matrix for carryover has been constructed in the previous data step, SET_1 and SET_2 are not specified as classification variables in the CLASSES statement in CLM. The source code is as follows.

```
PROC CLM DATA=DESIGN_2;
CLASSES SEQUENCE SUBJECT PERIOD TRT;
MODEL RESPONSE = SEQUENCE SUBJECT(SEQUENCE) PERIOD TRT SET_1 SET_2;
```

The set-to-zero contrasts compare carryover from each treatment effect with the carryover effect from the last treatment, the highest coded level, i.e., $H_0:\lambda_1-\lambda_3$ and $H_0:\lambda_2-\lambda_3$. An overall test for differential carryover, i.e., $H_0:\lambda_1-\lambda_2-\lambda_3$, can be tested using the following contrast statement.

```
CONTRAST 'CARRYOVER' SET_1 1 SET_2 0,
                SET_1 0 SET_2 1;
```

The overparameterized model imposes no constraints on the carryover parameters. The source code to construct the design matrix for one-period carryover effects for the overparameterized model is as follows, where again the observed data are in the data set called RAW_DATA.

```
DATA DESIGN_3; SET RAW_DATA;
RETAIN LAST_TRT;
C1=0; C2=0; C3=0;
IF PERIOD NE 1 THEN DO;
    IF LAST_TRT=1 THEN C1=1;
    IF LAST_TRT=2 THEN C2=1;
    IF LAST_TRT=3 THEN C3=1;
END;
LAST_TRT=TRT;
```

The parameters, C1, C2, and C3 represent the carryover effects that are caused by treatments 1, 2, and 3, respectively.

The GLM procedure is then used, calling the DESIGN_3 data set. Since the design matrix for carryover has been constructed in the previous data step, C1, C2, and C3 are not specified as classification variables in the CLASSES statement in GLM. The source code is shown below.

```
PROC GLM DATA=DESIGN_3;
CLASSES SEQUENCE SUBJECT PERIOD TRT;
MODEL RESPONSE = SEQUENCE SUBJECT(SEQUENCE) PERIOD TRT C1 C2 C3;
```

An overall test for differential carryover, i.e., $H_0: \lambda_1 = \lambda_2 = \lambda_3$, is tested through the following contrast statement.

```
CONTRAST 'CARRYOVER' C1 1 C2 -1 C3 0,
                   C1 1 C2 0 C3 -1,
                   C1 0 C2 1 C3 -1;
```

7. Example

An example analysis for a three-treatment Williams square design, balanced for one-period carryover effects, is illustrated with the overparameterized model. The data in Table 7 were generated with subject variation of 10, error variance of 1, $\mu_A = 5$, $\mu_B = 5$, and $\mu_C = 6$, and with carryover effects $\lambda_A = -1$, $\lambda_B = 0$, and $\lambda_C = 1$.

Table 7. Data Generated with Williams Square Sequence Structure

TREATMENT SEQUENCE			SUBJECT	PERIOD		
				1	2	3
A	B	C	1	-2.127	-4.008	-0.832
			2	7.778	5.976	6.862
			3	9.304	7.348	11.476
			4	5.495	5.900	8.063
			5	2.066	0.742	3.212
B	C	A	1	4.160	4.684	2.647
			2	-2.793	0.883	-1.706
			3	8.969	8.611	10.388
			4	2.169	2.207	2.263
			5	10.183	12.089	12.374
C	A	B	1	11.196	12.655	10.228
			2	3.769	5.442	1.516
			3	4.910	4.333	1.757
			4	7.128	7.397	4.206
			5	7.363	6.955	5.252
C	B	A	1	1.818	4.849	1.990
			2	9.109	12.065	10.098
			3	0.887	-0.064	-0.539
			4	7.929	8.430	6.498
			5	4.205	3.813	5.285
A	C	B	1	8.598	7.036	10.065
			2	7.458	6.977	7.922
			3	-0.153	-1.197	1.241
			4	3.286	1.147	3.762
			5	0.968	3.509	4.184
B	A	C	1	9.445	6.823	8.583
			2	5.698	7.125	5.971
			3	4.694	4.654	5.759
			4	6.966	6.956	7.259
			5	3.949	2.893	2.202

The analysis of variance table for the lack of fit test for the data in Table 7 is reported in Table 8.

Table 8. ANOVA Table for Williams Square Lack of Fit Test

<u>Source</u>	<u>DF</u>	<u>Type I SS</u>	<u>Mean Square</u>	<u>F Value</u>	<u>Pr > F</u>
SEQUENCE	5	44.8624	8.9725	9.70	0.0001
SUBJECT(SEQUENCE)	24	1103.7853	45.9911	49.73	0.0001
PERIOD	2	0.2111	0.1055	0.11	0.8924
TRT	2	3.4056	1.7028	1.84	0.1697
C1	1	41.2620	41.2620	44.61	0.0001
C2	1	7.1565	7.1565	7.74	0.0077
C3	0	0.0000			
SEQUENCE*TRT	6	4.1586	0.6931	0.75	0.6129

The hypothesis of lack of fit of the one-period carryover model is not rejected ($p = 0.6129$). Thus, the one-period carryover model is assumed to adequately describe the data.

For the analysis in Table 8, the contrast for one-period carryover is not estimable nor are the adjusted treatment (least squares) means.

Next, a one-period carryover model without the sequence by treatment interaction term is fit to the data in Table 7. The results are displayed in Table 9. The Type I sum of squares for treatment is the unadjusted treatment sum of squares while the Type III sum of squares is the adjusted treatment sum of squares, adjusted for one-period carryover effects.

Table 9. ANOVA Table for the Unadjusted and Adjusted Treatments

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQUENCE	5	44.8624	8.9725	9.98	0.0001
SUBJECT(SEQUENCE)	24	1103.7853	45.9911	51.15	0.0001
PERIOD	2	0.2111	0.1055	0.12	0.8895
TRT	2	3.4056	1.7028	1.89	0.1603
C1	1	41.2620	41.2620	45.89	0.0001
C2	1	7.1565	7.1565	7.96	0.0067
C3	0	0.0000			

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	56.8253	11.3651	12.64	0.0001
SUBJECT(SEQUENCE)	24	1103.7853	45.9911	51.15	0.0001
PERIOD	1	0.0513	0.0513	0.06	0.8121
TRT	2	15.1933	7.5966	8.45	0.0006
C1	0	0.0000			
C2	0	0.0000			
C3	0	0.0000			

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
CARRYOVER	2	48.418497	24.209249	26.93	0.0001

Significant differential one-period carryover effects ($p \leq 0.0001$) are indicated by the contrast statement in Table 9. No significant differences were found between the treatments before adjusting for the carryover effects ($p = 0.1603$). However, significant treatment differences ($p = 0.0006$) are detected using the Type III adjusted sum of squares.

The sum-to-zero hypotheses, i.e., $H_0: \lambda_1 = 1/2(\lambda_2 + \lambda_3)$, $H_0: \lambda_2 = 1/2(\lambda_1 + \lambda_3)$, and $H_0: \lambda_3 = 1/2(\lambda_1 + \lambda_2)$, are tested using the following contrast statements through the overparameterized model.

```

CONTRAST 'C1-CBAR' C1 2 C2 -1 C3 -1;
CONTRAST 'C2-CBAR' C1 -1 C2 2 C3 -1;
CONTRAST 'C3-CBAR' C1 -1 C2 -1 C3 2;

```

The results for the data in Table 7 are reported in Table 10.

Table 10. Contrasts of Carryover Effects From the Average Carryover

<u>Contrast</u>	<u>DF</u>	<u>Contrast SS</u>	<u>Mean Square</u>	<u>F Value</u>	<u>Pr > F</u>
C1-CBAR	1	41.261965	41.261965	45.89	0.0001
C2-CBAR	1	0.801041	0.801041	0.89	0.3494
C3-CBAR	1	30.564739	30.564739	33.99	0.0001

The set-to-zero hypotheses, $H_0:\lambda_1-\lambda_2$, $H_0:\lambda_1-\lambda_3$, and $H_0:\lambda_2-\lambda_3$, are tested using the following contrast statements through the overparameterized model.

```

CONTRAST 'C1-C2' C1 1 C2 -1 C3 0;
CONTRAST 'C1-C3' C1 1 C2 0 C3 -1;
CONTRAST 'C2-C3' C1 0 C2 1 C3 -1;

```

The results for the data in Table 7 are reported in Table 11.

Table 11. Contrasts Comparing the Differences of Carryover Effects

<u>Contrast</u>	<u>DF</u>	<u>Contrast SS</u>	<u>Mean Square</u>	<u>F Value</u>	<u>Pr > F</u>
C1-C2	1	17.853758	17.853758	19.86	0.0001
C1-C3	1	47.617456	47.617456	52.96	0.0001
C2-C3	1	7.156532	7.156532	7.96	0.0067

A complete listing of the program used to generate and analyze the data in Table 7 with a complete analysis output is provided in Appendix A.

8. Means and Least Squares Means

When crossover designs are used to compare treatments, a test for differential carryover effects is conducted. If significant, treatment effects are adjusted for the differential carryover effects. When carryover effects exist but the test for carryover is nonsignificant or

ignored in the estimation of treatment effects, the resulting treatment estimates are biased for the differential carryover effects.

The expected value of the unadjusted means for treatments A, B, and C for a Williams square involving three treatments are,

$$E(\bar{y}_A) = \mu + \bar{\pi} + \tau_A + 1/2 (\lambda_B + \lambda_C),$$

$$E(\bar{y}_B) = \mu + \bar{\pi} + \tau_B + 1/2 (\lambda_A + \lambda_C), \text{ and}$$

$$E(\bar{y}_C) = \mu + \bar{\pi} + \tau_C + 1/2 (\lambda_A + \lambda_B).$$

For the data presented in Table 7, the results of a multiple comparison of the unadjusted means based on the ANOVA table reported in Table 9 is given in Table 12. No significant treatment differences were detected, agreeing with the results of the unadjusted (Type I) test for the treatment reported in Table 9.

Table 12. Means for the Example Data

T tests (LSD) for variable: Y

Alpha= 0.05 df= 54 MSE= 0.899106

Critical Value of T= 2.00

Least Significant Difference= 0.4908

Means with the same letter are not significantly different.

T Grouping	Mean	N	TRT
A	5.427	30	C
A			
A	5.240	30	A
A			
A	4.954	30	B

The expected value of the adjusted means (least square means) for treatments A, B, and C are,

$$E(\hat{y}_A) = \mu + \bar{\pi} + r_A + 2/3 \bar{\lambda} ,$$

$$E(\hat{y}_B) = \mu + \bar{\pi} + r_B + 2/3 \bar{\lambda} , \text{ and}$$

$$E(\hat{y}_C) = \mu + \bar{\pi} + r_C + 2/3 \bar{\lambda} .$$

If differential carryover exists, the difference between two adjusted means is an unbiased estimate of the difference between the corresponding mean treatment effects. In contrast, the difference between two unadjusted means is biased, as shown above.

For the data presented in Table 7, the results of a multiple comparison of the adjusted least squares means based on the ANOVA table reported in Table 9 is given in Table 13. Significant differences between treatments A and C ($p = .0002$) and B and C ($p = .0042$) were detected.

Table 13. Least Squares Means for the Example Data

TRT	Y LSMEAN	Std Err LSMEAN	Pr > T HO:LSMEAN=0	LSMEAN Number
A	4.76128263	0.18698995	0.0001	1
B	5.02081496	0.18698995	0.0001	2
C	5.83923682	0.18698995	0.0001	3

Pr > |T| HO: LSMEAN(i)-LSMEAN(j)

i/j	1	2	3
1	.	0.3473	0.0002
2	0.3473	.	0.0042
3	0.0002	0.0042	.

9. Power Analysis - Williams Square versus Latin Square

Both a Latin square sequence structure and a Williams square sequence structure can be used to assign treatments to sequences in

constructing crossover designs. A Latin square sequence structure is not balanced for one-period carryover. Thus, the power for detecting one-period carryover effects is less than the power for a Williams square sequence structure for the same number of subjects per design. The sequence structures for both designs used in the power analysis are given in Table 14.

Table 14. Sequence Structures Used in the Power Analysis

Williams Square							
Sequence 1:	1	2	3	Sequence 4:	3	2	1
Sequence 2:	2	3	1	Sequence 5:	1	3	2
Sequence 3:	3	1	2	Sequence 6:	2	1	3

Latin Square			
Sequence 1:	1	2	3
Sequence 2:	2	3	1
Sequence 3:	3	1	2

To compare the power of the Latin square sequence structure with the Williams squares sequence structure, the following sets of treatment means were specified with subject and error variances set to zero.

	Treatment 1	Treatment 2	Treatment 3
Condition 1:	5	5	5
Condition 2:	5	5	6
Condition 3:	5	6	7

Each of these treatment combinations were paired with the following sets of carryover effects,

	Carryover 1	Carryover 2	Carryover 3
Condition 1:	-1	0	1
Condition 2:	-1	-1	2
Condition 3:	-1	-2	3

A program that computes the sums of squares necessary for the computation of the noncentrality parameters needed for various tests of hypotheses is given in Appendix B. The program to calculate the power curve for detecting unadjusted treatment effects, adjusted treatment effects, one-period carryover, and sequence by treatment interaction is listed in Appendix C. The sums of squares obtained through the program in Appendix B, which are given in Table 15, are used as input for the power program in Appendix C.

Table 15. Noncentrality Parameters With One Subject Per Sequence

<u>Treatment Effects</u>	<u>Carryover Effects</u>	<u>Adjusted Treatment</u>		<u>Differential Carryover</u>	
		<u>Williams</u>	<u>Latin</u>	<u>Williams</u>	<u>Latin</u>
5 5 5	-1 0 1	0.00	0.00	5.33	0.67
	-1 -1 2	0.00	0.00	16.00	2.00
	-1 -2 3	0.00	0.00	37.33	4.67
5 5 6	-1 0 1	3.20	0.40	5.33	0.67
	-1 -1 2	3.20	0.40	16.00	2.00
	-1 -2 3	3.20	0.40	37.33	4.67
5 6 7	-1 0 1	9.60	1.20	5.33	0.67
	-1 -1 2	9.60	1.20	16.00	2.00
	-1 -2 3	9.60	1.20	37.33	4.67

For each test of hypothesis, the sum of squares is multiplied in an iterative manner over a range of sample sizes in order to calculate the power curves.

The power of detecting unadjusted treatment differences, adjusted treatment differences, and differential carryover for both the Latin square sequence structure and the Williams square sequence structure for the various conditions described above are reported in Tables 16 through 24 at the end of this section. The powers are graphically compared in

Figures 1 through 15 immediately following the appropriate table. In each case, the Williams square sequence structure is as powerful or more powerful than the Latin square sequence structure. The 0.05 reported in Tables 16, 17, and 18 indicate the null hypothesis of equal adjusted treatment means is true. The 0.05 is interpreted as the level of significance for the test. Similarly, the 0.05 reported in Table 20 indicates the null hypothesis of equal unadjusted treatment means for the Williams square sequence structure is true. This is a consequence of the particular combination of values chosen for treatment and carryover effects and the balancing of the Williams square sequence structure. Again, the 0.05 is interpreted as the level of significance for the test.

The programs in Appendix B and C are useful for experiment planning and as a classroom tool. Specific treatment effects, carryover effects, and variances can be input to obtain sums of squares, which can then be used to calculate the power of detecting treatment differences.

Table 16

Power of Detecting Specified Effect

Treatment Means: 5, 5, 5
 Carryover Effects: -1, 0, 1
 Variance = 1.0, Alpha = 0.05

Experimental Design	Total Subjects	Unadjusted Treatment	Adjusted Treatment	Carryover
Latin Square	6	0.3439	0.0500	0.1178
	12	0.7702	0.0500	0.2505
	18	0.9355	0.0500	0.3802
	24	0.9845	0.0500	0.5007
	30	0.9967	0.0500	0.6068
	36	0.9993	0.0500	0.6964
	42	0.9999	0.0500	0.7697
	48	1.0000	0.0500	0.8279
	54	1.0000	0.0500	0.8732
	60	1.0000	0.0500	0.9077
	66	1.0000	0.0500	0.9335
	72	1.0000	0.0500	0.9526
	78	1.0000	0.0500	0.9666
	84	1.0000	0.0500	0.9766
	90	1.0000	0.0500	0.9837
	96	1.0000	0.0500	0.9888
102	1.0000	0.0500	0.9923	
108	1.0000	0.0500	0.9948	
114	1.0000	0.0500	0.9965	
120	1.0000	0.0500	0.9976	
Williams Square	6	0.1178	0.0500	0.3439
	12	0.2505	0.0500	0.7702
	18	0.3802	0.0500	0.9355
	24	0.5007	0.0500	0.9845
	30	0.6068	0.0500	0.9967
	36	0.6964	0.0500	0.9993
	42	0.7697	0.0500	0.9999
	48	0.8279	0.0500	1.0000
	54	0.8732	0.0500	1.0000
	60	0.9077	0.0500	1.0000
	66	0.9335	0.0500	1.0000
	72	0.9526	0.0500	1.0000
	78	0.9666	0.0500	1.0000
	84	0.9766	0.0500	1.0000
	90	0.9837	0.0500	1.0000
	96	0.9888	0.0500	1.0000
102	0.9923	0.0500	1.0000	
108	0.9948	0.0500	1.0000	
114	0.9965	0.0500	1.0000	
120	0.9976	0.0500	1.0000	

Figure 1

Power of Detecting Differential Carryover Effect

Treatment Means: 5, 5, 5
 Carryover Effects: -1, 0, 1
 Variance = 1.0, Alpha = 0.05

Legend: O - Latin Square Design
 * - Williams Square Design

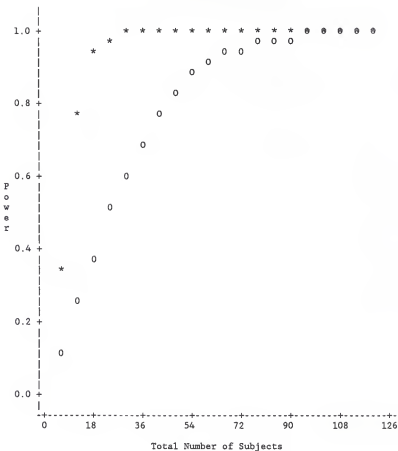


Table 17

Power of Detecting Specified Effect

Treatment Means: 5, 5, 5
 Carryover Effects: -1, -1, 2
 Variance = 1.0, Alpha = 0.05

Experimental Design	Total Subjects	Unadjusted Treatment	Adjusted Treatment	Carryover
Latin Square	6	0.7855	0.0500	0.2682
	12	0.9979	0.0500	0.6387
	18	1.0000	0.0500	0.8471
	24	1.0000	0.0500	0.9422
	30	1.0000	0.0500	0.9800
	36	1.0000	0.0500	0.9935
	42	1.0000	0.0500	0.9980
	48	1.0000	0.0500	0.9994
	54	1.0000	0.0500	0.9998
	60	1.0000	0.0500	1.0000
	66	1.0000	0.0500	1.0000
	72	1.0000	0.0500	1.0000
	78	1.0000	0.0500	1.0000
	84	1.0000	0.0500	1.0000
	90	1.0000	0.0500	1.0000
	96	1.0000	0.0500	1.0000
102	1.0000	0.0500	1.0000	
108	1.0000	0.0500	1.0000	
114	1.0000	0.0500	1.0000	
120	1.0000	0.0500	1.0000	
Williams Square	6	0.2682	0.0500	0.7855
	12	0.6387	0.0500	0.9979
	18	0.8471	0.0500	1.0000
	24	0.9422	0.0500	1.0000
	30	0.9800	0.0500	1.0000
	36	0.9935	0.0500	1.0000
	42	0.9980	0.0500	1.0000
	48	0.9994	0.0500	1.0000
	54	0.9998	0.0500	1.0000
	60	1.0000	0.0500	1.0000
	66	1.0000	0.0500	1.0000
	72	1.0000	0.0500	1.0000
	78	1.0000	0.0500	1.0000
	84	1.0000	0.0500	1.0000
	90	1.0000	0.0500	1.0000
	96	1.0000	0.0500	1.0000
102	1.0000	0.0500	1.0000	
108	1.0000	0.0500	1.0000	
114	1.0000	0.0500	1.0000	
120	1.0000	0.0500	1.0000	

Figure 2

Power of Detecting Differential Carryover Effect

Treatment Means: 5, 5, 5
Carryover Effects: -1, -1, 2
Variance = 1.0, Alpha = 0.05

Legend: O - Latin Square Design
* - Williams Square Design

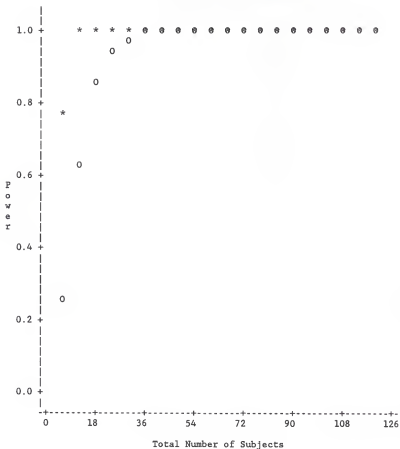


Table 18

Power of Detecting Specified Effect

Treatment Means: 5, 5, 5
 Carryover Effects: -1, -2, 3
 Variance = 1.0, Alpha = 0.05

Experimental Design	Total Subjects	Unadjusted Treatment	Adjusted Treatment	Carryover
Latin Square	6	0.9880	0.0500	0.5496
	12	1.0000	0.0500	0.9529
	18	1.0000	0.0500	0.9967
	24	1.0000	0.0500	0.9998
	30	1.0000	0.0500	1.0000
	36	1.0000	0.0500	1.0000
	42	1.0000	0.0500	1.0000
	48	1.0000	0.0500	1.0000
	54	1.0000	0.0500	1.0000
	60	1.0000	0.0500	1.0000
	66	1.0000	0.0500	1.0000
	72	1.0000	0.0500	1.0000
	78	1.0000	0.0500	1.0000
	84	1.0000	0.0500	1.0000
	90	1.0000	0.0500	1.0000
	96	1.0000	0.0500	1.0000
102	1.0000	0.0500	1.0000	
108	1.0000	0.0500	1.0000	
114	1.0000	0.0500	1.0000	
120	1.0000	0.0500	1.0000	
Williams Square	6	0.5496	0.0500	0.9880
	12	0.9529	0.0500	1.0000
	18	0.9967	0.0500	1.0000
	24	0.9998	0.0500	1.0000
	30	1.0000	0.0500	1.0000
	36	1.0000	0.0500	1.0000
	42	1.0000	0.0500	1.0000
	48	1.0000	0.0500	1.0000
	54	1.0000	0.0500	1.0000
	60	1.0000	0.0500	1.0000
	66	1.0000	0.0500	1.0000
	72	1.0000	0.0500	1.0000
	78	1.0000	0.0500	1.0000
	84	1.0000	0.0500	1.0000
	90	1.0000	0.0500	1.0000
	96	1.0000	0.0500	1.0000
102	1.0000	0.0500	1.0000	
108	1.0000	0.0500	1.0000	
114	1.0000	0.0500	1.0000	
120	1.0000	0.0500	1.0000	

Figure 3

Power of Detecting Differential Carryover Effect

Treatment Means: 5, 5, 5
Carryover Effects: -1, -2, 3
Variance = 1.0, Alpha = 0.05

Legend: 0 - Latin Square Design
* - Williams Square Design

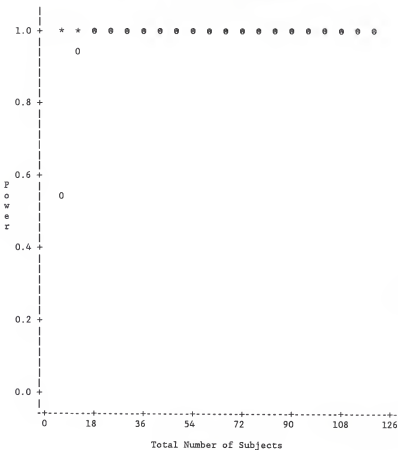


Table 19

Power of Detecting Specified Effect

Treatment Means: 5, 5, 6
 Carryover Effects: -1, 0, 1
 Variance = 1.0, Alpha = 0.05

Experimental Design	Total Subjects	Unadjusted Treatment	Adjusted Treatment	Carryover
Latin Square	6	0.5496	0.0897	0.1178
	12	0.9529	0.1652	0.2505
	18	0.9967	0.2421	0.3802
	24	0.9998	0.3196	0.5007
	30	1.0000	0.3955	0.6068
	36	1.0000	0.4680	0.6964
	42	1.0000	0.5359	0.7697
	48	1.0000	0.5983	0.8279
	54	1.0000	0.6548	0.8732
	60	1.0000	0.7054	0.9077
	66	1.0000	0.7501	0.9335
	72	1.0000	0.7892	0.9526
	78	1.0000	0.8232	0.9666
	84	1.0000	0.8524	0.9766
	90	1.0000	0.8774	0.9837
	96	1.0000	0.8986	0.9888
102	1.0000	0.9164	0.9923	
108	1.0000	0.9314	0.9948	
114	1.0000	0.9439	0.9965	
120	1.0000	0.9543	0.9976	
Williams Square	6	0.1178	0.2223	0.3439
	12	0.2505	0.5375	0.7702
	18	0.3802	0.7543	0.9355
	24	0.5007	0.8805	0.9845
	30	0.6068	0.9457	0.9967
	36	0.6964	0.9767	0.9993
	42	0.7697	0.9904	0.9999
	48	0.8279	0.9962	1.0000
	54	0.8732	0.9985	1.0000
	60	0.9077	0.9995	1.0000
	66	0.9335	0.9998	1.0000
	72	0.9526	0.9999	1.0000
	78	0.9666	1.0000	1.0000
	84	0.9766	1.0000	1.0000
	90	0.9837	1.0000	1.0000
	96	0.9888	1.0000	1.0000
102	0.9923	1.0000	1.0000	
108	0.9948	1.0000	1.0000	
114	0.9965	1.0000	1.0000	
120	0.9976	1.0000	1.0000	

Figure 4

Power of Detecting Adjusted Treatment Effect

Treatment Means: 5, 5, 6
 Carryover Effects: -1, 0, 1
 Variance = 1.0, Alpha = 0.05

Legend: O - Latin Square Design
 * - Williams Square Design

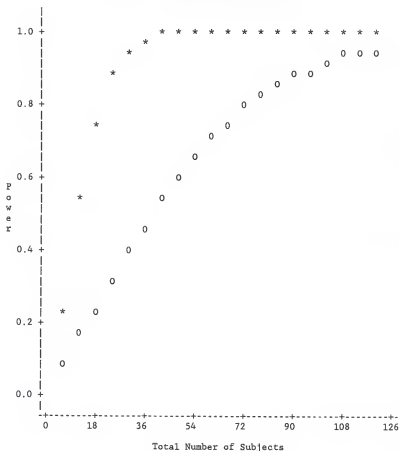


Figure 5

Power of Detecting Differential Carryover Effect

Treatment Means: 5, 5, 6
 Carryover Effects: -1, 0, 1
 Variance = 1.0, Alpha = 0.05

Legend: O - Latin Square Design
 * - Williams Square Design

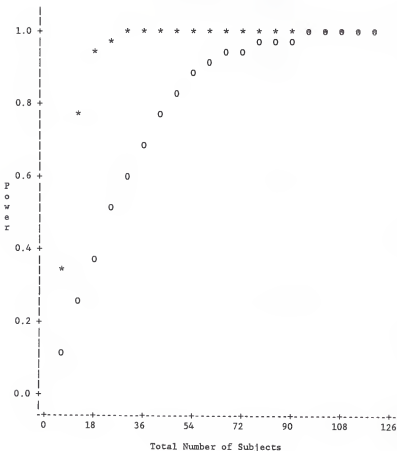


Table 20

Power of Detecting Specified Effect

Treatment Means: 5, 5, 6
 Carryover Effects: -1, -1, 2
 Variance = 1.0, Alpha = 0.05

Experimental Design	Total Subjects	Unadjusted Treatment	Adjusted Treatment	Carryover
Latin Square	6	0.6604	0.0897	0.2682
	12	0.9857	0.1652	0.6387
	18	0.9996	0.2421	0.8471
	24	1.0000	0.3196	0.9422
	30	1.0000	0.3955	0.9800
	36	1.0000	0.4680	0.9935
	42	1.0000	0.5359	0.9980
	48	1.0000	0.5983	0.9994
	54	1.0000	0.6548	0.9998
	60	1.0000	0.7054	1.0000
	66	1.0000	0.7501	1.0000
	72	1.0000	0.7892	1.0000
	78	1.0000	0.8232	1.0000
	84	1.0000	0.8524	1.0000
	90	1.0000	0.8774	1.0000
	96	1.0000	0.8986	1.0000
102	1.0000	0.9164	1.0000	
108	1.0000	0.9314	1.0000	
114	1.0000	0.9439	1.0000	
120	1.0000	0.9543	1.0000	
Williams Square	6	0.0500	0.2223	0.7855
	12	0.0500	0.5375	0.9979
	18	0.0500	0.7543	1.0000
	24	0.0500	0.8805	1.0000
	30	0.0500	0.9457	1.0000
	36	0.0500	0.9767	1.0000
	42	0.0500	0.9904	1.0000
	48	0.0500	0.9962	1.0000
	54	0.0500	0.9985	1.0000
	60	0.0500	0.9995	1.0000
	66	0.0500	0.9998	1.0000
	72	0.0500	0.9999	1.0000
	78	0.0500	1.0000	1.0000
	84	0.0500	1.0000	1.0000
	90	0.0500	1.0000	1.0000
	96	0.0500	1.0000	1.0000
102	0.0500	1.0000	1.0000	
108	0.0500	1.0000	1.0000	
114	0.0500	1.0000	1.0000	
120	0.0500	1.0000	1.0000	

Figure 6

Power of Detecting Adjusted Treatment Effect

Treatment Means: 5, 5, 6
Carryover Effects: -1, -1, 2
Variance = 1.0, Alpha = 0.05

Legend: O - Latin Square Design
* - Williams Square Design

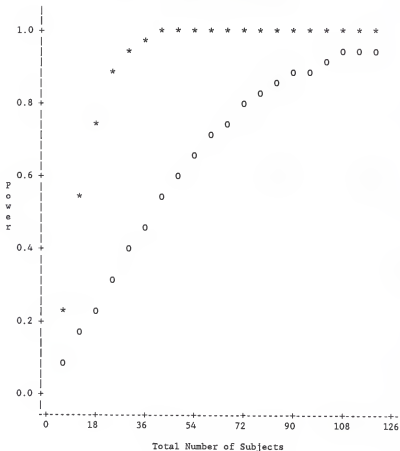


Figure 7

Power of Detecting Differential Carryover Effect

Treatment Means: 5, 5, 6
 Carryover Effects: -1, -1, 2
 Variance = 1.0, Alpha = 0.05

Legend: 0 - Latin Square Design
 * - Williams Square Design

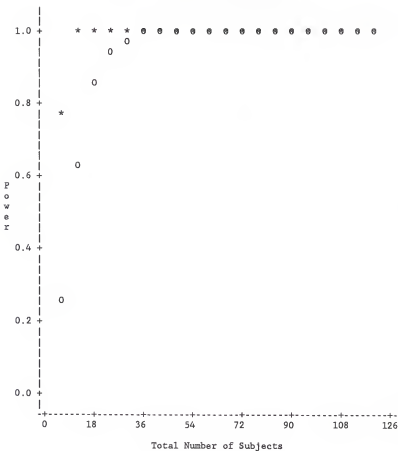


Table 21

Power of Detecting Specified Effect

Treatment Means: 5, 5, 6
 Carryover Effects: -1, -2, 3
 Variance = 1.0, Alpha = 0.05

Experimental Design	Total Subjects	Unadjusted Treatment	Adjusted Treatment	Carryover
Latin Square	6	0.9349	0.0897	0.5496
	12	1.0000	0.1652	0.9529
	18	1.0000	0.2421	0.9967
	24	1.0000	0.3196	0.9998
	30	1.0000	0.3955	1.0000
	36	1.0000	0.4680	1.0000
	42	1.0000	0.5359	1.0000
	48	1.0000	0.5983	1.0000
	54	1.0000	0.6548	1.0000
	60	1.0000	0.7054	1.0000
	66	1.0000	0.7501	1.0000
	72	1.0000	0.7892	1.0000
	78	1.0000	0.8232	1.0000
	84	1.0000	0.8524	1.0000
	90	1.0000	0.8774	1.0000
	96	1.0000	0.8986	1.0000
	102	1.0000	0.9164	1.0000
108	1.0000	0.9314	1.0000	
114	1.0000	0.9439	1.0000	
120	1.0000	0.9543	1.0000	
Williams Square	6	0.1178	0.2223	0.9880
	12	0.2505	0.5375	1.0000
	18	0.3802	0.7543	1.0000
	24	0.5007	0.8805	1.0000
	30	0.6068	0.9457	1.0000
	36	0.6964	0.9767	1.0000
	42	0.7697	0.9904	1.0000
	48	0.8279	0.9962	1.0000
	54	0.8732	0.9985	1.0000
	60	0.9077	0.9995	1.0000
	66	0.9335	0.9998	1.0000
	72	0.9526	0.9999	1.0000
	78	0.9666	1.0000	1.0000
	84	0.9766	1.0000	1.0000
	90	0.9837	1.0000	1.0000
	96	0.9888	1.0000	1.0000
	102	0.9923	1.0000	1.0000
108	0.9948	1.0000	1.0000	
114	0.9965	1.0000	1.0000	
120	0.9976	1.0000	1.0000	

Figure 8

Power of Detecting Adjusted Treatment Effect

Treatment Means: 5, 5, 6
 Carryover Effects: -1, -2, 3
 Variance = 1.0, Alpha = 0.05

Legend: O = Latin Square Design
 * = Williams Square Design

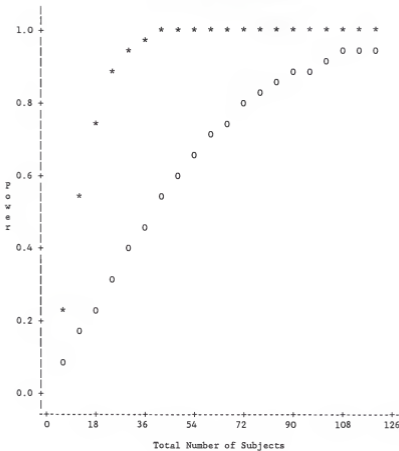


Figure 9

Power of Detecting Differential Carryover Effect

Treatment Means: 5, 5, 6
Carryover Effects: -1, -2, 3
Variance = 1.0, Alpha = 0.05

Legend: O = Latin Square Design
* = Williams Square Design

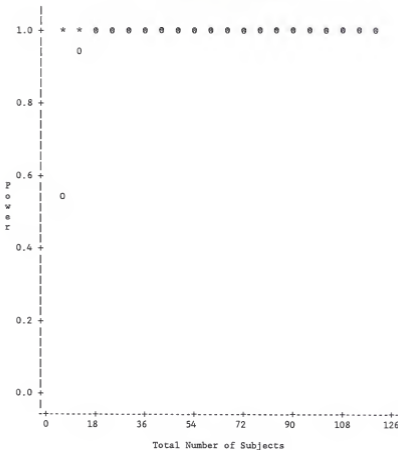


Table 22

Power of Detecting Specified Effect

Treatment Means: 5, 6, 7
 Carryover Effects: -1, 0, 1
 Variance = 1.0, Alpha = 0.05

Experimental Design	Total Subjects	Unadjusted Treatment	Adjusted Treatment	Carryover
Latin Square	6	0.5496	0.1768	0.1178
	12	0.9529	0.4210	0.2505
	18	0.9967	0.6216	0.3802
	24	0.9998	0.7673	0.5007
	30	1.0000	0.8639	0.6068
	36	1.0000	0.9235	0.6964
	42	1.0000	0.9584	0.7697
	48	1.0000	0.9781	0.8279
	54	1.0000	0.9887	0.8732
	60	1.0000	0.9943	0.9077
	66	1.0000	0.9972	0.9335
	72	1.0000	0.9986	0.9526
	78	1.0000	0.9993	0.9666
	84	1.0000	0.9997	0.9766
	90	1.0000	0.9999	0.9837
	96	1.0000	0.9999	0.9888
102	1.0000	1.0000	0.9923	
108	1.0000	1.0000	0.9948	
114	1.0000	1.0000	0.9965	
120	1.0000	1.0000	0.9976	
Williams Square	6	0.3439	0.5617	0.3439
	12	0.7702	0.9580	0.7702
	18	0.9355	0.9973	0.9355
	24	0.9845	0.9999	0.9845
	30	0.9967	1.0000	0.9967
	36	0.9993	1.0000	0.9993
	42	0.9999	1.0000	0.9999
	48	1.0000	1.0000	1.0000
	54	1.0000	1.0000	1.0000
	60	1.0000	1.0000	1.0000
	66	1.0000	1.0000	1.0000
	72	1.0000	1.0000	1.0000
	78	1.0000	1.0000	1.0000
	84	1.0000	1.0000	1.0000
	90	1.0000	1.0000	1.0000
	96	1.0000	1.0000	1.0000
102	1.0000	1.0000	1.0000	
108	1.0000	1.0000	1.0000	
114	1.0000	1.0000	1.0000	
120	1.0000	1.0000	1.0000	

Figure 10

Power of Detecting Adjusted Treatment Effect

Treatment Means: 5, 6, 7
 Carryover Effects: -1, 0, 1
 Variance - 1.0, Alpha - 0.05

Legend: O - Latin Square Design
 * - Williams Square Design

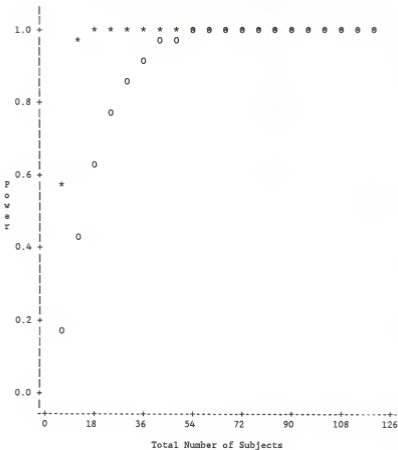


Figure 11

Power of Detecting Differential Carryover Effect

Treatment Means: 5, 6, 7
 Carryover Effects: -1, 0, 1
 Variance = 1.0, Alpha = 0.05

Legend: 0 = Latin Square Design
 * = Williams Square Design

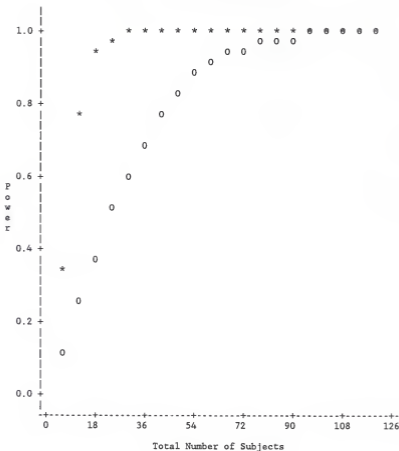


Table 23

Power of Detecting Specified Effect

Treatment Means: 5, 6, 7
 Carryover Effects: -1, -1, 2
 Variance = 1.0, Alpha = 0.05

Experimental Design	Total Subjects	Unadjusted Treatment	Adjusted Treatment	Carryover
Latin Square	6	0.2682	0.1768	0.2682
	12	0.6387	0.4210	0.6387
	18	0.8471	0.6216	0.8471
	24	0.9422	0.7673	0.9422
	30	0.9800	0.8639	0.9800
	36	0.9935	0.9235	0.9935
	42	0.9980	0.9584	0.9980
	48	0.9994	0.9781	0.9994
	54	0.9998	0.9887	0.9998
	60	1.0000	0.9943	1.0000
	66	1.0000	0.9972	1.0000
	72	1.0000	0.9986	1.0000
	78	1.0000	0.9993	1.0000
	84	1.0000	0.9997	1.0000
	90	1.0000	0.9999	1.0000
Williams Square	6	0.2682	0.5617	0.7855
	12	0.6387	0.9580	0.9979
	18	0.8471	0.9973	1.0000
	24	0.9422	0.9999	1.0000
	30	0.9800	1.0000	1.0000
	36	0.9935	1.0000	1.0000
	42	0.9980	1.0000	1.0000
	48	0.9994	1.0000	1.0000
	54	0.9998	1.0000	1.0000
	60	1.0000	1.0000	1.0000
	66	1.0000	1.0000	1.0000
	72	1.0000	1.0000	1.0000
	78	1.0000	1.0000	1.0000
	84	1.0000	1.0000	1.0000
	90	1.0000	1.0000	1.0000
96	1.0000	1.0000	1.0000	
102	1.0000	1.0000	1.0000	
108	1.0000	1.0000	1.0000	
114	1.0000	1.0000	1.0000	
120	1.0000	1.0000	1.0000	

Figure 12

Power of Detecting Adjusted Treatment Effect

Treatment Means: 5, 6, 7
 Carryover Effects: -1, -1, 2
 Variance = 1.0, Alpha = 0.05

Legend: O = Latin Square Design
 * = Williams Square Design

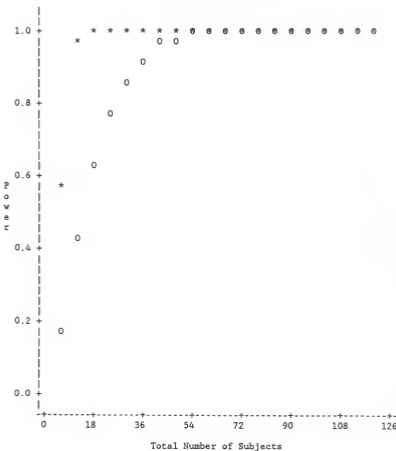


Figure 13

Power of Detecting Differential Carryover Effect

Treatment Means: 5, 6, 7
 Carryover Effects: -1, -1, 2
 Variance = 1.0, Alpha = 0.05

Legend: O - Latin Square Design
 * - Williams Square Design

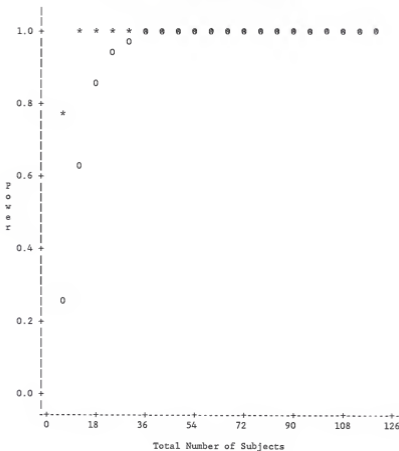


Table 24

Power of Detecting Specified Effect

Treatment Means: 5, 6, 7
 Carryover Effects: -1, -2, 3
 Variance = 1.0, Alpha = 0.05

Experimental Design	Total Subjects	Unadjusted Treatment	Adjusted Treatment	Carryover
Latin Square	6	0.5496	0.1768	0.5496
	12	0.9529	0.4210	0.9529
	18	0.9967	0.6216	0.9967
	24	0.9998	0.7673	0.9998
	30	1.0000	0.8639	1.0000
	36	1.0000	0.9235	1.0000
	42	1.0000	0.9584	1.0000
	48	1.0000	0.9781	1.0000
	54	1.0000	0.9887	1.0000
	60	1.0000	0.9943	1.0000
	66	1.0000	0.9972	1.0000
	72	1.0000	0.9986	1.0000
	78	1.0000	0.9993	1.0000
	84	1.0000	0.9997	1.0000
	90	1.0000	0.9999	1.0000
	96	1.0000	0.9999	1.0000
102	1.0000	1.0000	1.0000	
108	1.0000	1.0000	1.0000	
114	1.0000	1.0000	1.0000	
120	1.0000	1.0000	1.0000	
Williams Square	6	0.3439	0.5617	0.9880
	12	0.7702	0.9580	1.0000
	18	0.9355	0.9973	1.0000
	24	0.9845	0.9999	1.0000
	30	0.9967	1.0000	1.0000
	36	0.9993	1.0000	1.0000
	42	0.9999	1.0000	1.0000
	48	1.0000	1.0000	1.0000
	54	1.0000	1.0000	1.0000
	60	1.0000	1.0000	1.0000
	66	1.0000	1.0000	1.0000
	72	1.0000	1.0000	1.0000
	78	1.0000	1.0000	1.0000
	84	1.0000	1.0000	1.0000
	90	1.0000	1.0000	1.0000
	96	1.0000	1.0000	1.0000
102	1.0000	1.0000	1.0000	
108	1.0000	1.0000	1.0000	
114	1.0000	1.0000	1.0000	
120	1.0000	1.0000	1.0000	

Figure 14

Power of Detecting Adjusted Treatment Effect

Treatment Means: 5, 6, 7
 Carryover Effects: -1, -2, 3
 Variance = 1.0, Alpha = 0.05

Legend: O - Latin Square Design
 * - Williams Square Design

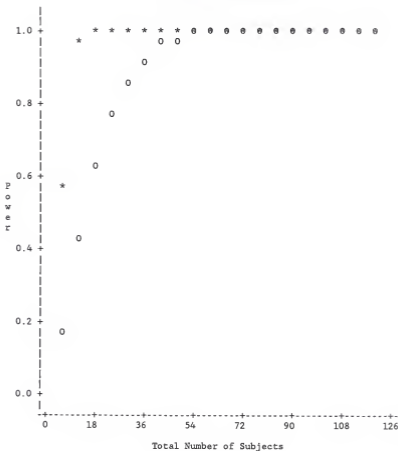
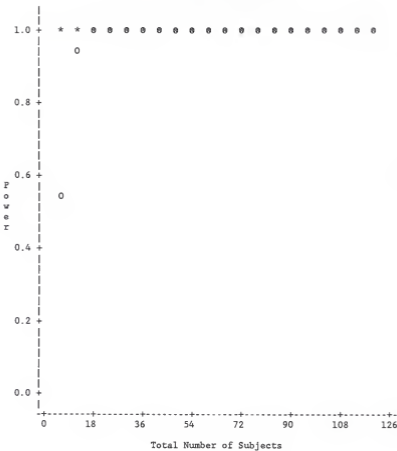


Figure 15

Power of Detecting Differential Carryover Effect

Treatment Means: 5, 6, 7
Carryover Effects: -1, -2, 3
Variance = 1.0, Alpha = 0.05

Legend: O - Latin Square Design
* - Williams Square Design



10. Summary

To analyze a Williams square sequence structure balanced for one-period carryover, the design matrix for the carryover effects must be constructed. The first step in the analysis is to include a lack of fit test for the one-period carryover model. A model fit using sequence, subjects within sequence, period, treatment, carryover, and a sequence by treatment interaction is appropriate for the lack of fit test. The significance of this interaction term indicates whether the one-period carryover model is adequate to describe the data. When the interaction is significant a one-period analysis is appropriate. However, when the interaction is insignificant the next step in the analysis is to check the equality of the carryover effects through contrast statements. This test for carryover determines the proper treatment comparisons. When carryover effects are equal, treatment comparisons may be made using the unadjusted treatment means. When differential carryover effects exist, the least squares means provide the appropriate treatment comparisons. A power analysis shows that experiments using the Williams square sequence structure are more powerful than experiments using the Latin square sequence structure for detecting adjusted treatment differences and differential carryover effects where each experiment utilizes the same total number of subjects.

References

- Bradley, J. V., (1958). Complete Counterbalancing of Immediate Sequential Effects in a Latin Square Design. Journal of American Statistics Association, 53, 525-528.
- Brown, Byron Wm., Jr., (1980). The Crossover Experiment for Clinical Trials. Biometrics 36, 69-79.
- Federer, Walter T., (1955). Experimental Design Theory and Application. Oxford & IBH Publishing Company, New Delhi.
- Fleiss, Joseph L., (1986). The Design and Analysis of Clinical Experiments. John Wiley & Sons, New York.
- Grizzle, James E., (1965). The Two-Period Change-Over Design and its Use in Clinical Trials. Biometrics 21, 467-480.
- Miliken, George A. and Johnson, Dallas E., (1984). Analysis of Messy Data. Volume 1, Van Nostrand Reinhold Company, New York.
- SAS Institute Inc., (1985). SAS User's Guide: Statistics. Version 5 Edition. Cary, North Carolina: SAS Institute Inc.
- Sharma, V. K., (1975). An Easy Method of Constructing Latin Square Designs Balanced for the Immediate Residual and Other Order Effects. The Canadian Journal of Statistics, Volume 3, No. 1, 119-124.
- Sharma, V. K., (1977). Change-Over Designs with Complete Balance for First and Second Residual Effects. The Canadian Journal of Statistics, Volume 5, No. 1, 121-132.
- Sheehe, Paul R. and Bross, Irwin D.J., (1961). Latin Squares to Balance Immediate Residual, and Other Order Effects. Biometrics, September, 405-414.
- Wallenstein, Sylvan and Fisher, Alan C., (1977). The Analysis of the Two-Period Repeated Measurements Crossover Design with Application to Clinical Trials. Biometrics 33, 261-269.
- Williams, E. J. (1949). Experimental Designs Balanced for the Estimation of Residual Effects of Treatments. Australian Journal of Scientific Research, Series A, Volume 2, 149-168.
- Williams, E. J. (1950). Experimental Designs Balanced for Pairs of Residual Effects. Australian Journal of Scientific Research, Series A, Volume 3, 351-363.
- Winer, B. J., (1962). Statistical Principles in Experimental Design. Second Edition. McGraw-Hill Inc., New York.

Appendix A

NOTE: Copyright(c) 1985,86,87 SAS Institute Inc., Cary, NC 27512-8000, U.S.A.

NOTE: SAS (r) Proprietary Software Release 6.03
Licensed to KANSAS STATE UNIVERSITY, Site 11175001.

NOTE: AUTOEXEC processing completed.

```
1  option nonumber nodate ls=72 ps=56 missing= ' ';
2  TITLE1 'Williams Square Analysis';
3  DATA A;
4
5  SEED_SEQ=0      ; VAR_SEQ= 0;
6  SEED_SUB=98442; VAR_SUB= 10;
7  SEED_PER=0     ; VAR_PER= 0;
8  SEED_ERR=56613; VAR_ERR= 1;
9
10 N_SUBJ=5;
11 TRT_1=5; FC_1=-1; SC_1=0;
12 TRT_2=5; FC_2= 0; SC_2=0;
13 TRT_3=6; FC_3= 1; SC_3=0;
14
15 ARRAY TRT_MEAN (3) TRT_1 TRT_2 TRT_3;
16 ARRAY FC_OVER (3) FC_1 FC_2 FC_3;
17 ARRAY SC_OVER (3) SC_1 SC_2 SC_3;
18 DO SEQUENCE=1 TO 6;
19 IF VAR_SEQ NE 0 THEN E_SEQ=RANNOR(SEED_SEQ)*SQRT(VAR_SEQ);
20 ELSE E_SEQ=0;
21 DO SUBJECT=1 TO N_SUBJ;
22 IF VAR_SUB NE 0 THEN E_SUBJ=RANNOR(SEED_SUB)*SQRT(VAR_SUB);
23 ELSE E_SUBJ=0;
24 DO PERIOD=1 TO 3;
25 IF VAR_ERR NE 0 THEN ERROR=RANNOR(SEED_ERR)*SQRT(VAR_ERR);
26 ELSE ERROR=0;
27 IF SEQUENCE=1 THEN DO;
28     IF PERIOD=1 THEN TRT=1;
29     IF PERIOD=2 THEN DO; TRT=2; RESID=1; END;
30     IF PERIOD=3 THEN DO; TRT=3; RESID=2; RESID2=1; END;
31 END;
32 IF SEQUENCE=2 THEN DO;
33     IF PERIOD=1 THEN TRT=2;
34     IF PERIOD=2 THEN DO; TRT=3; RESID=2; END;
35     IF PERIOD=3 THEN DO; TRT=1; RESID=3; RESID2=2; END;
36 END;
37 IF SEQUENCE=3 THEN DO;
38     IF PERIOD=1 THEN TRT=3;
39     IF PERIOD=2 THEN DO; TRT=1; RESID=3; END;
40     IF PERIOD=3 THEN DO; TRT=2; RESID=1; RESID2=3; END;
41 END;
42 IF SEQUENCE=4 THEN DO;
43     IF PERIOD=1 THEN TRT=3;
44     IF PERIOD=2 THEN DO; TRT=2; RESID=3; END;
45     IF PERIOD=3 THEN DO; TRT=1; RESID=2; RESID2=3; END;
46 END;
47 IF SEQUENCE=5 THEN DO;
48     IF PERIOD=1 THEN TRT=1;
```

```

49     IF PERIOD=2 THEN DO; TRT=3; RESID=1; END;
50     IF PERIOD=3 THEN DO; TRT=2; RESID=3; RESID2=1; END;
51     END;
52     IF SEQUENCE=6 THEN DO;
53         IF PERIOD=1 THEN TRT=2;
54         IF PERIOD=2 THEN DO; TRT=1; RESID=2; END;
55         IF PERIOD=3 THEN DO; TRT=3; RESID=1; RESID2=2; END;
56     END;
57     IF PERIOD=1 THEN Y=E_SEQ+E_SUBJ+TRT_MEAN(TRT)+ERROR;
58     ELSE IF PERIOD=2 THEN
59         Y=E_SEQ+E_SUBJ+TRT_MEAN(TRT)+FC_OVER(RESID)+ERROR;
60     ELSE IF PERIOD=3 THEN
61         Y=E_SEQ+E_SUBJ+TRT_MEAN(TRT)+FC_OVER(RESID)+SC_OVER(RESID2)+ERROR;
62     OUTPUT;
63     END;
64     END;
65     END;
66     run;
NOTE: The data set WORK.A has 90 observations and 28 variables.
NOTE: The DATA statement used 1.63 minutes.
67     PROC SORT; BY PERIOD;
68     run;
NOTE: The data set WORK.A has 90 observations and 28 variables.
NOTE: The PROCEDURE SORT used 23.00 seconds.
69     DATA B; SET A; BY PERIOD;
70     RETAIN E_PER;
71     IF FIRST.PERIOD THEN DO;
72     IF VAR_PER NE 0 THEN E_PER=RANNOR(SEED_PER)*SQRT(VAR_PER);
73     ELSE E_PER=0;
74     Y=Y+E_PER;
75     END;
76     run;
NOTE: The data set WORK.B has 90 observations and 29 variables.
NOTE: The DATA statement used 33.00 seconds.
77     PROC SORT DATA=B; BY SEQUENCE SUBJECT PERIOD;
78     run;
NOTE: The data set WORK.B has 90 observations and 29 variables.
NOTE: The PROCEDURE SORT used 23.00 seconds.
79     PROC PRINT SPLIT='*'; BY SEQUENCE SUBJECT;
80     ID SEQUENCE SUBJECT;
81     VAR PERIOD TRT Y;
82     LABEL SEQUENCE='SEQUENCE*-----'
83           SUBJECT='SUBJECT*-----'
84           PERIOD='PERIOD*-----'
85           TRT='TREATMENT*-----'
86           Y='RESPONSE*-----';
87     FORMAT Y 7.3;
88     run;
NOTE: The PROCEDURE PRINT used 1.07 minutes.
89     PROC SORT DATA=B; BY SEQUENCE TRT;
90     run;
NOTE: The data set WORK.B has 90 observations and 29 variables.
NOTE: The PROCEDURE SORT used 22.00 seconds.
91     PROC SORT DATA=B; BY SEQUENCE SUBJECT PERIOD;

```



```

92     run;
NOTE: The data set WORK.B has 90 observations and 29 variables.
NOTE: The PROCEDURE SORT used 22.00 seconds.
93     DATA C; SET B;
94     RETAIN LAST_TRT;
95     C1=0; C2=0; C3=0;
96     IF PERIOD NE 1 THEN DO;
97         IF LAST_TRT=1 THEN C1=1;
98         IF LAST_TRT=2 THEN C2=1;
99         IF LAST_TRT=3 THEN C3=1;
100    END;
101    LAST_TRT=TRT;
102    run;
NOTE: The data set WORK.C has 90 observations and 33 variables.
NOTE: The DATA statement used 46.00 seconds.
103    PROC CLM DATA=C;
104    TITLE3 'Analysis Adjusted for Carryover Effects';
105    TITLE4 'Overparameterized Model';
106    CLASSES SEQUENCE SUBJECT PERIOD TRT;
107    MODEL Y = SEQUENCE SUBJECT(SEQUENCE) PERIOD TRT C1 C2 C3
SEQUENCE*TRT;
108    TEST H=SEQUENCE E=SUBJECT(SEQUENCE);
109    run;
110    CONTRAST 'CARRYOVER' C1 1 C2 -1 C3 0,
111             C1 1 C2 0 C3 -1;
112    CONTRAST 'C1-C2' C1 1 C2 -1 C3 0;
113    CONTRAST 'C1-C3' C1 1 C2 0 C3 -1;
114    CONTRAST 'C2-C3' C1 0 C2 1 C3 -1;
115    CONTRAST 'C1-CBAR' C1 2 C2 -1 C3 -1;
116    CONTRAST 'C2-CBAR' C1 -1 C2 2 C3 -1;
117    CONTRAST 'C3-CBAR' C1 -1 C2 -1 C3 2;
118    ESTIMATE 'C1-C2' C1 1 C2 -1 C3 0;
119    ESTIMATE 'C1-C3' C1 1 C2 0 C3 -1;
120    ESTIMATE 'C2-C3' C1 0 C2 1 C3 -1;
121    ESTIMATE 'C1-CBAR' C1 2 C2 -1 C3 -1 / DIVISOR=3;
122    ESTIMATE 'C2-CBAR' C1 -1 C2 2 C3 -1 / DIVISOR=3;
123    ESTIMATE 'C3-CBAR' C1 -1 C2 -1 C3 2 / DIVISOR=3;
124    MEANS TRT / LSD;
125    LSMEANS TRT / STDERR PDIF;
126    run;
NOTE: CONTRAST CARRYOVER is not estimable.
NOTE: CONTRAST C1-C2 is not estimable.
NOTE: CONTRAST C1-C3 is not estimable.
NOTE: CONTRAST C2-C3 is not estimable.
NOTE: CONTRAST C1-CBAR is not estimable.
NOTE: CONTRAST C2-CBAR is not estimable.
NOTE: CONTRAST C3-CBAR is not estimable.
NOTE: C1-C2 is not estimable.
NOTE: C1-C3 is not estimable.
NOTE: C2-C3 is not estimable.
NOTE: C1-CBAR is not estimable.
NOTE: C2-CBAR is not estimable.
NOTE: C3-CBAR is not estimable.
127    quit;
NOTE: The PROCEDURE CLM used 4.17 minutes.

```

```

128   PROC GLM DATA=C;
129   TITLE3 'Analysis Adjusted for One-Period Carryover';
130   TITLE4 'Overparameterized Model';
131   CLASSES SEQUENCE SUBJECT PERIOD TRT;
132   MODEL Y = SEQUENCE SUBJECT(SEQUENCE) PERIOD TRT C1 C2 C3;
133   TEST H=SEQUENCE E=SUBJECT(SEQUENCE);
134   run;
135   CONTRAST 'CARRYOVER' C1 1 C2 -1 C3 0,
136             C1 1 C2 0 C3 -1;
137   CONTRAST 'C1-C2' C1 1 C2 -1 C3 0;
138   CONTRAST 'C1-C3' C1 1 C2 0 C3 -1;
139   CONTRAST 'C2-C3' C1 0 C2 1 C3 -1;
140   CONTRAST 'C1-CBAR' C1 2 C2 -1 C3 -1;
141   CONTRAST 'C2-CBAR' C1 -1 C2 2 C3 -1;
142   CONTRAST 'C3-CBAR' C1 -1 C2 -1 C3 2;
143   ESTIMATE 'C1-C2' C1 1 C2 -1 C3 0;
144   ESTIMATE 'C1-C3' C1 1 C2 0 C3 -1;
145   ESTIMATE 'C2-C3' C1 0 C2 1 C3 -1;
146   ESTIMATE 'C1-CBAR' C1 2 C2 -1 C3 -1 / DIVISOR=3;
147   ESTIMATE 'C2-CBAR' C1 -1 C2 2 C3 -1 / DIVISOR=3;
148   ESTIMATE 'C3-CBAR' C1 -1 C2 -1 C3 2 / DIVISOR=3;
149   MEANS TRT / LSD;
150   LSMEANS TRT / STDERR PDIFF;
151   run;
152   quit;
NOTE: The PROCEDURE GLM used 3.82 minutes.
153   DATA D; SET B; BY SEQUENCE SUBJECT;
154   RETAIN N MEAN;
155   IF FIRST.SUBJECT THEN DO;
156       N=0; MEAN=0;
157   END;
158   N=N+1;
159   MEAN=MEAN+Y;
160   IF PERIOD=3 THEN DO;
161       MEAN=MEAN/N;
162       IF TRT=1 THEN DO; L1=0; L2=1/3; L3=1/3; END;
163       ELSE IF TRT=2 THEN DO; L1=1/3; L2=0; L3=1/3; END;
164       ELSE IF TRT=3 THEN DO; L1=1/3; L2=1/3; L3=0; END;
165       OUTPUT;
166   END;
167   run;
NOTE: The data set WORK.D has 30 observations and 34 variables.
NOTE: The DATA statement used 41.00 seconds.
168   PROC GLM DATA=D;
169   TITLE3 'Between Subject Estimation of One-Period Carryover
Effects';
170   MODEL MEAN=L1 L2 L3 / SOLUTION;
171   run;
172   CONTRAST 'CARRYOVER' L1 1 L2 -1 L3 0,
173             L1 1 L2 0 L3 -1;
174   CONTRAST 'L1-L2' L1 1 L2 -1 L3 0;
175   CONTRAST 'L1-L3' L1 1 L2 0 L3 -1;
176   CONTRAST 'L2-L3' L1 0 L2 1 L3 -1;
177   ESTIMATE 'L1-L2' L1 1 L2 -1 L3 0;
178   ESTIMATE 'L1-L3' L1 1 L2 0 L3 -1;

```

```
179 ESTIMATE 'L2-L3' L1 0 L2 1 L3 -1;
180 run;
181 quit;
NOTE: The PROCEDURE GLM used 1.42 minutes.
```

Williams Square Analysis

SEQUENCE	SUBJECT	PERIOD	TREATMENT	RESPONSE
-----	-----	-----	-----	-----
1	1	1	1	-2.127
		2	2	-4.008
		3	3	-0.832
1	2	1	1	7.778
		2	2	5.976
		3	3	6.862
1	3	1	1	9.304
		2	2	7.348
		3	3	11.476
1	4	1	1	5.495
		2	2	5.900
		3	3	8.063
1	5	1	1	2.066
		2	2	0.742
		3	3	3.212
2	1	1	2	4.160
		2	3	4.684
		3	1	2.647
2	2	1	2	-2.793
		2	3	0.883
		3	1	-1.706
2	3	1	2	8.969
		2	3	8.611
		3	1	10.388
2	4	1	2	2.169
		2	3	2.207
		3	1	2.263
2	5	1	2	10.183
		2	3	12.089
		3	1	12.374
3	1	1	3	11.196
		2	1	12.655
		3	2	10.228
3	2	1	3	3.769
		2	1	5.442
		3	2	1.516

Williams Square Analysis

SEQUENCE	SUBJECT	PERIOD	TREATMENT	RESPONSE
3	3	1	3	4.910
		2	1	4.333
		3	2	1.757
3	4	1	3	7.128
		2	1	7.397
		3	2	4.206
3	5	1	3	7.363
		2	1	6.955
		3	2	5.252
4	1	1	3	1.818
		2	2	4.849
		3	1	1.990
4	2	1	3	9.109
		2	2	12.065
		3	1	10.098
4	3	1	3	0.887
		2	2	-0.064
		3	1	-0.539
4	4	1	3	7.929
		2	2	8.430
		3	1	6.498
4	5	1	3	4.205
		2	2	3.813
		3	1	5.285
5	1	1	1	8.598
		2	3	7.036
		3	2	10.065
5	2	1	1	7.458
		2	3	6.977
		3	2	7.922
5	3	1	1	-0.153
		2	3	-1.197
		3	2	1.241
5	4	1	1	3.286
		2	3	1.147
		3	2	3.762

Williams Square Analysis

SEQUENCE	SUBJECT	PERIOD	TREATMENT	RESPONSE
-----	-----	-----	-----	-----
5	5	1	1	0.968
		2	3	3.509
		3	2	4.184
6	1	1	2	9.445
		2	1	6.823
		3	3	8.583
6	2	1	2	5.698
		2	1	7.125
		3	3	5.971
6	3	1	2	4.694
		2	1	4.654
		3	3	5.759
6	4	1	2	6.966
		2	1	6.956
		3	3	7.259
6	5	1	2	3.949
		2	1	2.893
		3	3	2.202

Williams Square Analysis

Analysis Adjusted for Carryover Effects
Overparameterized Model

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SEQUENCE	6	1 2 3 4 5 6
SUBJECT	5	1 2 3 4 5
PERIOD	3	1 2 3
TRT	3	1 2 3

Number of observations in data set = 90

Williams Square Analysis

Analysis Adjusted for Carryover Effects
Overparameterized Model

General Linear Models Procedure

Dependent Variable: Y

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	41	1204.8416	29.3864	31.77	0.0001
Error	48	44.3931	0.9249		
Corrected Total	89	1249.2347			
	R-Square	C.V.	Root MSE		Y Mean
	0.964464	18.46886	0.9617		5.207111

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQUENCE	5	44.8624	8.9725	9.70	0.0001
SUBJECT(SEQUENCE)	24	1103.7853	45.9911	49.73	0.0001
PERIOD	2	0.2111	0.1055	0.11	0.8924
TRT	2	3.4056	1.7028	1.84	0.1697
C1	1	41.2620	41.2620	44.61	0.0001
C2	1	7.1565	7.1565	7.74	0.0077
C3	0	0.0000			
SEQUENCE*TRT	6	4.1586	0.6931	0.75	0.6129

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	56.8253	11.3651	12.29	0.0001
SUBJECT(SEQUENCE)	24	1103.7853	45.9911	49.73	0.0001
PERIOD	0	0.0000			
TRT	2	15.1933	7.5966	8.21	0.0009
C1	0	0.0000			
C2	0	0.0000			
C3	0	0.0000			
SEQUENCE*TRT	6	4.1586	0.6931	0.75	0.6129

Tests of Hypotheses using the Type III MS for
SUBJECT(SEQUENCE) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	56.825306	11.365061	0.25	0.9372

Williams Square Analysis
Analysis Adjusted for Carryover Effects
Overparameterized Model

General Linear Models Procedure

T tests (LSD) for variable: Y

NOTE: This test controls the type I comparisonwise error rate not the experimentwise error rate.

Alpha- 0.05 df- 48 MSE- 0.924856
Critical Value of T- 2.01
Least Significant Difference- 0.4993

Means with the same letter are not significantly different.

T Grouping	Mean	N	TRT
A	5.427	30	3
A			
A	5.240	30	1
A			
A	4.954	30	2

Williams Square Analysis

Analysis Adjusted for Carryover Effects
Overparameterized Model

General Linear Models Procedure
Least Squares Means

TRT	Y LSMEAN
1	Non-est
2	Non-est
3	Non-est

Williams Square Analysis

Analysis Adjusted for One-Period Carryover
Overparameterized Model

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SEQUENCE	6	1 2 3 4 5 6
SUBJECT	5	1 2 3 4 5
PERIOD	3	1 2 3
TRT	3	1 2 3

Number of observations in data set = 90

Williams Square Analysis

Analysis Adjusted for One-Period Carryover
Overparameterized Model

General Linear Models Procedure

Dependent Variable: Y

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	35	1200.6830	34.3052	38.15	0.0001
Error	54	48.5517	0.8991		
Corrected Total	89	1249.2347			
	R-Square	C.V.	Root MSE		Y Mean
	0.961135	18.20994	0.9482		5.207111

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQUENCE	5	44.8624	8.9725	9.98	0.0001
SUBJECT(SEQUENCE)	24	1103.7853	45.9911	51.15	0.0001
PERIOD	2	0.2111	0.1055	0.12	0.8895
TRT	2	3.4056	1.7028	1.89	0.1603
C1	1	41.2620	41.2620	45.89	0.0001
C2	1	7.1565	7.1565	7.96	0.0067
C3	0	0.0000			

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	56.8253	11.3651	12.64	0.0001
SUBJECT(SEQUENCE)	24	1103.7853	45.9911	51.15	0.0001
PERIOD	1	0.0513	0.0513	0.06	0.8121
TRT	2	15.1933	7.5966	8.45	0.0006
C1	0	0.0000			
C2	0	0.0000			
C3	0	0.0000			

Tests of Hypotheses using the Type III MS for
SUBJECT(SEQUENCE) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQUENCE	5	56.825306	11.365061	0.25	0.9372

Williams Square Analysis
Analysis Adjusted for One-Period Carryover
Overparameterized Model

General Linear Models Procedure

T tests (LSD) for variable: Y

NOTE: This test controls the type I comparisonwise error rate not
the experimentwise error rate.

Alpha= 0.05 df= 54 MSE= 0.899106
Critical Value of T= 2.00
Least Significant Difference= 0.4908

Means with the same letter are not significantly different.

T Grouping	Mean	N	TRT
A	5.427	30	3
A			
A	5.240	30	1
A			
A	4.954	30	2

Williams Square Analysis
 Analysis Adjusted for One-Period Carryover
 Overparameterized Model

General Linear Models Procedure
 Least Squares Means

TRT	Y LSMEAN	Std Err LSMEAN	Pr > T HO:LSMEAN=0	LSMEAN Number
1	4.76128263	0.18698995	0.0001	1
2	5.02081496	0.18698995	0.0001	2
3	5.83923682	0.18698995	0.0001	3

Pr > |T| HO: LSMEAN(i)-LSMEAN(j)

i/j	1	2	3
1	.	0.3473	0.0002
2	0.3473	.	0.0042
3	0.0002	0.0042	.

NOTE: To ensure overall protection level, only probabilities associated with pre-planned comparisons should be used.

Williams Square Analysis

Analysis Adjusted for One-Period Carryover
Overparameterized Model

General Linear Models Procedure

Dependent Variable: Y

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
CARRYOVER	2	48.418497	24.209249	26.93	0.0001
C1-C2	1	17.853758	17.853758	19.86	0.0001
C1-C3	1	47.617456	47.617456	52.96	0.0001
C2-C3	1	7.156532	7.156532	7.96	0.0067
C1-CBAR	1	41.261965	41.261965	45.89	0.0001
C2-CBAR	1	0.801041	0.801041	0.89	0.3494
C3-CBAR	1	30.564739	30.564739	33.99	0.0001

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
C1-C2	-1.63647905	-4.46	0.0001	0.36724097
C1-C3	-2.67256776	-7.28	0.0001	0.36724097
C2-C3	-1.03608871	-2.82	0.0067	0.36724097
C1-CBAR	-1.43634894	-6.77	0.0001	0.21202667
C2-CBAR	0.20013011	0.94	0.3494	0.21202667
C3-CBAR	1.23621882	5.83	0.0001	0.21202667

Williams Square Analysis
Between Subject Estimation of One-Period Carryover Effects
General Linear Models Procedure
Number of observations in data set = 30

Williams Square Analysis

Between Subject Estimation of One-Period Carryover Effects

General Linear Models Procedure

Dependent Variable: MEAN

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.1626086	0.0813043	0.01	0.9943
Error	27	382.7199843	14.1748142		
Corrected Total	29	382.8825929			
	R-Square	C.V.	Root MSE	MEAN Mean	
	0.000425	72.30391	3.7649	5.207111	

Source	DF	Type I SS	Mean Square	F Value	Pr > F
L1	1	0.1226750	0.1226750	0.01	0.9266
L2	1	0.0399336	0.0399336	0.00	0.9581
L3	0	0.0000000			

Source	DF	Type III SS	Mean Square	F Value	Pr > F
L1	0	0			
L2	0	0			
L3	0	0			

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
INTERCEPT	5.206045778 B	2.52	0.0178	2.06214555
L1	0.272900963 B	0.05	0.9573	5.05120437
L2	-0.268105346 B	-0.05	0.9581	5.05120437
L3	0.000000000 B			

NOTE: The X'X matrix has been found to be singular and a generalized inverse was used to solve the normal equations. Estimates followed by the letter 'B' are biased, and are not unique estimators of the parameters.

Williams Square Analysis

Between Subject Estimation of One-Period Carryover Effects

General Linear Models Procedure

Dependent Variable: MEAN

Contrast	DF	Contrast SS	Mean Square	F Value	Pr > F
CARRYOVER	2	0.1626086	0.0813043	0.01	0.9943
L1-L2	1	0.1626043	0.1626043	0.01	0.9155
L1-L3	1	0.0413750	0.0413750	0.00	0.9573
L2-L3	1	0.0399336	0.0399336	0.00	0.9581

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
L1-L2	0.54100631	0.11	0.9155	5.05120437
L1-L3	0.27290096	0.05	0.9573	5.05120437
L2-L3	-0.26810535	-0.05	0.9581	5.05120437

Appendix B

```

option nonumber nodate ls=72 ps=56 missing= ' ';
TITLE 'Williams Square Analysis';
DATA A;

SEED_SEQ=0; VAR_SEQ= 0;
SEED_SUB=0; VAR_SUB= 0;
SEED_PER=0; VAR_PER= 0;
SEED_ERR=0; VAR_ERR= 0;

N_SUBJ=1;
TRT_1=5; FC_1=-1; SC_1=0;
TRT_2=5; FC_2= 0; SC_2=0;
TRT_3=6; FC_3= 1; SC_3=0;

ARRAY TRT MEAN (3) TRT_1 TRT_2 TRT_3;
ARRAY FC_OVER (3) FC_1 FC_2 FC_3;
ARRAY SC_OVER (3) SC_1 SC_2 SC_3;
DO SEQUENCE=1 TO 6;
IF VAR_SEQ NE 0 THEN E_SEQ=RANNOR(SEED_SEQ)*SQRT(VAR_SEQ);
ELSE E_SEQ=0;
DO SUBJECT=1 TO N_SUBJ;
IF VAR_SUB NE 0 THEN E_SUBJ=RANNOR(SEED_SUB)*SQRT(VAR_SUB);
ELSE E_SUBJ=0;
DO PERIOD=1 TO 3;
IF VAR_ERR NE 0 THEN ERROR=RANNOR(SEED_ERR)*SQRT(VAR_ERR);
ELSE ERROR=0;
IF SEQUENCE=1 THEN DO;
  IF PERIOD=1 THEN TRT=1;
  IF PERIOD=2 THEN DO; TRT=2; RESID=1; END;
  IF PERIOD=3 THEN DO; TRT=3; RESID=2; RESID2=1; END;
END;
IF SEQUENCE=2 THEN DO;
  IF PERIOD=1 THEN TRT=2;
  IF PERIOD=2 THEN DO; TRT=3; RESID=2; END;
  IF PERIOD=3 THEN DO; TRT=1; RESID=3; RESID2=2; END;
END;
IF SEQUENCE=3 THEN DO;
  IF PERIOD=1 THEN TRT=3;
  IF PERIOD=2 THEN DO; TRT=1; RESID=3; END;
  IF PERIOD=3 THEN DO; TRT=2; RESID=1; RESID2=3; END;
END;
IF SEQUENCE=4 THEN DO;
  IF PERIOD=1 THEN TRT=3;
  IF PERIOD=2 THEN DO; TRT=2; RESID=3; END;
  IF PERIOD=3 THEN DO; TRT=1; RESID=2; RESID2=3; END;
END;
IF SEQUENCE=5 THEN DO;
  IF PERIOD=1 THEN TRT=1;
  IF PERIOD=2 THEN DO; TRT=3; RESID=1; END;
  IF PERIOD=3 THEN DO; TRT=2; RESID=3; RESID2=1; END;
END;
IF SEQUENCE=6 THEN DO;
  IF PERIOD=1 THEN TRT=2;
  IF PERIOD=2 THEN DO; TRT=1; RESID=2; END;
  IF PERIOD=3 THEN DO; TRT=3; RESID=1; RESID2=2; END;

```

```

END;
IF PERIOD=1 THEN Y=E SEQ+E_SUBJ+TRT_MEAN(TRT)+ERROR;
ELSE IF PERIOD=2 THEN
  Y=E SEQ+E_SUBJ+TRT_MEAN(TRT)+FC_OVER(RESID)+ERROR;
ELSE IF PERIOD=3 THEN
  Y=E_SEQ+E_SUBJ+TRT_MEAN(TRT)+FC_OVER(RESID)+SC_OVER(RESID2)+ERROR;
OUTPUT;
END;
END;
END;
run;
PROC SORT; BY PERIOD;
run;
DATA B; SET A; BY PERIOD;
RETAIN E_PER;
IF FIRST.PERIOD THEN DO;
IF VAR_PER NE 0 THEN E_PER=RANNOR(SEED_PER)*SQRT(VAR_PER);
ELSE E_PER=0;
Y=Y+E_PER;
END;
run;
PROC SORT DATA=B; BY SEQUENCE SUBJECT PERIOD;
run;
PROC PRINT SPLIT='*'; BY SEQUENCE SUBJECT;
ID SEQUENCE SUBJECT;
VAR PERIOD TRT Y;
LABEL SEQUENCE='SEQUENCE*-----'
      SUBJECT='SUBJECT*-----'
      PERIOD='PERIOD*-----'
      TRT='TREATMENT*-----'
      Y='RESPONSE*-----';
FORMAT Y 7.3;
run;
PROC SORT DATA=B; BY SEQUENCE TRT;
run;
PROC SORT DATA=B; BY SEQUENCE SUBJECT PERIOD;
run;
DATA C; SET B;
RETAIN LAST_TRT;
C1=0; C2=0; C3=0;
IF PERIOD NE 1 THEN DO;
  IF LAST_TRT=1 THEN C1=1;
  IF LAST_TRT=2 THEN C2=1;
  IF LAST_TRT=3 THEN C3=1;
END;
LAST_TRT=TRT;
run;
PROC CLM DATA=C;
TITLE3 'Analysis Adjusted for Carryover Effects';
TITLE4 'Overparameterized Model';
CLASSES SEQUENCE SUBJECT PERIOD TRT;
MODEL Y = SEQUENCE SUBJECT(SEQUENCE) PERIOD TRT C1 C2 C3 SEQUENCE*TRT;
TEST H=SEQUENCE E=SUBJECT(SEQUENCE);
run;
CONTRAST 'CARRYOVER' C1 1 C2 -1 C3 0,

```

```

          C1  1 C2  0 C3 -1;
CONTRAST 'C1-C2' C1  1 C2 -1 C3  0;
CONTRAST 'C1-C3' C1  1 C2  0 C3 -1;
CONTRAST 'C2-C3' C1  0 C2  1 C3 -1;
CONTRAST 'C1-CBAR' C1  2 C2 -1 C3 -1;
CONTRAST 'C2-CBAR' C1 -1 C2  2 C3 -1;
CONTRAST 'C3-CBAR' C1 -1 C2 -1 C3  2;
ESTIMATE 'C1-C2' C1  1 C2 -1 C3  0;
ESTIMATE 'C1-C3' C1  1 C2  0 C3 -1;
ESTIMATE 'C2-C3' C1  0 C2  1 C3 -1;
ESTIMATE 'C1-CBAR' C1  2 C2 -1 C3 -1 / DIVISOR=3;
ESTIMATE 'C2-CBAR' C1 -1 C2  2 C3 -1 / DIVISOR=3;
ESTIMATE 'C3-CBAR' C1 -1 C2 -1 C3  2 / DIVISOR=3;
MEANS TRT / LSD;
LSMEANS TRT / STDERR PDIFF;
run;
quit;
PROC GLM DATA=C;
TITLE3 'Analysis Adjusted for One-Period Carryover';
TITLE4 'Overparameterized Model';
CLASSES SEQUENCE SUBJECT PERIOD TRT;
MODEL Y = SEQUENCE SUBJECT(SEQUENCE) PERIOD TRT C1 C2 C3;
TEST H=SEQUENCE E=SUBJECT(SEQUENCE);
run;
CONTRAST 'CARRYOVER' C1  1 C2 -1 C3  0,
          C1  1 C2  0 C3 -1;
CONTRAST 'C1-C2' C1  1 C2 -1 C3  0;
CONTRAST 'C1-C3' C1  1 C2  0 C3 -1;
CONTRAST 'C2-C3' C1  0 C2  1 C3 -1;
CONTRAST 'C1-CBAR' C1  2 C2 -1 C3 -1;
CONTRAST 'C2-CBAR' C1 -1 C2  2 C3 -1;
CONTRAST 'C3-CBAR' C1 -1 C2 -1 C3  2;
ESTIMATE 'C1-C2' C1  1 C2 -1 C3  0;
ESTIMATE 'C1-C3' C1  1 C2  0 C3 -1;
ESTIMATE 'C2-C3' C1  0 C2  1 C3 -1;
ESTIMATE 'C1-CBAR' C1  2 C2 -1 C3 -1 / DIVISOR=3;
ESTIMATE 'C2-CBAR' C1 -1 C2  2 C3 -1 / DIVISOR=3;
ESTIMATE 'C3-CBAR' C1 -1 C2 -1 C3  2 / DIVISOR=3;
MEANS TRT / LSD;
LSMEANS TRT / STDERR PDIFF;
run;
quit;
DATA D; SET B; BY SEQUENCE SUBJECT;
RETAIN N MEAN;
IF FIRST.SUBJECT THEN DO;
  N=0; MEAN=0;
END;
N=N+1;
MEAN=MEAN+Y;
IF PERIOD=3 THEN DO;
  MEAN=MEAN/N;
  IF TRT=1 THEN DO; L1=0; L2=1/3; L3=1/3; END;
  ELSE IF TRT=2 THEN DO; L1=1/3; L2=0; L3=1/3; END;
  ELSE IF TRT=3 THEN DO; L1=1/3; L2=1/3; L3=0; END;
OUTPUT;

```

```
END;
run;
PROC GLM DATA=D;
TITLE3 'Between Subject Estimation of One-Period Carryover Effects';
MODEL MEAN=L1 L2 L3 / SOLUTION;
run;
CONTRAST 'CARRYOVER' L1 1 L2 -1 L3 0 ,
          L1 1 L2 0 L3 -1;
CONTRAST 'L1-L2' L1 1 L2 -1 L3 0;
CONTRAST 'L1-L3' L1 1 L2 0 L3 -1;
CONTRAST 'L2-L3' L1 0 L2 1 L3 -1;
ESTIMATE 'L1-L2' L1 1 L2 -1 L3 0;
ESTIMATE 'L1-L3' L1 1 L2 0 L3 -1;
ESTIMATE 'L2-L3' L1 0 L2 1 L3 -1;
run;
quit;
```

Appendix C


```

title1 'Power Analysis';

%let trt=%str( 5, 5, 6);
%let carry=%str(-1, -1, 2);
%let var=1.0;
%let alpha=0.05;

option nodate nonumber ls=72 ps=58 missing= ' ';
proc format;
value t_code 1='Unadjusted Treatment'
              2='Adjusted Treatment'
              3='Carryover'
              4='Sequence by Treatment';
value $d_code '0'='Latin Square'
              '*='='Williams Square';

run;
data a;
var = &var;
alpha = &alpha;
input test num_df ws ls;
label='0';
n_seq = 3;
n_per = 3;
n_trt = 3;
if ls ne 0.0 then do n_subj = 2 to 40 by 2;
n_total = n_seq*n_subj;
err_df = n_total*(n_trt-1) - (n_per-1) - 2*(n_trt-1);
lambda = n_subj*ls/var;
if lambda gt 44.0 then lambda=44.0;
f = finv((1.0-alpha),num_df,err_df,0);
power = 1-probf(f,num_df,err_df,lambda);
if lambda=44.0 then power = 1.0;
output;
end;
label='*';
n_seq = 6;
n_per = 3;
n_trt = 3;
if ws ne 0.0 then do n_subj = 1 to 20;
n_total = n_seq*n_subj;
resid_df = (n_seq-1)*(n_trt-1) - (n_per-1) - (n_trt-1);
err_df = n_total*(n_trt-1) - (n_per-1) - 2*(n_trt-1);
if test eq 4 then err_df = err_df - resid_df;
lambda = n_subj*ws/var;
if lambda gt 44.0 then lambda=44.0;
f = finv((1.0-alpha),num_df,err_df,0);
power = 1-probf(f,num_df,err_df,lambda);
if lambda=44.0 then power = 1.0;
output;
end;
keep test label n_total power;

* test 1='Unadjusted Treatment'
      2='Adjusted Treatment'
      3='Carryover'

```

```

4='Sequence by Treatment';

cards;
1 2
2 2
3 2
4 6
run;
data a1; set a;
if test=1;
rename power=unadj;
run;
data a2; set a;
if test=2;
rename power=adj;
run;
data a3; set a;
if test=3;
rename power=carry;
run;
data a4; set a;
if test=4;
rename power=seq_trt;
run;
data aa; merge a1 a2 a3 a4;
by label n_total notsorted;
run;
proc print split='*' data=aa; by label notsorted;
title1 'Table #';
title3 'Power of Detecting Specified Effect';
title5 " Treatment Means: &trt";
title6 "Carryover Effects: &carry";
title7 " Variance = &var, Alpha = &alpha";
id label;
var n_total unadj adj carry seq_trt;
label label='Experimental*Design*-----'
n_total='Total*Subjects*-----'
unadj='Unadjusted*Treatment*-----'
adj='Adjusted*Treatment*-----'
carry='Carryover*-----'
seq_trt='Sequence by*Treatment*-----';
format label $d_code. unadj adj carry seq_trt 6.4;
run;
proc plot data=a nolegend; by test;
title1 'Figure #';
title3 'Power of Detecting Specified Effect';
title5 " Treatment Means: &trt";
title6 "Carryover Effects: &carry";
title7 " Variance = &var, Alpha = &alpha";
title9 'Legend: 0 = Latin Square Design ';
title10 ' * = Williams Square Design';
plot power*n_total=label / vaxis=0.0 to 1.0 by .2;
label power='Power'
n_total='Total Number of Subjects';
format test t_code.;

```

run;
quit;

ANALYSIS OF A WILLIAMS SQUARE SEQUENCE STRUCTURE

by

Joyce E. Little

B.S., Kansas State University, 1986

AN ABSTRACT OF A REPORT

submitted in partial fulfillment of the

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When different treatments are applied in succession to the same subject, it is necessary to determine if there is carryover effect, an effect of the preceding treatment on the current treatment. A Williams square sequence structure, which is balanced for one-period carryover effects, is defined with a discussion of a detailed analysis using the SAS system. A power analysis shows that experiments using the Williams square sequence structure are more powerful than experiments using the Latin square sequence structure for detecting adjusted treatment differences and differential carryover effects where each experiment utilizes the same total number of subjects.