SAMPLE SIZE CALCULATION WHEN HIGH DOSE CANNOT BE
ADMINISTERED FIRST IN A THREE-PERIOD CROSSOVER DESIGN

A Thesis
Presented to the
Faculty of
San Diego State University

In Partial Fulfillment
of the Requirements for the Degree
Master of Science in Statistics
with a Concentration in
Biostatistics

by
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Spring 2015
SAN DIEGO STATE UNIVERSITY

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Three-Period Crossover Design

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11/01/2014
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ABSTRACT OF THE THESIS

Sample Size Calculation When High Dose Cannot be Administered First in a Three-Period Crossover Design

by

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Master of Science in Statistics with a Concentration in Biostatistics
San Diego State University, 2015

We derive a sample size calculation formula for a three-treatment three-period crossover design with continuous outcomes and with restriction on treatment sequences that lower dose must be administered prior to higher dose of a drug. The three-period crossover is defined by these three sequences, $D_0 \rightarrow D_1 \rightarrow D_2$, $D_1 \rightarrow D_0 \rightarrow D_2$ and $D_1 \rightarrow D_2 \rightarrow D_0$, where $D_0$, $D_1$ and $D_2$ are referred to as placebo, the low dose and the high dose, respectively.

Appropriate contrast coefficients are derived for model 1 without carry-over effect, and for model 2 with carry-over effect as well. Based on these coefficients, the unbiased contrast variances are estimated and a sample size formula is derived in terms of hypothesis testing with normal distribution of assumption. Parameters introduced for sample size calculation include contrast coefficients, the number of contrasts, the desired differences of treatment effects, and common within-subject variance.

Using the developed formula, we calculate the minimum sample size required for determining the differences between treatment effects for models with or without carry-over. Further, Monte Carlo simulations are carried out to evaluate the performance of this formula. The results show that the formula can work well to achieve desired power for model 1 and model 2. Finally, the formula is demonstrated in an example of comparing Tacrine at the low dose (40mg/day) and the high dose (80mg/day) with a zero dose (placebo).
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ACKNOWLEDGEMENTS

I would like to thank professor Kung-Jong Lui, my supervisor for his support and guidance which made completion of this degree possible. Also thanks to my thesis committee members, professor Chii-Dean Lin and professor John E. Alcaraz for their support and help. Special thanks to my husband Lujian, my mother Fuzhen and my kids Antony and Annabelle for their support and encouragements.
CHAPTER 1

INTRODUCTION

1.1 CROSSOVER DESIGN

A crossover trial is defined by Senn [1] as that subjects are given sequences of treatments with the object of studying differences between individual treatments. That is, a crossover design is applied to compare responses of the same subject to different treatments, which is distinguished from other designs applied to compare the effects of treatments. The two-treatment two-period or $2 \times 2$ trial is the simplest and the most common crossover design, in which each subject receives consecutively two different treatments. Approximately half of the subjects receive treatment $A$ first and then cross over to treatment $B$, whereas the rest of the subjects receive $B$ first and then cross over to $A$ [2]. A crossover design is deemed as an appropriate study to compare the treatment effects on patients with chronic diseases including angina, asthma, rheumatism, migraine, cancer chemotherapy, hypertension, and epilepsy [3-6]. When compared with parallel group trials, crossover trials are expected to recruit fewer subjects to obtain the same number of observations, and require fewer observations to achieve the same precision in estimation [1]. Garcia et al. [4] have pointed out that a cross-over design is expected to recruit 4-10 times less subjects than the corresponding parallel design to obtain the same power. Jones and Lewis [7] argued “crossover trials remain a potentially valuable research tool in the development of new medicines at all stages including phase III”.

The carry-over, also known as residual effect, which is defined as that the effect of a treatment given in one period is still present at the following period, is a potential problem and is commonly concerned when a crossover design is applied. The carry-over can change the effect of the following treatment so that it’s no longer accurate. Therefore, a washout period is often applied between treatments in a trial to eliminate the impact of carry-over effect. Additionally, Grizzle [8] recommended that carry-over effects needed to be pre-tested when a researcher was analyzing data from crossover designs, and only the data from the first period would be analyzed just like doing a parallel study if the carry-over effects were
significant. However, Freeman [9] has shown that this method leads to bias, and Senn and Potvin [10] did not recommend a testing of carry-over effect before choosing an analysis method. In this thesis, we consider two models, one without carry-over effects, and the other with carry-over effects.

1.2 Dose-Response Study

Approaches to dose-response studies have been discussed (see ref. [11, 12]), and a variety of methods have been also adopted to statistically analyze these dose-response designs [13]. Dose-response studies are conducted typically using parallel designs but sometimes using crossover designs in clinical research, especially in phase I and early phase II studies, because fewer subjects are required [14]. The sample size is important in clinical trials due to ethical issue, and we therefore aim to find out which dose of a drug is superior after studying the minimum number of patients.

In clinical trials, the treatments usually consist of a series of doses of a drug, and the lowest dose (or a zero dose) is often a placebo. A number of different doses are compared to the placebo control to determine the minimally effective dose of a drug. Williams [15, 16] has discussed the determination of the lowest dose level at which there is evidence of a dose response. In general, three doses, including a placebo control, the lower dose and the higher dose of a drug, are studied in many trials. Since the higher dose is more likely to be associated with stronger side effects, an investigator may be not willing to administer the higher dose to a patient before observing the response of the lower dose of a new drug on the patient with safety concerns. In the present study, we are interested in the development of a sample size calculation formula for detecting the differences between dose effects in a particular three-treatment three-period crossover design where the low dose must be administered before the high dose. Lui and Chang [17] have derived asymptotic test procedures for testing equality between treatments, and interval estimators to assess the relative treatment effects in this special crossover design with binary outcomes.

1.3 Contrast Analysis and Contrast Coefficients

A contrast is a weighted linear function of means or occasionally other statistics, and whose coefficients (or weights) must have a zero sum [18]. An ANOVA provides an F-test (or called an omnibus test); while contrasts provide an important alternative to F-test with
pairwise comparisons, and each pairwise comparison is a contrast. For this approach, there are debates in some articles [19-22]. The contrast strategy is widely used in dose response detection since it is not restricted by any particular model, in other words, other factors can be modeled in order to increase the efficiency of the analysis [23, 24]. Contrast analysis can deliver precise conclusions for the specific questions that investigators are interested in, and contrast coefficients reflect the prediction [25]. For example, Williams' test [15, 16] and Dunnett's test [26] are using contrast procedures to analyze dose responses.

Contrasts consist of planned and post hoc contrasts. The planned or priori contrasts are selected before a study is started. By contrast, the post hoc or posteriori contrasts are decided after a study has been carried out. In the present study, we wish to calculate sample size for detecting a desire difference between doses, planned contrasts are therefore selected. Furthermore, all contrasts here are non-orthogonal, which means that their contrast coefficients are correlated. When testing several hypotheses expressed as contrasts, non-orthogonal contrasts are much more complicated than orthogonal contrasts. We apply the classical approach, which evaluates each non-orthogonal contrast as if it is from orthogonal contrasts, to correct for the multiple testing.

1.4 Sample Size Determination for Crossover Trial

Jones and Kenward [2] developed the formula of sample size determination for simple AB/BA crossover trials when observations were considered being normally distributed. However, it’s not an appropriate formula applied in a three-treatment three-period crossover design with three sequences. In the present study, we derive appropriate contrast coefficients (weights) to calculate weighted sums of cells and achieve unbiased variances with consideration of that the expected outcome differences include treatment, subject, period, and/or carry-over effects. We propose a procedure for sample size calculation under normal distribution assumption and then perform Monte Carlo simulations to demonstrate this procedure.

As an example, Parke-Davis Pharmaceutical Research Division performed a three-treatment three-period crossover design and measured the cognitive component of the Alzheimer’s dementia scale (ADAS-Cog). If wanting to carry out a similar study, we need
an estimate of how many minimal subjects to study in order to detect a desired difference between treatment effects.
CHAPTER 2

THEORETICAL ISSUES

2.1 STATISTICAL MODEL

A three-treatment three-period crossover design with three sequences represented schematically in Table 2.1 is applied to demonstrate treatment effects. We assume that patients are equally and randomly assigned to three sequences: \( D_0 \rightarrow D_1 \rightarrow D_2 \), \( D_1 \rightarrow D_0 \rightarrow D_2 \) and \( D_1 \rightarrow D_2 \rightarrow D_0 \), where \( D_0 \), \( D_1 \) and \( D_2 \) denote placebo, the low dose and the high dose respectively, for example, sequence \( D_0 \rightarrow D_1 \rightarrow D_2 \) denotes \( n \) patients receive treatment \( D_0 \) (or placebo) at period 1, treatment \( D_1 \) (or the low dose) at period 2 and then treatment \( D_2 \) (or the high dose) at period 3. A total of \( 3n \) patients are recruited in the trial. According to whether carry-over effects are considered or not, two models are generated for this crossover trial.

Table 2.1. The Three-Treatment Three-Period Crossover Design

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( D_0 )</td>
<td>( D_1 )</td>
<td>( D_2 )</td>
</tr>
<tr>
<td>2</td>
<td>( D_1 )</td>
<td>( D_0 )</td>
<td>( D_2 )</td>
</tr>
<tr>
<td>3</td>
<td>( D_1 )</td>
<td>( D_2 )</td>
<td>( D_0 )</td>
</tr>
</tbody>
</table>

Note: \( D_0 \)=Placebo, \( D_1 \)= the low dose, \( D_2 \)= the high dose.

2.1.1 The Model without Carry-Over Effects

In order to achieve an unbiased estimator of treatment effects, we assume the following model 1 holds:

\[
Y_{gjz} = \mu + S_{gj} + \pi_2 P_{gj2} + \pi_3 P_{gj3} + \tau_1 T_{gj1} + \tau_2 T_{gj2} + \epsilon_{gjz}
\]  (2.1)

with an assumption that \( \epsilon_{gjz} \) is independent and \( \sim N (0, \sigma^2) \). \( Y_{gjz} \) is the measurement made on the \( j \)th (=1, 2, ..., \( n \)) patient in the \( g \)th (=1, 2, 3) sequence at period \( z \) (=1, 2, 3). \( \mu \) is the mean of placebo-treated subjects in the first period. \( S_{gj} \) is considered random subject effect and assumed to be independently and identically distributed as normal probability density with
mean 0 and variance \( \sigma^2 \). \( P_{gj2} \) and \( P_{gj3} \) are the indicator variables of periods, and \( P_{gj2}=1 \) at period 2, and =0, otherwise; \( P_{gj3}=1 \) at period 3, and =0, otherwise. \( \pi_2 \) and \( \pi_3 \) denote the effects of period 2 and period 3 compared to period 1 respectively. \( T_{gj1} \) and \( T_{gj2} \) are the indicator variables of treatments, and \( T_{gj1}=1 \) if the \( j \)th patient in the \( g \)th sequence at period \( z \) receives the low dose, and =0, otherwise; and \( T_{gj2}=1 \) if the \( j \)th patient in the \( g \)th sequence at period \( z \) receives the high dose, and =0, otherwise. \( \tau_1 \) and \( \tau_2 \) denote the effects of the low dose and the high dose compared to placebo respectively. \( \varepsilon_{gj} \) is the within-patient random measurement error.

### 2.1.2 The Model with Carry-Over Effects

When we are considering that carry-over effect exists, model 2 holds:

\[
Y_{gjz} = \mu + S_g + \pi_2 P_{gj2} + \pi_3 P_{gj3} + \tau_1 T_{gj1} + \tau_2 T_{gj2} + \gamma_1 C_{gj1} + \gamma_2 C_{gj2} + \varepsilon_{gjz} \tag{2.2}
\]

where, \( C_{gj1} \) and \( C_{gj2} \) are the indicator variables of carry-over effects, and \( C_{gj1}=1 \) if the \( j \)th patient in the \( g \)th sequence at period \((z-1)\) receives the low dose, and =0, otherwise; and \( C_{gj2}=1 \) if the \( j \)th patient in the \( g \)th sequence at period \((z-1)\) receives the high dose, and =0, otherwise. \( \gamma_1 \) and \( \gamma_2 \) denote the carry-over effects of the low dose and the high dose compared to placebo respectively.

### 2.2 Derivation of Contrast Coefficients

In the present study, a contrast, usually reflecting the hypotheses researchers want to test, is defined as a linear combination of contrast coefficients and cell means (symbolized in Table 2.2) of the design. \( \bar{y}_{g+z} \) denotes the mean of response observed in the \( g \)th sequence at period \( z \) with \( g=1, 2, 3 \) and \( z=1, 2, 3 \).

<table>
<thead>
<tr>
<th>Table 2.2. Subject Means in Each Period and Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence</td>
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<tr>
<td>----------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>
Contrasts $\psi_1$, $\psi_2$, and $\psi_3$ are the comparisons of the low dose with placebo, the high dose with placebo, and the high dose with the low dose, respectively. To conduct hypothesis tests for treatment effects, appropriate coefficients need to be developed. The coefficients ($k_1$ to $k_9$) for nine cell means are set out as follows.

\[
\begin{array}{ccc}
  k_1 & k_2 & k_3 \\
  k_4 & k_5 & k_6 \\
  k_7 & k_8 & k_9 \\
\end{array}
\]

Suppose that we are interested in analyzing the contrast $\psi_1$, the comparison of the low dose (or $D_1$) to placebo (or $D_0$). The contrast coefficients in each column have to be added to zero if the period effects need to be eliminated. Similarly, the coefficients along each row should be added to zero if we want to get rid of the effects of subjects [1]. We can thus write the coefficients like these following:

\[
\begin{array}{ccc}
  k_1 & k_2 & -k_1-k_2 \\
  k_4 & k_5 & -k_4-k_5 \\
- k_1-k_4 & - k_2-k_5 & k_1+k_2+k_4+k_5 \\
\end{array}
\]

In addition, if we want to detect the difference in effects between the low dose (or $D_1$) and placebo (or $D_0$), the sum of the coefficients related to $D_1$ must equal 1, so $k_2 + k_4 + (-k_1-k_4) = 1$, and then we get:

\[
k_2 = 1 + k_1 \quad \text{(2.3)}
\]

Also, the sum of the coefficients related to $D_0$ must equal -1, so $2k_1+2k_5 + k_2 + k_4 = -1$, and then we get:

\[
k_2 = -1 - 2k_1 - 2k_5 - k_4 \quad \text{(2.4)}
\]

When equation (2.3) is introduced to equation (2.4), we get $k_4 = -3k_1-2k_5-2$, and may write the coefficients as follows.

\[
\begin{array}{ccc}
  k_1 & 1 + k_1 & -1 - 2k_1 \\
-3k_1-2k_5-2 & k_5 & 3k_1+k_5+2 \\
2+2k_1+2k_5 & -1-k_1-k_5 & -1-k_1-k_5 \\
\end{array}
\]
2.2.1 Contrast Coefficients for the Model without Carry-Over Effect

Assuming that there are no carry-over effects when an adequate washout is applied, and thus the sum of coefficients associated with $D_0$ and $D_1$ (in parenthesis) in sequence $D_0 \rightarrow D_1 \rightarrow D_2$ equals that in sequence $D_1 \rightarrow D_0 \rightarrow D_2$.

\[
\begin{array}{ccc}
  k_1 (D_0) & 1+k_1 (D_1) & -1-2k_1 \\
-3k_1-2k_5-2 (D_1) & k_5 (D_0) & 3k_1+k_5+2 \\
2+2k_1+2k_5 & -1-k_1-k_5 & -1-k_1-k_5 \\
\end{array}
\]

That is, $k_1+(1+k_1)= (-3k_1-2k_5-2)+k_5$, and then

\[ k_5 = -5k_1-3 \tag{2.5} \]

Also, the sum of coefficients associated with $D_0$ and $D_2$ (in parenthesis) in sequence $D_1 \rightarrow D_0 \rightarrow D_2$ equals that in sequence $D_1 \rightarrow D_2 \rightarrow D_0$.

\[
\begin{array}{ccc}
  k_1 & 1+k_1 & -1-2k_1 \\
-3k_1-2k_5-2 & k_5(D_0) & 3k_1+k_5+2 (D_2) \\
2+2k_1+2k_5 & -1-k_1-k_5 (D_2) & -1-k_1-k_5 (D_0) \\
\end{array}
\]

That is, $k_5+(3k_1+k_5+2) = (-1-k_1-k_5)+(1-k_1-k_5)$, and then

\[ 4k_5 = -5k_1-4 \tag{2.6} \]

We introduce equation (2.5) into equation (2.6) to get $k_1 = -8/15$, $k_5 = -5/15$.

Now, the actual values of coefficients for the contrast $\psi_1$ are established. Similarly, we can get values of coefficients for the contrasts $\psi_2$ and $\psi_3$, the comparisons of the high dose (or $D_2$) to placebo (or $D_0$) and of the high dose (or $D_2$) to the low dose (or $D_1$) respectively, which are shown in Table 2.3. These values of coefficients are identical to the contrast constants Peace and Koch [14] developed.

2.2.2 Contrast Coefficients for the Model with Carry-Over Effect

Assuming that there exist carry-over effects, a schema of the three-period crossover design is shown in Table 2.4. The letters in parentheses correspond to simple carry-over.
Table 2.3. The Values of Contrast Coefficients in the Three-Treatment Crossover Design without Carry-Over Effect

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Sequence</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\psi_1$</td>
<td>1</td>
<td>-8/15</td>
<td>7/15</td>
<td>1/15</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4/15</td>
<td>-5/15</td>
<td>1/15</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4/15</td>
<td>-2/15</td>
<td>-2/15</td>
</tr>
<tr>
<td>$\psi_2$</td>
<td>1</td>
<td>-2/15</td>
<td>-2/15</td>
<td>4/15</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1/15</td>
<td>-5/15</td>
<td>4/15</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1/15</td>
<td>7/15</td>
<td>-8/15</td>
</tr>
<tr>
<td>$\psi_3$</td>
<td>1</td>
<td>6/15</td>
<td>-9/15</td>
<td>3/15</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-3/15</td>
<td>0</td>
<td>3/15</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>-3/15</td>
<td>9/15</td>
<td>-6/15</td>
</tr>
</tbody>
</table>

Table 2.4. The Three-Period Crossover Design with Carry-Over Effect

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$D_0$</td>
<td>$D_1 (D_0)$</td>
<td>$D_2 (D_1)$</td>
</tr>
<tr>
<td>2</td>
<td>$D_1$</td>
<td>$D_0 (D_1)$</td>
<td>$D_2 (D_0)$</td>
</tr>
<tr>
<td>3</td>
<td>$D_1$</td>
<td>$D_2 (D_1)$</td>
<td>$D_0 (D_2)$</td>
</tr>
</tbody>
</table>

When the carry-over effect is considered, the sum of coefficients related to the same letter in parentheses have to be zero, so that

$$-1-k_1-k_5 = 0$$  \hspace{1cm} (2.7)

and

$$(-1-2k_1)+k_5 + (-1-k_1-k_5) = 0$$  \hspace{1cm} (2.8)

After solving equations (2.7) and (2.8), we can get $k_1=-2/3$ and $k_5=-1/3$. We now establish the actual values of the coefficients for contrasts $\psi_1$, $\psi_2$ and $\psi_3$ shown in Table 2.5, which are also the same as the contrast constants developed by Peace and Koch [14].

**2.3 Sample Size Calculation**

We develop a formula of sample size calculation by use of contrast coefficients (or contrast weights) derived in 2.2. Multiple hypotheses will be tested when we wish to perform
Table 2.5. The Values of Contrast Coefficients in the Three-Treatment Crossover Design with Carry-Over Effect

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Sequence</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\psi_1$</td>
<td>1</td>
<td>-2/3</td>
<td>1/3</td>
<td>1/3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2/3</td>
<td>-1/3</td>
<td>-1/3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$\psi_2$</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>-1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>$\psi_3$</td>
<td>1</td>
<td>2/3</td>
<td>-1/3</td>
<td>-1/3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1/3</td>
<td>-2/3</td>
<td>1/3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>-1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Multiple comparisons such as $D_1-D_0$, $D_2-D_0$, and $D_2-D_1$. If individual tests are carried out at Type I error rate of $\alpha (=0.05)$, the probability to falsely reject a true null hypothesis will be extremely high when thousands of tests are conducted at this error rate (see [18] for more information). Therefore, a correction or adjustment should be done to avoid high false positive rate.

### 2.3.1 Bonferroni Correction

In the following contrast analyses, we decide the total number of tests first, and then carry out Bonferroni corrections, the most conservative method for error rate adjustment [27], for these non-orthogonal priori contrasts derived in 2.2. Here, we test three contrasts and evaluate each contrast at Type I error of $0.05/(2*3)=0.0083$ and of $0.1/(2*3)=0.0167$ respectively[25].

### 2.3.2 Normal Distribution Hypothesis Testing Procedure

Before calculating sample size of a trial, we have to decide what type of analysis will be used, and to choose values of Type I error as well as the desired power and relative difference size. Suppose that we want to study whether there is a difference in effects between doses by testing the null hypothesis $H_0: \psi_l=0$, against $H_1: \psi_l \neq 0$, $l=1, 2, 3$, and a
normal distribution hypothesis testing procedure is applied. A large sample size is assumed, so that \( \hat{\psi}_i / \sqrt{\text{var}(\hat{\psi}_i)} \sim N(0, 1) \) for null hypothesis. We may reject null hypothesis at the \( \alpha \) level (two-sided) if either of the following two inequalities holds:

\[
\hat{\psi}_i / \sqrt{\text{var}(\hat{\psi}_i)} \geq Z_{\alpha/2c} \text{ or } \hat{\psi}_i / \sqrt{\text{var}(\hat{\psi}_i)} \leq -Z_{\alpha/2c}
\]  

(2.9)

where, \( c \) denodes the number of contrasts we wish to test. The contrasts \( \psi_l \) can be estimated by combination of coefficients and cell means (symbolized in Table 2.2).

\[
\hat{\psi}_l = k_1\bar{y}_{1+1} + k_2\bar{y}_{1+2} + k_3\bar{y}_{1+3} + k_4\bar{y}_{2+1} + k_5\bar{y}_{2+2} + k_6\bar{y}_{2+3} + k_7\bar{y}_{3+1} + k_8\bar{y}_{3+2} + k_9\bar{y}_{3+3}
\]  

(2.10)

Assuming that there are \( n \) subjects per cell with common within-subject variance \( \sigma^2 \), and suppose that the cells between sequences are independent, but the cells in the same sequence are correlated, so that,

\[
cov(\bar{y}_{g+z}, \bar{y}_{g+z'}) = cov\left(\frac{\sum_{j=1}^{n} y_{g+jz}}{n}, \frac{\sum_{j=1}^{n} y_{g+jz'}}{n}\right) = \frac{\sum_{j=1}^{n} \sigma^2}{n^2} = \frac{\sigma^2}{n}
\]

where, \( g = 1, 2, 3; \) \( z = 1, 2, 3; \) \( z \neq z' \). We have defined that a contrast is a weighted linear function of means, thus, the variances of the contrasts \( \psi_l \) can be estimated with the variance-covariance matrix.

\[
\text{var}(\hat{\psi}_l) = \text{var}(k^\top Y) = k^\top Y k
\]

Since assuming that subjects between sequences are independent, the big matrix can be divided into three matrixes as

\[
\text{var}(\hat{\psi}_l) = (1/n)(([k_1 \quad k_2 \quad k_3] [\sigma^2 + \sigma_s^2 \quad \sigma_s^2 \quad \sigma_s^2 \quad \sigma_s^2 \quad \sigma_s^2]) [k_2]) + ([k_4 \quad k_5 \quad k_6] [\sigma_s^2 \quad \sigma^2 + \sigma_s^2 \quad \sigma_s^2 \quad \sigma_s^2 \quad \sigma_s^2] [k_5]) + ([k_7 \quad k_8 \quad k_9] [\sigma_s^2 \quad \sigma^2 + \sigma_s^2 \quad \sigma_s^2 \quad \sigma_s^2 \quad \sigma_s^2] [k_9])
\]

and then,
\[
\text{var}(\hat{\psi}_1) = \frac{1}{n}((k_1^2 \sigma^2 + k_2^2 \sigma^2 + k_3^2 \sigma^2 + k_4^2 \sigma^2 + k_5^2 \sigma^2 + k_6^2 \sigma^2 + k_7^2 \sigma^2 + k_8^2 \sigma^2 + k_9^2 \sigma^2) \\
+ (k_2 k_3 \sigma^2 + k_1 k_5 \sigma^2 + k_2 k_3 \sigma^2 + k_2 k_3 \sigma^2 + k_3^2 \sigma^2 + k_3^2 \sigma^2 + k_3^2 \sigma^2 + k_3 k_6 \sigma^2) \\
+ (k_4^2 \sigma^2 + k_5^2 \sigma^2 + k_4 k_6 \sigma^2 + k_4 k_5 \sigma^2 + k_5^2 \sigma^2 + k_5^2 \sigma^2 + k_5 k_6 \sigma^2) \\
+ (k_4 k_6 \sigma^2 + k_5 k_6 \sigma^2 + k_6^2 \sigma^2 + k_6^2 \sigma^2 + k_7^2 \sigma^2 + k_7^2 \sigma^2 + k_7 k_8 \sigma^2 + k_7 k_9 \sigma^2) \\
+ (k_7 k_8 \sigma^2 + k_7 k_9 \sigma^2 + k_8 k_9 \sigma^2 + k_8 k_9 \sigma^2 + k_9 k_9 \sigma^2 + k_9 k_9 \sigma^2 + k_9 \sigma^2 + k_9 \sigma^2))
\]

so that,
\[
\text{var}(\hat{\psi}_1) = \frac{1}{n}((k_1^2 \sigma^2 + k_2^2 \sigma^2 + k_3^2 \sigma^2 + (k_1 + k_2 + k_3)^2 \sigma^2) \\
+ (k_4^2 \sigma^2 + k_5^2 \sigma^2 + k_6^2 \sigma^2 + (k_4 + k_5 + k_6)^2 \sigma^2) + (k_7^2 \sigma^2 + k_8^2 \sigma^2 + k_9^2 \sigma^2) \\
+ (k_7 + k_8 + k_9)^2 \sigma^2))
\]

Since \(k_1 + k_2 + k_3 = 0, k_4 + k_5 + k_6 = 0, \) and \(k_7 + k_8 + k_9 = 0, \) then
\[
\text{var}(\hat{\psi}_1) = \frac{1}{n}((k_1^2 \sigma^2 + k_2^2 \sigma^2 + k_3^2 \sigma^2) + \\
(k_4^2 \sigma^2 + k_5^2 \sigma^2 + k_6^2 \sigma^2) + (k_7^2 \sigma^2 + k_8^2 \sigma^2 + k_9^2 \sigma^2))
\]

so that,
\[
\text{var}(\hat{\psi}_1) = \frac{1}{n} \Sigma_{i=1}^{9} k_i^2
\]

(2.11)

Based on equation (2.11) and contrast coefficients in Table 2.4 and Table 2.5, the variances of contrasts for estimating treatment effects can be obtained and shown in Table 2.6.

### Table 2.6. Variances of Contrasts for Estimating Treatment Effects

<table>
<thead>
<tr>
<th>Contrast</th>
<th>( \psi_1 )</th>
<th>( \psi_2 )</th>
<th>( \psi_3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Variance</td>
<td>(4\sigma^2/5n)</td>
<td>(4\sigma^2/3n)</td>
<td>(4\sigma^2/5n)</td>
</tr>
</tbody>
</table>

The power of the test is

\[
\text{power} = 1 - \beta = P\left(\frac{\hat{\psi}_1 - \delta}{\sqrt{\frac{\sigma^2}{n} \Sigma_{i=1}^{9} k_i^2}} > \frac{Z_{\alpha/2c}}{\sqrt{\frac{\sigma^2}{n} \Sigma_{i=1}^{9} k_i^2}}\right)
\]

(2.12)

In the alternative hypothesis, the difference \(\delta\) between treatments is assumed not to be zero.

We know

\[
1 - \beta = P\left(\frac{\hat{\psi}_1 - \delta}{\sqrt{\frac{\sigma^2}{n} \Sigma_{i=1}^{9} k_i^2}} > \frac{Z_{\alpha/2c}}{\sqrt{\frac{\sigma^2}{n} \Sigma_{i=1}^{9} k_i^2}}\right)
\]

(2.13)
Where, \( \frac{\varphi_{1} - \delta}{\sqrt{\left( \frac{\pi^2}{\alpha} \sum_{i=1}^{9} k_i^2 \right)}} \sim N(0,1) \), that is,

\[
-Z_\beta = \frac{Z_{\alpha} \sqrt{\left( \frac{\pi^2}{\alpha} \sum_{i=1}^{9} k_i^2 - \delta \right)}}{\sqrt{\left( \frac{\pi^2}{\alpha} \sum_{i=1}^{9} k_i^2 \right)}}
\]  

(2.14)

so that,

\[
n = \text{Ceil}\left\{ \frac{\left( \frac{Z_{\alpha} + Z_\beta}{\sqrt{\sigma^2 \sum_{i=1}^{9} k_i^2}} \right)^2}{\delta^2} \right\}
\]  

(2.15)

The required sample size \( n \) can be obtained by solving (2.14). The equation (2.15) is a formula to calculate the sample size per sequence which is required to detect difference (\( \delta \)) of treatment effects at two-sided \( \alpha \) per cent level with power of \( (1-\beta) \) per cent. \( \text{Ceil}\{x\} \) is the smallest integer \( \geq x \). \( Z_{\alpha} \) denotes the upper 100(\( \alpha \) )th percentile of the standard normal distribution. \( c \) is the number of contrasts that investigators wish to test, so that for \( \alpha=0.05 \), \( Z_{0.05} = 2.395 \) if \( c=3 \); for \( \beta=0.2 \), \( Z_{0.20} = 0.8416 \). \( \sigma^2 \) and \( k_i \) are the within-subject variance and contrast coefficients.

### 2.4 Monte Carlo Simulation

Suppose that parameters in the models are known, Monte Carlo simulation is applied to evaluate the performance of the proposed procedure in the present study. SAS codes (in Appendix) for simulation are generated based on the programs wrote by Lui [28], and normal distributions with the expected values of responses displayed in Table 2.7 and Table 2.8 are simulated respectively.

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \mu + S_{1j} )</td>
<td>( \mu + S_{1j} + \pi_2 + \tau_1 )</td>
<td>( \mu + S_{1j} + \pi_3 + \tau_2 )</td>
</tr>
<tr>
<td>2</td>
<td>( \mu + S_{2j} + \tau_1 )</td>
<td>( \mu + S_{2j} + \pi_2 )</td>
<td>( \mu + S_{2j} + \pi_3 + \tau_2 )</td>
</tr>
<tr>
<td>3</td>
<td>( \mu + S_{3j} + \tau_1 )</td>
<td>( \mu + S_{3j} + \pi_2 + \tau_2 )</td>
<td>( \mu + S_{3j} + \pi_3 )</td>
</tr>
</tbody>
</table>
According to a previous study [14], we consider $\mu = -0.5$; $\tau_1 = -0.2$; $\tau_2 = -1.0, -0.7, -0.4$. In addition, the relative period effects are more likely to be smaller than the relative treatment effects [28]. therefore, the period effect ($\pi_2$) of the second period compared to the first period is assumed to be -0.1; the period effect ($\pi_3$) of the third period compared to the first period is also -0.1. The relationship between variances and the intraclass correlation is that $\rho = \sigma_s^2 / (\sigma_s^2 + \sigma^2)[2]$, and then

$$\sigma^2 = \sigma_s^2 ((1-\rho)/\rho)$$

(2.16)

where $\sigma_s^2$ and $\sigma^2$ are the between-subject and the within-subject variances respectively.

According to the previous publication [28], we consider an intraclass correlation $\rho = 0.1, 0.5, 0.8$; sigmas (standard deviation $\sigma_s$) = 2.5, 3.5, 4.5. In terms of equation (2.16), sigma is calculated and shown in Table 2.9. Given these parameter values, we obtain the minimum number of patients $n$ per sequence to detect the difference $\delta$ between treatment effects with desired power (=$0.80$) when employing sample size calculation formula (2.15).

**Table 2.9. The Calculated Sigma $\sigma_s$**

<table>
<thead>
<tr>
<th>$\rho$</th>
<th>$\sigma_s$</th>
<th>$\sigma_s$</th>
<th>$\sigma_s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>7.50</td>
<td>10.50</td>
<td>13.50</td>
</tr>
<tr>
<td>0.5</td>
<td>2.50</td>
<td>3.50</td>
<td>4.50</td>
</tr>
<tr>
<td>0.8</td>
<td>1.25</td>
<td>1.75</td>
<td>2.25</td>
</tr>
</tbody>
</table>

In Monte Carlo simulation, observations ($y_{giz}$) are drawn from normal distributions. For example, in model 1, $y_{1j3}$ is drawn from a normal distribution $(\mu + S_{1j} + \pi_3 + \tau_2, \sigma^2)$; while the expectation $E(y_{1j3}) = \mu + S_{1j} + \pi_3 + \tau_2$, shown in Table 2.7. In each iteration, $n$ samples are
drawn, the contrasts \( \tilde{\psi}_1 = k_1(\sum_j y_{1j1}/n) + k_2(\sum_j y_{1j2}/n) + k_3(\sum_j y_{1j3}/n) + k_4(\sum_j y_{2j1}/n) + k_5(\sum_j y_{2j2}/n) + k_6(\sum_j y_{2j3}/n) + k_7(\sum_j y_{3j1}/n) + k_8(\sum_j y_{3j2}/n) + k_9(\sum_j y_{3j3}/n) \). The common within-variance \( \sigma^2 \) is estimated in terms of the variance \( (\sigma_D^2) \) of the sum of the difference between periods. Now, we estimate the pooled \( \sigma_D^2 \). For model 1, carry-over effect is not considered, then the period differences are:

- \( d_{121} = y_{1j2} - y_{1j1} \) for the \( j \)th subject in the first sequence
- \( d_{212} = y_{2j1} - y_{2j2} \) for the \( j \)th subject in the second sequence
- \( d_{313} = y_{3j1} - y_{3j3} \) for the \( j \)th subject in the third sequence

the variance \( (\sigma_D^2) \) can be estimated via

\[
\text{var}(\tilde{d}_{g+1} + \tilde{d}_{g+2}) = \left( \frac{1}{3(n-1)} \right) \left( \sum_{j=1}^{n} ((d_{121j} + d_{131j}) - (\tilde{d}_{121} + \tilde{d}_{131}))^2 + \sum_{j=1}^{n} ((d_{212j} + d_{232j}) - (\tilde{d}_{212} + \tilde{d}_{232}))^2 + \sum_{j=1}^{n} ((d_{313j} + d_{323j}) - (\tilde{d}_{313} + \tilde{d}_{323}))^2 \right)
\]

Also,

\[
\text{var}(\tilde{d}_{g+1} + \tilde{d}_{g+2}) = 2\sigma^2 + 2\sigma^2 + \text{cov}(\tilde{d}_{g+1}, \tilde{d}_{g+2}) = 2\sigma^2 + 2\sigma^2 + 2\text{cov}(\tilde{d}_{g+1}, \tilde{d}_{g+2})
\]

\[
= 2\sigma^2 + 2\sigma^2 + 2\text{cov}(\tilde{y}_{g+2} - \tilde{y}_{g+1}, \tilde{y}_{g+3} - \tilde{y}_{g+1}) = 2\sigma^2 + 2\sigma^2 + 2(\sigma_s^2 - \sigma_s^2 - \sigma_s^2 + \sigma^2) = 6\sigma^2
\]

Therefore, and \( \sigma^2 \) can be calculated via \( \sigma^2 = (1/6)\sigma_D^2 = (1/6)((\sum_j(\sum_{j=1}^{n} (d_{121j} + d_{131j}))^2/(\sum_j(\sum_{j=1}^{n} (d_{121j} + d_{131j}))))^2/(n)) + (\sum_j(\sum_{j=1}^{n} (d_{212j} + d_{232j}))^2/(\sum_j(\sum_{j=1}^{n} (d_{212j} + d_{232j}))))^2/(n)) + (\sum_j(\sum_{j=1}^{n} (d_{313j} + d_{323j}))^2/(\sum_j(\sum_{j=1}^{n} (d_{313j} + d_{323j}))))^2/(n)) / (3(n-1)) \). The variance of the estimated contrasts is obtained by equation (2.11), \( Z \) equals the ratio of the estimated contrast \( \psi_l \) and the standard error of the estimated \( \psi_l \). If \( Z \geq 2.359 \) or \( Z \leq -2.359 \), then we reject \( H_0: \psi_l = 0 \). We generate 10000 iterations to simulate contrasts \( \psi_l \) and the common within-variance \( \sigma^2 \). The corresponding powers with the desired values of
parameters are calculated in terms of how many times null hypothesis $H_0$ is rejected in 10000 iterations, and the results are presented in Table 2.10 for model 1 and model 2.

2.5 AN EXAMPLE

Peace and Koch [14] developed methods to analyze the Tacrine dataset which produced by Parke-Davis Pharmaceutical Research Division of Warner Lambert Company (Committee Meeting, 1991). In this thesis, we adopt the descriptive statistics presented by Pearce and Koch [14] to demonstrate the proposed formula. Parke-Davis Pharmaceutical Research Division performed a double blind and placebo controlled crossover design that is scale (ADAS-Cog) was observed as continuous outcome. The formula derived in the present study assumes that sequences are balanced, and outcomes are normally distributed, we thus just consider the balanced dataset cell means of change from baseline in ADAS-Cog, which are organized in Table 2.11 and Table 2.12, referred from Peace and Koch [14]. From these descriptive statistics, we obtain some knowledge about differences of treatment effects and standard deviations.

Pearce and Koch in their article [14] have demonstrated that the carry-over effects are not significant, so the model 1 without carry-over effect is applied reasonably for sample size determination. We want to determinate the minimum number $n$ of patients per sequence needed to achieve the desired power (80%) to detect -0.90, -0.88, -0.86 of the differences between the high dose of Tacrine and placebo. Since the variance of contrast $\psi_2$ is 0.218, we consider that sigma (standard deviation $\sigma$) is from 2.75 to 3.25. Since the between-subject variance is usually far greater than within-subject variance [2], we consider sigmas = 5.5, 6.0, 6.5, and there is a large intraclass correlation $\rho$ between subjects with value of 0.8. Additionally, Pearce and Koch have found the period effect of $P_{gj2}$ compared to $P_{gj1}$ is not significant, we consider $\pi_2=0$. Using these values, Monte Carlo simulations with 10000 iterations are performed to estimate minimum sample size and the correspond power. The simulation results show that $n$ is approximately from 79 to 120 with the correspond power close to the desire power. According to the descriptive statistics of the Tacrine dataset in Table 2.11 & 2.12, we assume parameters $\tau_1=-0.13$, $\tau_2=-0.88$, and sigma=3.0. In order to detect -0.88 of the difference of contrast $\psi_2$, the minimum required number $n$ per sequence is
Table 2.10. The Calculated Minimum Sample Size n per Sequence Required to Detect the Differences Between Treatment Effects for a Power of 0.8 Using the Developed Formula for Model 1 & 2, and the Simulated Corresponding Power (in Parenthesis)

<table>
<thead>
<tr>
<th>Contrast</th>
<th>ρ</th>
<th>δ</th>
<th>Sigmas</th>
<th>Model 1 without Carry-Over Effect</th>
<th>Model 2 with Carry-Over Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.5</td>
<td>3.5</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>0.1</td>
<td>-0.3</td>
<td>5240(0.820)</td>
<td>10269(0.808)</td>
<td>16975(0.801)</td>
<td>8732(0.807)</td>
</tr>
<tr>
<td></td>
<td>-0.2</td>
<td>11788(0.788)</td>
<td>23105(0.780)</td>
<td>38193(0.792)</td>
<td>19647(0.773)</td>
</tr>
<tr>
<td></td>
<td>-0.1</td>
<td>47152(0.797)</td>
<td>92418(0.804)</td>
<td>153E3(0.793)</td>
<td>78587(0.774)</td>
</tr>
<tr>
<td>0.5</td>
<td>-0.3</td>
<td>583(0.775)</td>
<td>1141(0.803)</td>
<td>1887(0.797)</td>
<td>971(0.803)</td>
</tr>
<tr>
<td></td>
<td>-0.2</td>
<td>1310(0.784)</td>
<td>2568(0.826)</td>
<td>4244(0.810)</td>
<td>2183(0.780)</td>
</tr>
<tr>
<td></td>
<td>-0.1</td>
<td>5240(0.792)</td>
<td>10269(0.784)</td>
<td>16975(0.779)</td>
<td>8732(0.803)</td>
</tr>
<tr>
<td>0.8</td>
<td>-0.3</td>
<td>146(0.790)</td>
<td>286(0.785)</td>
<td>472(0.795)</td>
<td>243(0.791)</td>
</tr>
<tr>
<td></td>
<td>-0.2</td>
<td>328(0.806)</td>
<td>642(0.799)</td>
<td>1061(0.775)</td>
<td>546(0.773)</td>
</tr>
<tr>
<td></td>
<td>-0.1</td>
<td>1310(0.791)</td>
<td>2568(0.801)</td>
<td>4244(0.798)</td>
<td>2183(0.800)</td>
</tr>
<tr>
<td>0.1</td>
<td>-1</td>
<td>472(0.798)</td>
<td>925(0.798)</td>
<td>1528(0.799)</td>
<td>2358(0.800)</td>
</tr>
<tr>
<td></td>
<td>-0.7</td>
<td>963(0.802)</td>
<td>1887(0.798)</td>
<td>3118(0.800)</td>
<td>4812(0.806)</td>
</tr>
<tr>
<td></td>
<td>-0.4</td>
<td>2947(0.798)</td>
<td>5777(0.800)</td>
<td>9549(0.806)</td>
<td>14735(0.805)</td>
</tr>
<tr>
<td>0.5</td>
<td>-1</td>
<td>53(0.804)</td>
<td>103(0.804)</td>
<td>170(0.801)</td>
<td>262(0.807)</td>
</tr>
<tr>
<td></td>
<td>-0.7</td>
<td>107(0.800)</td>
<td>210(0.807)</td>
<td>347(0.799)</td>
<td>535(0.803)</td>
</tr>
<tr>
<td></td>
<td>-0.4</td>
<td>328(0.799)</td>
<td>642(0.802)</td>
<td>1061(0.804)</td>
<td>1638(0.797)</td>
</tr>
<tr>
<td>0.8</td>
<td>-1</td>
<td>14(0.827)</td>
<td>26(0.805)</td>
<td>43(0.807)</td>
<td>66(0.806)</td>
</tr>
<tr>
<td></td>
<td>-0.7</td>
<td>27(0.803)</td>
<td>53(0.800)</td>
<td>87(0.799)</td>
<td>134(0.799)</td>
</tr>
<tr>
<td></td>
<td>-0.4</td>
<td>82(0.807)</td>
<td>161(0.803)</td>
<td>266(0.802)</td>
<td>410(0.802)</td>
</tr>
<tr>
<td>0.1</td>
<td>-0.7</td>
<td>1444(0.798)</td>
<td>2830(0.806)</td>
<td>4677(0.797)</td>
<td>4010(0.801)</td>
</tr>
<tr>
<td></td>
<td>-0.6</td>
<td>1965(0.796)</td>
<td>3851(0.795)</td>
<td>6366(0.796)</td>
<td>5458(0.796)</td>
</tr>
<tr>
<td></td>
<td>-0.5</td>
<td>2830(0.801)</td>
<td>5546(0.807)</td>
<td>9167(0.805)</td>
<td>7859(0.797)</td>
</tr>
<tr>
<td>0.5</td>
<td>-0.7</td>
<td>161(0.794)</td>
<td>315(0.804)</td>
<td>520(0.805)</td>
<td>446(0.791)</td>
</tr>
<tr>
<td></td>
<td>-0.6</td>
<td>219(0.791)</td>
<td>428(0.807)</td>
<td>708(0.797)</td>
<td>607(0.803)</td>
</tr>
<tr>
<td></td>
<td>-0.5</td>
<td>315(0.795)</td>
<td>617(0.799)</td>
<td>1019(0.808)</td>
<td>874(0.805)</td>
</tr>
<tr>
<td>0.8</td>
<td>-0.7</td>
<td>41(0.805)</td>
<td>79(0.804)</td>
<td>130(0.797)</td>
<td>112(0.806)</td>
</tr>
<tr>
<td></td>
<td>-0.6</td>
<td>55(0.806)</td>
<td>107(0.803)</td>
<td>177(0.798)</td>
<td>152(0.799)</td>
</tr>
<tr>
<td></td>
<td>-0.5</td>
<td>79(0.807)</td>
<td>155(0.806)</td>
<td>255(0.813)</td>
<td>219(0.798)</td>
</tr>
</tbody>
</table>

Note: * 1000 iterations are generated.
Table 2.11. Means of ADAS-Cog in Each Cell

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.4331 (Placebo)</td>
<td>-0.7006 (40mg)</td>
<td>-2.0318 (80mg)</td>
</tr>
<tr>
<td>2</td>
<td>-1.4331 (40mg)</td>
<td>-1.3503 (Placebo)</td>
<td>-2.7962 (80mg)</td>
</tr>
<tr>
<td>3</td>
<td>-1.6242 (40mg)</td>
<td>-2.5860 (80mg)</td>
<td>-2.2803 (Placebo)</td>
</tr>
</tbody>
</table>

Table 2.12. Estimates of Treatment Effects from Model 1 and Model 2

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Estimate</th>
<th>StaErr</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>(\psi_1)</td>
<td>-0.134</td>
<td>-0.195</td>
<td>0.218</td>
<td>0.281</td>
</tr>
<tr>
<td>(\psi_2)</td>
<td>-0.881</td>
<td>-1.045</td>
<td>0.218</td>
<td>0.487</td>
</tr>
<tr>
<td>(\psi_3)</td>
<td>-0.747</td>
<td>-0.849</td>
<td>0.266</td>
<td>0.444</td>
</tr>
</tbody>
</table>

about 98 with fixed Type I and Type II errors 1.7% (two-tailed) and 20% respectively. The simulated powers are all close to the desired power (=80%).

Similarly, we run Monte Carlo simulations to estimate minimum sample size and the correspond powers for detecting the differences in treatment effects between the low dose and placebo, and the differences between the high dose and the low dose as well. We assume \(\tau_2=-0.88\) and \(\sigma=3.0\). In order to detect -0.13 of the difference of contrast \(\psi_1\), the minimum required number \(n\) per sequence is about 4202. In addition, to detect -0.75 of the difference of contrast \(\psi_3\), the minimum required number \(n\) per group is about 253. All simulated powers are approximately 80%.

Since no washout period is applied between treatment periods in this crossover trial, the model 2 with carry-over effect is also considered. We assume the intraclass correlation \(\rho =0.8\), the standard deviation \(\sigma_g=6.0\) (that is, \(\sigma=3.0\)), \(\gamma_1=-0.05\), and \(\gamma_2=-0.2\). After re-running Monte Carlo simulations, we notice that the corresponding powers are all close to the desire power. To detect -0.195 of the difference of contrast \(\psi_1\), -1.045 of the difference of contrast \(\psi_2\), and -0.85 of the difference of contrast \(\psi_3\), the minimum required number \(n\) per group are 3307, 346, 436 with fixed Type I and Type II errors 1.7% (two-tailed) and 20% respectively.
CHAPTER 3

SUMMARY

Under normal distribution assumption, we propose a sample size calculation procedure for three-treatment three-period crossover design with three sequences: $D_0 \rightarrow D_1 \rightarrow D_2$, $D_1 \rightarrow D_0 \rightarrow D_2$ and $D_1 \rightarrow D_2 \rightarrow D_0$, where $D_0$, $D_1$ and $D_2$ denote placebo, the low dose and the high dose respectively. This design has restriction of that the high dose cannot be administered before the low dose, and may be useful for the investigators who are unwilling to administer a higher dose of a new drug to a patient before administering a lower dose [14]. Two explanatory models are considered in this thesis, and both of them include fixed period and treatment effects, and fixed subject effects as well. Model 2 also includes fixed residual or carry-over effects besides the effects represented in model 1.

In this thesis, we wish to address how many subjects are required to detect the differences between treatments if we want to test hypotheses of equality of pairwise treatment effects. Appropriate contrast coefficients are derived to estimate the unbiased pairwise differences between treatments, and their variances. Contrasts are linear combination of contrast coefficients and cell means, and the variances of the contrasts are functions of the within-patient variance component. The within-patient variance is unknown and can be estimated based on the early experiments.

Using the formula (2.15), minimum required sample size is calculated for both models to detect the differences of effects between treatments. The results show that the sample size required for detecting the difference between the high dose and placebo for model 2 with carry-over effects is much larger than that for model 1 without carry-over effects. Monte Carlo simulations show that the simulated powers for the two models are all near to the desired power. An example of the cognitive component of the Alzheimer’s disease assessment scale collected from a crossover trial is conducted to illustrate the proposed procedure (2.15).
CHAPTER 4

DISCUSSION

In the present study, a formula for sample size calculation has been derived under a normal distribution assumption for a three-treatment three-period crossover trial. Like $3 \times 3$ *Latin square* design, this design is still a $3 \times 3$ trial, but has a lower efficiency than *Latin square*, and therefore requires much more sample size to maintain the power for testing the differences between treatment effects [14]. In the proposed procedure (2.15) for sample size calculation, we notice that the within-subject variance and the difference of treatment effects are unknown. We need to estimate them, which is one of the most important components in the sample size calculation, from early experiences or a number of studies. In Monte Carlo simulation, the expected values of responses are not known either, we have to estimate these values based on the similar experiments from other literatures.

When employing the formula (2.15), we notice that the sample size is increasing along with within-subject variances increasing or with the desired differences of treatment effects decreasing. As for constant between-subject variance ($\sigma^2$), from equation (2.16), the higher the intraclass correlation ($\rho$) is, the lower the within-subject variance ($\sigma^2$) is, so that the lower the consequent sample size will be. Therefore, the formula does not include parameter $\rho$, but it affects the sample size due to the correlation with between-subject variance. The corresponding powers, nearly close to the desired power ($=0.8$), are noticed to remain constant when the intraclass correlation increases from 0.1 to 0.8 for both of models. We can therefore assign $\rho=0.5$ if there is no information about $\rho$ from previous experiments [28].

We notice that the minimum sample size required for detecting the differences of treatment effects in the model with carryover is much larger than that in the model without carryover. Senn [1] in his book has argued that the use of the crossover design is effectively under the assumption of minimal carry-over effect of a treatment. That is, all treatment effects on subjects return to baseline before starting the next succeeding treatment. Also, Lui [28] pointed out that the crossover trial might lose its efficiency when carry-over effects
needed to be considered in order to avoid bias. Crossover designs are more sensitive to bias than parallel group designs [29]. Therefore, an adequate washout period should be considered to minimize carry-over effect so that the assumption of no carry-over effect can be reasonably applied to reduce sample size requirements. For our example, however, there is no washout period between consecutive treatments. From table 2.11, we notice that the low and the high doses affect the next placebo treatment effect, e.g., with placebo ($D_0$) treatment, the mean of ADAS-Cog is -0.4331 in sequence $D_0 \rightarrow D_1 \rightarrow D_2$, but becomes -1.3503 and -2.2803 in sequences $D_1 \rightarrow D_0 \rightarrow D_2$ and $D_1 \rightarrow D_2 \rightarrow D_0$ respectively. Therefore, although the analysis results from Peace and Koch [14] show that the carryover effects are not statistically significant, the model 2 with carryover might be more appropriate for the designs without washout period to lead to more precise inferences on the sample size.

Furthermore, Peace and Koch [14] mentioned in their example that a total of 632 patients were randomized to the three-sequence crossover trial. After excluding 161, the balanced dataset of 471 patients (157 patients per sequence) was obtained and analyzed by the methods they developed. Analysis results of the two models show that the comparison of the high dose to placebo is statistically significant. However, 98 and 346 patients are required to detect significant differences between the high dose and placebo from model 1 and model 2 respectively after sample size calculations using the formula (2.15), and hence, the minimum required number of patients to achieve a desired power (=0.8) and to detect statistically significant differences of treatment effects from model 2 with carryover is 346, which is much larger than 157. Peace and Koch [14] did not consider high false positive rate due to multiple comparisons, so that minimum required sample size may be underestimated.

Finally, as discussed before, this special design has a lower efficiency than 3 x 3 Latin square and even a regular three-treatment crossover design with six sequences. In order to maintain a desired power, a larger sample size is required. Therefore, an investigator might not employ this special crossover design and the formula developed in this study except that he/she would like to administer the low dose of a drug to a patient before administering the high dose.
REFERENCES

[15] D. A. Williams, A test for differences between treatment means when several dose levels are compared with a zero dose control, Biometrics, 27 (1971), pp. 103–117.


APPENDIX

SAS® LOG OF MONTE CARLO SIMULATIONS
/*For Model 1 without Carry-Over Effect*/
/* The low dose vs. Placebo*/
data crossoverD1D0;
array powerlabel (m) ssig1-ssig3;
array an(m) sig1-sig3;
z$=0.842;
za=2.395;
desired=0.8;
w1=-8/15;w2=7/15;w3=1/15;w4=4/15;w5=-5/15;w6=1/15;w7=4/15;w8=-2/15;w9=-2/15;
array coef(9) w1-w9;
array coefsqu(9) sw1-sw9;
weight=0;
do i=1 to 9;
   coefsqu(i)=coef(i)**2;
   weight+coefsqu(i);
end;
nsimul=1000;
mu=-0.5;
taoH=-0.8;
pe2=-0.1;
pe3=-0.1;
do rho=0.1,0.5,0.8;
   do taoL=-0.3,-0.2,-0.1;
      do sigmas=2.5,3.5,4.5;
         sigma= sigmas*sqrt((1-rho)/rho);
         n=ceil(((za+z$)**2)*weight/((taoL/sigma)**2));
         sumrej=0;
         do sim=1 to nsimul;
            subj=sigmas*rannor(10047);
            sx11=(mu+subj)+sigma*rannor(16783);
            sx11+x11;
            sx12=(mu+subj+taoL+pe2)+sigma*rannor(65535);
            sx12+x12;
x13=(mu+subj+taoH+pe3)+sigma*rannor(17383);
 sx13+x13;
 d121=x12-x11;
 d131=x13-x11;
 d1=d121+d131;
 sumd1+d1;
 sumd1s2+d1**2;
 subj=sigmas*rannor(10047);
 x21=(mu+subj+taoL)+sigma*rannor(12047);
 sx21+x21;
 x22=(mu+subj+pe2)+sigma*rannor(16783);
 sx22+x22;
 x23=(mu+subj+taoH+pe3)+sigma*rannor(16393);
 sx23+x23;
 d212=x22-x21;
 d232=x23-x22;
 d2=d212+d232;
 sumd2+d2;
 sumd2s2+d2**2;
 subj=sigmas*rannor(10047);
 x31=(mu+subj+taoL)+sigma*rannor(12047);
 sx31+x31;
 x32=(mu+subj+taoH+pe2)+sigma*rannor(12383);
 sx32+x32;
 x33=(mu+subj+pe3)+sigma*rannor(16783);
 sx33+x33;
 d313=x31-x33;
 d323=x32-x33;
 d3=d313+d323;
 sumd3+d3;
 sumd3s2+d3**2;
 end; ** end of do num=1 to n;

 sscd1=sumd1s2-((sumd1**2)/n);
 sscd2=sumd2s2-((sumd2**2)/n);
 sscd3=sumd3s2-((sumd3**2)/n);
 esigmad2=(1/(3*(n-1)))*(sscd1+sscd2+sscd3);
 esigma2=(1/6)*esigmad2;
 ztest=w1*(sx11/n)+w2*(sx12/n)+w3*(sx13/n)+w4*(sx21/n)+
 w5*(sx22/n)+w6*(sx23/n)+w7*(sx31/n)+w8*(sx32/n)+w9*(sx33/n);
 convar=weight*((esigma2)/n);
 z=ztest/sqrt(convar);
 if z gt 2.395 or z lt -2.395 then sumrej+1;
 end; ** end of do sim=1 to nsimul;

 sappower=sumrej/nsimul;
if sigmas=2.5 then do; m = 1; an=n; powerlabel=sappower; end;
if sigmas=3.5 then do; m = 2; an=n; powerlabel=sappower; end;
if sigmas=4.5 then do; m = 3; an=n; powerlabel=sappower; end;
if m eq 3 then do;
put rho 1-4 2 taoL 7-11 2 sig1 13-17 @18 "(" ssig1 19-23 3 @24 ")"
sig2 26-30 @31 "(" ssig2 32-36 3 @37 ")"
sig3 39-43 @44 "(" ssig3 45-49 3 @50 ");"
end;** end of if m eq 3;
end; ** end of do rho;
run;

Output

NOTE: The data set WORK.CROSSOVERD1D0 has 1 observations and 86 variables.
NOTE: At least one W.D format was too small for the number to be printed. The decimal
may be shifted
   by the "BEST" format.

/* The high dose vs. Placebo*/
data crossoverD2D0;
array powerlabel (m) ssig1-ssig3;
array an(m) sig1-sig3;
zbb=0.842;
zaa=2.395;
desired=0.8;
w1=-2/15;w2=-2/15;w3=4/15;w4=1/15;w5=-5/15;w6=4/15;w7=1/15;w8=7/15;w9=-8/15;
array coef(9) w1-w9;
array coefsqu(9) sw1-sw9;
weight=0;
do i=1 to 9;
   coefsqu(i)=coef(i)**2;
   weight+coefsqu(i);
end;
nsimul=10000;
mu=-0.5;
taoL=-0.2;
pe2=-0.1;
pe3=-0.1;
do rho=0.1,0.5,0.8;
do  taoH=-1.0,-0.7,-0.4;
do sigmas=2.5,3.5,4.5;
sigma= sigmas*sqrt((1-rho)/rho);
n=ceil(((za+zg)**2)*weight)/((taoH/sigma)**2));
sumrej=0;
do sim=1 to nsimul;
sx11=0;sx21=0;sx31=0;sx12=0;sx22=0;sx32=0;
sx13=0;sx23=0;sx33=0;
sumd1=0;sumd2=0;sumd3=0;
sumd1s2=0;sumd2s2=0;sumd3s2=0;
do num=1 to n;
subj=sigmas*rannor(10047);
x11=(mu+subj)+sigma*rannor(16783);
sx11+x11;
x12=(mu+subj+taoL+pe2)+sigma*rannor(65535);
sx12+x12;
x13=(mu+subj+taoH+pe3)+sigma*rannor(17383);
sx13+x13;
d121=x12-x11;
d131=x13-x11;
d1=d121+d131;
sumd1+d1;
sumd1s2+d1**2;
subj=sigmas*rannor(10047);
x21=(mu+subj+taoL)+sigma*rannor(12047);
sx21+x21;
x22=(mu+subj+pe2)+sigma*rannor(16783);
sx22+x22;
x23=(mu+subj+taoH+pe3)+sigma*rannor(16393);
sx23+x23;
d212=x21-x22;
d232=x23-x22;
d2=d212+d232;
sumd2+d2;
sumd2s2+d2**2;
subj=sigmas*rannor(10047);
x31=(mu+subj+taoL)+sigma*rannor(12047);
sx31+x31;
x32=(mu+subj+taoH+pe2)+sigma*rannor(12383);
sx32+x32;
x33=(mu+subj+pe3)+sigma*rannor(16783);
sx33+x33;
d313=x31-x33;
d323=x32-x33;
d3=d313+d323;
sumd3+d3;
sumd3s2+d3**2;
end; ** end of do num=1 to n;

sscd1=sumd1s2-((sumd1**2)/n);
sscd2=sumd2s2-((sumd2**2)/n);
sscd3=sumd3s2-((sumd3**2)/n);
esigmad2=(1/(3*(n-1)))*((sscd1+sscd2+sscd3);
esigma2=(1/6)*esigmad2;
ztest=w1*(sx11/n)+w2*(sx12/n)+w3*(sx13/n)+w4*(sx21/n)+
w5*(sx22/n)+w6*(sx23/n)+w7*(sx31/n)+w8*(sx32/n)+w9*(sx33/n);
convar=weight*((esigma2)/n);
z=ztest/sqrt(convar);
if z gt 2.395 or z lt -2.395 then sumrej+1;
end; ** end of do sim=1 to nsimul;
sappower=sumrej/nsimul;
if sigmas=2.5 then do; m = 1; an=n; powerlabel=sappower; end;
if sigmas=3.5 then do; m = 2; an=n; powerlabel=sappower; end;
if sigmas=4.5 then do; m = 3; an=n; powerlabel=sappower; end;
if m eq 3 then do;
put rho 1-4 2 taoH 7-11 2 sig1 13-17 @18 "(" ssig1 19-23 3 @24 ")"
sig2 26-30 @31 "(" ssig2 32-36 3 @37 ")"
sig3 39-43 @44 "(" ssig3 45-49 3 @50 ")";
end; ** end of if m eq 3;
end; ** end of do sigmas;
end; ** end of do taoH;
end; ** end of do rho;
run;

Output

| 0.10 | -1.00 | 472(0.798) | 925(0.798) | 1528(0.799) |
| 0.10 | -0.70 | 963(0.802) | 1887(0.798) | 3118(0.800) |
| 0.10 | -0.40 | 2947(0.798) | 5777(0.800) | 9549(0.806) |
| 0.50 | -1.00 | 53(0.804) | 103(0.804) | 170(0.801) |
| 0.50 | -0.70 | 107(0.800) | 210(0.807) | 347(0.799) |
| 0.50 | -0.40 | 328(0.799) | 642(0.802) | 1061(0.804) |
| 0.80 | -1.00 | 14(0.827) | 26(0.805) | 43(0.807) |
| 0.80 | -0.70 | 27(0.803) | 53(0.800) | 87(0.799) |
| 0.80 | -0.40 | 82(0.807) | 161(0.803) | 266(0.802) |

NOTE: The data set WORK.CROSSOVERD2D0 has 1 observations and 86 variables.
NOTE: DATA statement used (Total process time):
real time 12:39.91
cpu time 12:28.66
/ The high dose vs. the low dose*/
data crossoverD2D1;
array powerlabel (m) ssig1-ssig3;
array an(m) sig1-sig3;
zb=0.842;
za=2.395;
desired=0.8;
w1=6/15;w2=-9/15;w3=3/15;w4=-3/15;w5=0;w6=3/15;w7=-3/15;w8=9/15;w9=-6/15;
array coef(9) w1-w9;
array coefsqu(9) sw1-sw9;
weight=0;
do i=1 to 9;
  coefsqu(i)=coef(i)**2;
  weight+coefsqu(i);
end;
nsimul=5000;
mu=-0.5;
taoH=-0.8;
pe2=-0.1;
pe3=-0.1;
do rho=0.1,0.5,0.8;
do taoL=-0.3,-0.2,-0.1;
taoHL=taoH-taoL;
do sigmas=2.5,3.5,4.5;
sigma= sigmas*sqrt((1-rho)/rho);
n=ceil(((za+zb)**2)*weight)/((taoHL/sigma)**2));
sumrej=0;
do sim=1 to nsimul;
sx11=0;sx21=0;sx31=0;sx12=0;sx22=0;sx32=0;
sx13=0;sx23=0;sx33=0;
sumd1=0;sumd2=0;sumd3=0;
sumd1s2=0;sumd2s2=0;sumd3s2=0;
do num=1 to n;
subj=sigmas*rannor(10047);
x11=(mu+subj)+sigma*rannor(16783);
sx11+x11;
x12=(mu+subj+taoL+pe2)+sigma*rannor(65535);
sx12+x12;
x13=(mu+subj+taoH+pe3)+sigma*rannor(17383);
sx13+x13;
d121=x12-x11;
d131=x13-x11;
d1=d121+d131;
sumd1+d1;
sumd1s2+d1**2;
subj=sigmas*rannor(10047);
x21=(mu+subj+taoL)+sigma*rannor(12047);
sx21+x21;
x22=(mu+subj+pe2)+sigma*rannor(16783);
sx22+x22;
x23=(mu+subj+taoH+pe3)+sigma*rannor(16393);
sx23+x23;
d212=x21-x22;
d232=x23-x22;
d2=d212+d232;
sumd2+d2;
sumd2s2+d2**2;
subj=sigmas*rannor(10047);
x31=(mu+subj+taoL)+sigma*rannor(12047);
sx31+x31;
x32=(mu+subj+taoH+pe2)+sigma*rannor(12383);
sx32+x32;
x33=(mu+subj+pe3)+sigma*rannor(16783);
sx33+x33;
d313=x31-x33;
d323=x32-x33;
d3=d313+d323;
sumd3+d3;
sumd3s2+d3**2;
end; ** end of do num=1 to n;

sscd1=sumd1s2-((sumd1**2)/n);
sscd2=sumd2s2-((sumd2**2)/n);
sscd3=sumd3s2-((sumd3**2)/n);
esigmad2=(1/(3*(n-1)))*(sscd1+sscd2+sscd3);
esigma2=(1/6)*esigmad2;
ztest=w1*(sx11/n)+w2*(sx12/n)+w3*(sx13/n)+w4*(sx21/n)+w5*(sx22/n)+w6*(sx23/n)+w7*(sx31/n)+w8*(sx32/n)+w9*(sx33/n);
convar=weight*((esigma2)/n);
z=ztest/sqrt(convar);
if z gt 2.395 or z lt -2.395 then sumrej+1;
end; ** end of do sim=1 to nsimul;

sappower=sumrej/nsimul;
if sigmas=2.5 then do; m = 1; an=n; powerlabel=sappower; end;
if sigmas=3.5 then do; m = 2; an=n; powerlabel=sappower; end;
if sigmas=4.5 then do; m = 3; an=n; powerlabel=sappower; end;
if m eq 3 then do;
put rho 1-4 2 taoHL 7-11 2 sig1 13-17 @18 "(" ssig1 19-23 3 @24 ")"
sig2 26-30 @31 "(" ssig2 32-36 3 @37 ")"
sig3 39-43 @44 "(" ssig3 45-49 3 @50 ");"
end; ** end of if m eq 3;
end;  ** end of do sigmas;
end;  ** end of do taoHL;
end; ** end of do rho;
run;

Output

<table>
<thead>
<tr>
<th>rho</th>
<th>taoL</th>
<th>0.10</th>
<th>0.50</th>
<th>0.80</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>-0.50</td>
<td>2830(0.801)</td>
<td>5546(0.807)</td>
<td>9167(0.805)</td>
</tr>
<tr>
<td>0.10</td>
<td>-0.60</td>
<td>1965(0.796)</td>
<td>3851(0.795)</td>
<td>6366(0.796)</td>
</tr>
<tr>
<td>0.50</td>
<td>-0.50</td>
<td>315(0.795)</td>
<td>617(0.799)</td>
<td>1019(0.808)</td>
</tr>
<tr>
<td>0.50</td>
<td>-0.60</td>
<td>219(0.791)</td>
<td>428(0.807)</td>
<td>708(0.797)</td>
</tr>
<tr>
<td>0.50</td>
<td>-0.70</td>
<td>161(0.794)</td>
<td>315(0.804)</td>
<td>520(0.805)</td>
</tr>
<tr>
<td>0.80</td>
<td>-0.50</td>
<td>79(0.807)</td>
<td>155(0.806)</td>
<td>255(0.813)</td>
</tr>
<tr>
<td>0.80</td>
<td>-0.60</td>
<td>55(0.806)</td>
<td>107(0.803)</td>
<td>177(0.798)</td>
</tr>
<tr>
<td>0.80</td>
<td>-0.70</td>
<td>41(0.805)</td>
<td>79(0.804)</td>
<td>130(0.797)</td>
</tr>
</tbody>
</table>

NOTE: The data set WORK.CROSSOVERD2D1 has 1 observations and 87 variables.
NOTE: DATA statement used (Total process time):
  real time     8:30.18
  cpu time      8:28.40

/* For Model 2 with Carry-Over Effect */
/* The low dose vs. Placebo */
data crossoverD1D0carryover;
array powerlabel (m) ssig1-ssig3;
array an(m) sig1-sig3;
zb=0.842;
za=2.395;
desired=0.8;
w1=-2/3;w2=1/3;w3=1/3;w4=2/3;w5=-1/3;w6=-1/3;w7=0;w8=0;w9=0;
array coef(9) w1-w9;
array coefsq(9) sw1-sw9;
weight=0;
do i=1 to 9;
   coefsq(i)=coef(i)**2;
   weight+coefsq(i);
end;
simul=1000;
mu=-0.5;
taoH=-0.8;
pe2=-0.1;
pe3=-0.1;
cal=-0.05;
c2=-0.2;
do rho=0.1,0.5,0.8;
do taoL=-0.3,-0.2,-0.1;
do sigmas=2.5,3.5,4.5;
sigmat= sigma*sqrt((1-rho)/rho);

n=ceil(((za+zrb)**2)*weight)/((taoL/sigma)**2));
sumrej=0;
do sim=1 to nsimul;
sx11=0;sx21=0;sx31=0;sx12=0;sx22=0;sx32=0;
sx13=0;sx23=0;sx33=0;
sumd1=0;sumd2=0;sumd3=0;
sumd1s2=0;sumd2s2=0;sumd3s2=0;
do num=1 to n;
subj=sigmas*rannor(10047);
  x11=(mu+subj)+sigma*rannor(16783);
sx11+x11;
  x12=(mu+subj+taoL+pe2)+sigma*rannor(65535);
sx12+x12;
  x13=(mu+subj+taoH+pe3)+sigma*rannor(17383);
  x13c=(mu+subj+taoH+pe3+ca1)+sigma*rannor(17383);
sx13+x13c;
  d121=x12-x11;
  d131=x13-x11;
  d1=d121+d131;
  sumd1+d1;
  sumd1s2+d1**2;
subj=sigmas*rannor(10047);
  x21=(mu+subj+taoL)+sigma*rannor(12047);
sx21+x21;
  x22=(mu+subj+pe2)+sigma*rannor(16783);
  x22c=(mu+subj+pe2+ca1)+sigma*rannor(16783);
sx22+x22c;
  x23=(mu+subj+taoH+pe3)+sigma*rannor(16393);
  x23c=(mu+subj+taoH+pe3+ca1)+sigma*rannor(16393);
sx23+x23c;
  d212=x21-x22;
  d232=x23-x22;
  d2=d212+d232;
  sumd2+d2;
  sumd2s2+d2**2;
subj=sigmas*rannor(10047);
  x31=(mu+subj+taoL)+sigma*rannor(12047);
sx31+x31;
  x32=(mu+subj+taoH+pe2)+sigma*rannor(12383);
  x32c=(mu+subj+taoH+pe2+ca1)+sigma*rannor(12383);
sx32+x32c;
  x33=(mu+subj+pe3)+sigma*rannor(16783);
  x33c=(mu+subj+pe3+ca2)+sigma*rannor(16783);
sx33+x33c;
d313=x31-x33;
d323=x32-x33;
d3=d313+d323;
sumd3+d3;
sumd3s2+d3**2;
end; ** end of do num=1 to n;

sscd1=sumd1s2-((sumd1**2)/n);
sscd2=sumd2s2-((sumd2**2)/n);
sscd3=sumd3s2-((sumd3**2)/n);
esigmad2=(1/(3*(n-1)))*(sscd1+sscd2+sscd3);
esigma2=(1/6)*esigmad2;
ztest=w1*(sx11/n)+w2*(sx12/n)+w3*(sx13/n)+w4*(sx21/n)+
w5*(sx22/n)+w6*(sx23/n)+w7*(sx31/n)+w8*(sx32/n)+w9*(sx33/n);
convar=weight*((esigma2)/n);
z=ztest/sqrt(convar);
if z gt 2.395 or z lt -2.395 then sumrej+1;
end; ** end of do sim=1 to nsimul;
sappower=sumrej/nsimul;
if sigmas=2.5 then do; m = 1; an=n; powerlabel=sappower; end;
if sigmas=3.5 then do; m = 2; an=n; powerlabel=sappower; end;
if sigmas=4.5 then do; m = 3; an=n; powerlabel=sappower; end;
if m eq 3 then do;
put rho 1-4 2 taoL 7-11 2 sig1 13-17 @18 "(" ssig1 19-23 3 @24 ")"
sig2 26-30 @31 "(" ssig2 32-36 3 @37 ")"
sig3 39-43 @44 "(" ssig3 45-49 3 @50 ");
end; ** end of if m eq 3;
end; ** end of do sigmas;
end; ** end of do taoL;
end; ** end of do rho;
run;

NOTE: The data set WORK.CROSSOVERD1D0CARRYOVER has 1 observations and 92 variables.
NOTE: At least one W.D format was too small for the number to be printed. The decimal
may be shifted
by the "BEST" format.
NOTE: DATA statement used (Total process time):
   real time       30:51.89
   cpu time        30:43.71

Output

0.10  -0.30  8732(0.807) 17115(0.790) 28292(0.798)
0.10  -0.20  19647(0.773) 38508(0.799) 63655(0.814)
The high dose vs. Placebo

data crossoverD2D0carryover;
array powerlabel (m) ssig1-ssig3;
array an(m) sig1-sig3;
zb=0.842;
za=2.395;
desired=0.8;
w1=0;w2=0;w3=0;w4=1;w5=-1;w6=0;w7=-1;w8=1;w9=0;
array coef(9) w1-w9;
array coefsqu(9) sw1-sw9;
weight=0;
do i=1 to 9;
    coefsqu(i)=coef(i)**2;
    weight+coefsqu(i);
end;
nsimul=10000;
mu=-0.5;
taoL=-0.2;
pe2=-0.1;
pe3=-0.1;
ca1=-0.05;
ca2=-0.2;
do rho=0.1,0.5,0.8;
do taoH=-1.0,-0.7,-0.4;
do sigmas=2.5,3.5,4.5;
sigma= sigmas*sqrt((1-rho)/rho);
n=ceil(((za+zb)**2)*weight)/((taoH/sigma)**2));
sumrej=0;
do sim=1 to nsimul;
sx11=0;sx21=0;sx31=0;sx12=0;sx22=0;sx32=0;
sx13=0;sx23=0;sx33=0;
sumd1=0;sumd2=0;sumd3=0;
sumd1s2=0;sumd2s2=0;sumd3s2=0;
do num=1 to n;
    subj=sigmas*rannor(10047);
    x11=(mu+subj)+sigma*rannor(16783);
    sx11+x11;
    x12=(mu+subj+taoL+pe2)+sigma*rannor(65535);
    sx12+x12;
x13=(mu+subj+taoH+pe3)+sigma*rannor(17383);
x13c=(mu+subj+taoH+pe3+ca1)+sigma*rannor(17383);
sx13+x13c;
d121=x12-x11;
d131=x13-x11;
d1=d121+d131;
suml+d1;
sumd1s2+d1**2;
subj=sigmas*rannor(10047);
x21=(mu+subj+taoL)+sigma*rannor(12047);
sx21+x21;
x22=(mu+subj+pe2)+sigma*rannor(16783);
x22c=(mu+subj+pe2+ca1)+sigma*rannor(16783);
sx22+x22c;
x23=(mu+subj+taoH+pe3)+sigma*rannor(16393);
sx23+x23;
d212=x21-x22;
d232=x23-x22;
d2=d212+d232;
sumd2+d2;
sumd2s2+d2**2;
subj=sigmas*rannor(10047);
x31=(mu+subj+taoL)+sigma*rannor(12047);
sx31+x31;
x32=(mu+subj+taoH+pe2)+sigma*rannor(12383);
x32c=(mu+subj+taoH+pe2+ca1)+sigma*rannor(12383);
sx32+x32c;
x33=(mu+subj+pe3)+sigma*rannor(16783);
x33c=(mu+subj+pe3+ca2)+sigma*rannor(16783);
sx33+x33c;
d313=x31-x33;
d323=x32-x33;
d3=d313+d323;
sumd3+d3;
sumd3s2+d3**2;
end; ** end of do num=1 to n;

sscd1=sumd1s2-((sumd1**2)/n);
sscd2=sumd2s2-((sumd2**2)/n);
sscd3=sumd3s2-((sumd3**2)/n);
esigmad2=(1/(3*(n-1)))*(sscd1+sscd2+sscd3);
esigma2=(1/6)*esigmad2;
ztest=w1*(sx11/n)+w2*(sx12/n)+w3*(sx13/n)+w4*(sx21/n)+w5*(sx22/n)+w6*(sx23/n)+w7*(sx31/n)+w8*(sx32/n)+w9*(sx33/n);
convar=weight*((esigma2)/n);
z=ztest/sqrt(convar);
if z gt 2.395 or z lt -2.395 then sumrej+1;
end; /* end of do sim=1 to nsimul;

sappower=sumrej/nsimul;
if sigmas=2.5 then do; m = 1; an=n; powerlabel=sappower; end;
if sigmas=3.5 then do; m = 2; an=n; powerlabel=sappower; end;
if sigmas=4.5 then do; m = 3; an=n; powerlabel=sappower; end;
if m eq 3 then do;
put rho 1-4 2 taoH 7-11 2 sig1 13-17 @18 "(" ssig1 19-23 3 @24 ")"
sig2 26-30 @31 "(" ssig2 32-36 3 @37 ")"
sig3 39-43 @44 "(" ssig3 45-49 3 @50 ")";
end; /* end of if m eq 3;
end; /* end of do sigmas;
end; /* end of do taoH;
end; /* end of do rho;
run;

Output

0.10  -1.00  2358(0.800)  4621(0.804)  7639(0.798)
0.10  -0.70  4812(0.806)  9431(0.790) 15589(0.798)
0.10  -0.40 14735(0.805) 28881(0.797) 47742(0.803)
0.50  -1.00  262(0.807)  514(0.802)  849(0.799)
0.50  -0.70  535(0.803)  1048(0.797) 1733(0.805)
0.50  -0.40 1638(0.797)  3209(0.807)  5305(0.799)
0.80  -1.00  66(0.806)   129(0.804)   213(0.807)
0.80  -0.70  134(0.799)  262(0.804)  434(0.794)
0.80  -0.40  410(0.802)  803(0.804) 1327(0.805)
NOTE: The data set WORK.CROSSOVERD2D0CARRYOVER has 1 observations and 92 variables.
NOTE: DATA statement used (Total process time):
  real time   1:04:06.49
  cpu time    1:03:50.07

/* The high dose vs. the low dose*/
data crossoverD2D1carryover;
array powerlabel (m) ssig1-ssig3;
array an(m) sig1-sig3;
zb=0.842;
za=2.395;
desired=0.8;
w1=2/3;w2=-1/3;w3=-1/3;w4=1/3;w5=-2/3;w6=1/3;w7=-1;w8=1;w9=0;
array coef(9) w1-w9;
array coefsqu(9) sw1-sw9;
weight=0;
do i=1 to 9;
coefsqu(i)=coef(i)**2;
weight+coefsqu(i);
end;
nsimul=10000;
mu=-0.5;
taoH=-0.8;
pe2=-0.1;
pe3=-0.1;
ca1=-0.05;
ca2=-0.2;
do rho=0.1,0.5,0.8;

do taoL=-0.1,-0.2,-0.3;
taoHL=taoH-taoL;
do sigmas=2.5,3.5,4.5;
sigma= sigmas*sqrt((1-rho)/rho);
n=ceil(((za+zb)**2)*weight)/((taoHL/sigma)**2));
sumrej=0;
do sim=1 to nsimul;
sx11=0;sx21=0;sx31=0;sx12=0;sx22=0;sx32=0;
sx13=0;sx23=0;sx33=0;
sumd1=0;sumd2=0;sumd3=0;
sumd1s2=0;sumd2s2=0;sumd3s2=0;
do num=1 to n;
subj=sigmas*rannor(10047);
x11=(mu+subj)+sigma*rannor(16783);
sx11+x11;
x12=(mu+subj+taoL+pe2)+sigma*rannor(65535);
sx12+x12;
x13=(mu+subj+taoH+pe3)+sigma*rannor(17383);
x13c=(mu+subj+taoH+pe3+ca1)+sigma*rannor(17383);
sx13+x13c;
d121=x12-x11;
d131=x13-x11;
d1=d121+d131;
sumd1+d1;
sumd1s2+d1**2;
subj=sigmas*rannor(10047);
x21=(mu+subj+taoL)+sigma*rannor(12047);
sx21+x21;
x22=(mu+subj+pe2)+sigma*rannor(16783);
x22c=(mu+subj+pe2+ca1)+sigma*rannor(16783);
sx22+x22c;
x23=(mu+subj+taoH+pe3)+sigma*rannor(16393);
sx23+x23;
d212=x21-x22;
d232=x23-x22;
\[ d_2 = d_{212} + d_{232}; \]
\[ \text{sum} d_2 + d_2; \]
\[ \text{sum} d_2 s_2 + d_2^{**2}; \]
\[ \text{subj} = \text{sigmas} \times \text{rannor}(10047); \]
\[ x_{31} = (\mu + \text{subj} + \tau_0\text{L}) + \text{sigma} \times \text{rannor}(12047); \]
\[ s x_{31} + x_{31}; \]
\[ x_{32} = (\mu + \text{subj} + \tau_0\text{H} + \text{pe}2) + \text{sigma} \times \text{rannor}(12383); \]
\[ s x_{32} + x_{32}; \]
\[ x_{33} = (\mu + \text{subj} + \text{pe}3) + \text{sigma} \times \text{rannor}(16783); \]
\[ x_{33c} = (\mu + \text{subj} + \text{pe}3 + \text{ca}2) + \text{sigma} \times \text{rannor}(16783); \]
\[ s x_{33} + x_{33c}; \]
\[ d_{313} = x_{31} - x_{33}; \]
\[ d_{323} = x_{32} - x_{33}; \]
\[ d_3 = d_{313} + d_{323}; \]
\[ \text{sum} d_3 + d_3; \]
\[ \text{sum} d_3 s_2 + d_3^{**2}; \]
end; ** end of do num=1 to n;

\[ \text{sscd}1 = \text{sum}d_1 s_2 - ((\text{sum}d_1^{**2})/n); \]
\[ \text{sscd}2 = \text{sum}d_2 s_2 - ((\text{sum}d_2^{**2})/n); \]
\[ \text{sscd}3 = \text{sum}d_3 s_2 - ((\text{sum}d_3^{**2})/n); \]
\[ \text{esigm}a2 = \left[ 1/(3*(n-1)) \right] * (\text{sscd}1 + \text{sscd}2 + \text{sscd}3); \]
\[ \text{esigma}2 = \left[ 1/6 \right] * \text{esigm}a2; \]
\[ \text{ztest} = w_1^*(s x_{11}/n) + w_2^*(s x_{12}/n) + w_3^*(s x_{13}/n) + w_4^*(s x_{21}/n) + w_5^*(s x_{22}/n) + w_6^*(s x_{23}/n) + w_7^*(s x_{31}/n) + w_8^*(s x_{32}/n) + w_9^*(s x_{33}/n); \]
\[ \text{convar} = \text{weight}^* (\text{esigma}2/n); \]
\[ \text{z} = \text{ztest}/\sqrt{\text{convar}}; \]
\[ \text{if} \text{ z gt 2.395 or z lt -2.395 then sumrej+1}; \]
end; ** end of do sim=1 to nsimul;

\[ \text{sappower} = \text{sumrej}/\text{nsimul}; \]
if sigmas=2.5 then do; m = 1; an=n; powerlabel=sappower; end;
if sigmas=3.5 then do; m = 2; an=n; powerlabel=sappower; end;
if sigmas=4.5 then do; m = 3; an=n; powerlabel=sappower; end;
if m eq 3 then do;
put rho 1-4 2 taoHL 7-11 2 sig1 13-17 @ 18 "(" s sig1 19-23 3 @ 24 ")"
\[ \text{sig}2 26-30 @ 31 "(" s sig2 32-36 3 @ 37 ")"\]
\[ \text{sig}3 39-43 @ 44 "(" s sig3 45-49 3 @ 50 ");\]
end; ** end of if m eq 3;
end; ** end of do sigmas;
end; ** end of do taoHL;
end; ** end of do rho;
run;
Output

0.10  -0.70  4010(0.801)  7859(0.803)  12991(0.801)
0.10  -0.60  5458(0.796)  10697(0.800)  17682(0.800)
0.10  -0.50  7859(0.797)  15403(0.803)  25462(0.800)
0.50  -0.70  446(0.791)   874(0.801)   1444(0.800)
0.50  -0.60  607(0.803)   1189(0.804)  1965(0.800)
0.50  -0.50  874(0.805)   1712(0.797)  2830(0.802)
0.80  -0.70  112(0.806)   219(0.801)   361(0.797)
0.80  -0.60  152(0.799)   298(0.806)   492(0.798)
0.80  -0.50  219(0.798)   428(0.797)   708(0.808)

NOTE: The data set WORK.CROSSOVERD2DICARRYOVER has 1 observations and 93 variables.
NOTE: DATA statement used (Total process time):
   real time   1:02:53.54
   cpu time    1:01:33.