A SAS® Program for the Assessment of Unbalanced Data in Two-Sequence, Three-Period Crossover Trials

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ABSTRACT

In clinical trials or bioavailability and bioequivalence studies, replicated crossover designs such as a two-sequence, three-period are often used to assess treatment and carry-over effects between drug products. However, data observed from a replicated crossover design may be unbalanced due to potential dropouts. In this case, standard statistical methods may not be directly applied. Chow and Shao (1996) proposed two methods, namely the ordinary least squares method and the maximum likelihood method based on the period differences to assess the treatment and carry-over effects. In this paper, a SAS program is developed to compute the estimates of treatment and carry-over effects based on these two methods. In addition, a test statistic and the corresponding p-value are obtained for the comparison of these two methods. An example is presented to illustrate the use of the developed SAS program.

Key Words: Bioavailability, Bioequiv.ence; Replicated crossover design; Treatment effect; Carry-over effect.

1. INTRODUCTION

In clinical trials or bioavailability and bioequivalence studies, replicated crossover designs are often used to assess treatment and carry-over effects. For example, in bioavailability/bioequivalence studies, the standard two-sequence, two-period crossover design is viewed favorably by the U.S. Food and Drug Administration (FDA) for assessment of bioequivalence between a test and a reference drug product (See Chow and Liu, 1992a,b). However, the standard two-sequence, two-period crossover design does not provide unbiased estimates of treatment and carry-over effects when carry-over effects are present. As an alternative, it is recommended that a replicated crossover design be used (Liu, 1995). The simplest and the most commonly used replicated crossover design is probably the two-sequence, three-period crossover design. It can be obtained by adding an additional period to the standard two-sequence, two-period crossover design. For a two-sequence, three-period crossover design, subjects are likely to dropout at the third period. As a result, the data set may be unbalanced in the sense that there are fewer data at the third period as compared to the first two periods. In this case, the commonly used standard statistical methods may not be appropriate. Chow and Shao (1996) proposed two approaches to assess the treatment and carry-over effects. These two methods are the ordinary least squares method and the maximum likelihood method which are derived based on the period differences.

The purpose of this paper is to develop a SAS program for the computation of the estimates of the treatment and carry-over effects based on the method of ordinary least squares and the method of maximum likelihood. In addition, a test statistic and the corresponding p-value are obtained for the comparison of these two methods.

In the next section, the test statistics of the methods proposed by Chow and Shao (1996) are briefly outlined. The SAS program is given in section 3. An example is presented to illustrate the use of the developed SAS program in the last section.

2. TEST STATISTICS

2.1 Statistical Model

Let $y_{ij}$ be the response of the $i$th subject in the $k$th sequence at the $j$th period. Then $y_{ij}$ can be described by the following model:

$$y_{ij} = \mu + p_j + q_k + t_{g(k,j)} + c_{k(k,j)} + \epsilon_{ij}$$

where

- $\mu$ = the overall mean;
- $p_j$ = the fixed effect of the $j$th period, $j=1, 2, 3$ and $p_1 + p_2 + p_3 = 0$;
- $q_k$ = the fixed effect of the $k$th sequence, $k=1, 2$, and $q_1 + q_2 = 0$;
- $t_{g(k,j)}$ = the fixed treatment effect,
  - $g(k,j) = A$ if $k = j$ or $g(k,j) = (2,3)$,
\[ g(k,j)=B \] Otherwise, and \( t_A + t_B = 0 \);

\[ c_{k,k,j} = \text{the fixed carry-over effect of treatment} \]
\[ A \text{ or } B, \quad c_{k,k,j} = c_{k,(k+1),j} = 0, \]
where
\[ h(1,2) = h(2,3) = A, \]
\[ h(2,2) = h(1,3) = B, \]
and \( c_A + c_B = 0; \)

\[ r_{ij} = \text{random effect of the } i\text{th subject in the } k\text{th sequence, } i=1, 2, \ldots, n_k; \]

\[ e_{kij} = \text{the random error in observing } Y_{kij}. \]

In the above model, \( e_{kij} \) are assumed to be independent and identically normally distributed with mean 0 and variance \( \sigma_e^2 \).

### 2.2 Notations and Parameters

Assume that in the \( k \)th sequence, the first \( m_k \) subjects have data for all three periods and the remaining of \( n_k - m_k \) subjects have data for periods 1 and 2. It is also assumed that \( n = (n_1, n_2) \) and \( m = (m_1, m_2) \) are independent of \( Y_{kij} \)'s. The parameters of interest are summarized below:

- **Parameters**: \( \mu, \rho_1, \rho_2, q_1, t_A, c_A \)
- **Treatment effect**: \( \delta = t_A - t_B = 2t_A \)
- **Carry-over effect**: \( \gamma = c_A + c_B = 2c_A \)

### 2.3 The Method of Least Squares

Let \( \bar{Y}_{kij} = \frac{1}{n_k} \sum_{i=1}^{n_k} Y_{kij} \)
\( \bar{Y}_{k3} = \frac{1}{m_k} \sum_{i=1}^{m_k} Y_{kij} \) where \( k=1, 2 \).

Then, as indicated in Chow and Shao (1996), the least squares estimates of \( \delta \) and \( \gamma \), denoted by \( \hat{\delta}_{ls} \) and \( \hat{\gamma}_{ls} \), are given by:

- **Treatment Effect**:
\[
\hat{\delta}_{ls} = \frac{1}{2} \frac{1}{\bar{Y}_u - \bar{Y}_v + \frac{1}{4} \bar{Y}_w + \frac{1}{4} \bar{Y}_x},
\]

- **Carry-over Effect**:
\[
\hat{\gamma}_{ls} = \frac{1}{2} \left( \frac{1}{2} - \frac{1}{4} \bar{Y}_u - \frac{1}{4} \bar{Y}_w + \frac{1}{2} \bar{Y}_x \right).
\]

### 2.4 The Method of Maximum Likelihood Based on Difference

Consider period difference \( d_{kij} \) as defined below:

- \( d_{1i1} = y_{1i1} - y_{1i2} \)
- \( d_{1i2} = y_{1i2} - y_{1i3} \)
- \( d_{2i1} = y_{2i1} - y_{2i2} \)
- \( d_{2i2} = y_{2i2} - y_{2i3} \)

with \( j=1, 2 \) when \( 1 \leq i \leq m_k \), and \( j=1 \) when \( m_k + 1 \leq i \leq n_k \).

Let \( \bar{d}_{kij} = \frac{1}{n_k} \sum_{i=1}^{n_k} d_{kij} \) and \( \bar{d}_{kij} = \frac{1}{m_k} \sum_{i=1}^{m_k} d_{kij} \)

\( j=1, 2 \), \( k=1, 2 \). Then as indicated by Chow and Shao (1996), the maximum likelihood estimates of \( \delta \) and \( \gamma \), denoted by \( \hat{\delta}_{ml} \) and \( \hat{\gamma}_{ml} \), are given below:

- **Treatment Effect**:
\[
\hat{\delta}_{ml} = \frac{1}{2} \left( \frac{1}{4} \bar{d}_u + \frac{1}{2} \bar{d}_h + \frac{1}{4} \bar{d}_n - \frac{3}{4} \bar{d}_n \right)
\]

- **Carry-over Effect**:
\[
\hat{\gamma}_{ml} = \frac{1}{2} \left( \frac{1}{2} \bar{d}_u + \frac{1}{2} \bar{d}_h + \frac{1}{2} \bar{d}_n - \frac{1}{2} \bar{d}_n \right).
\]

Moreover, \( \sigma_e^2 \) can be estimated by
\[
\hat{\sigma}_e^2 = \frac{1}{df} \sum_{i=1}^{2} \sum_{j=m+1}^{m+2} (d^2_{kij} + d^2_{kj2} + d_{kij}d_{kj2})
\]
\[ + \frac{1}{2} \sum_{i=n+m+1}^{2} \bar{d}_{kij}^2 - \frac{1}{2} \bar{d}_{kij}^2 - \frac{1}{2} (\hat{\delta}_{ml} + \hat{\gamma}_{ml})^2 \]

where \( df = n_1 + m_1 + n_2 + m_2 - 4 \)

The exact 95% confidence intervals for treatment and carry-over effects are:

- **Treatment Effect**:
\[
\hat{\delta}_{ml} \pm t_{0.025,df} \hat{\sigma}_e \sqrt{\frac{1}{32} \left( \frac{3}{n_1} + \frac{3}{n_2} + \frac{1}{m_1} + \frac{1}{m_2} \right)}
\]
Statistics, Data Analysis, and Modeling

2.5 The Comparison of the Two Methods

To assess the efficiency between the two methods, we may consider the following hypotheses.

\[ H_0: 2\sigma_e^2 \leq \sigma^2 \quad \text{vs} \quad H_A: 2\sigma_e^2 > \sigma^2 \]

Define

\[ z_{ki} = \frac{1}{2} \left( y_{ki1} + y_{ki2} + y_{ki3} \right) \quad \text{when} \quad 1 \leq i \leq m_k \]

\[ z_k = \frac{1}{2} \left( y_{k1} + y_{k2} \right) \quad \text{when} \quad m_k + 1 \leq i \leq n_k \]

Therefore, we reject \( H_0 \) if

\[
F = \frac{6s_e^2 / 5 + s_k^2}{(n_1 + n_2 - 4)\hat{\sigma}_e^2} > F_{n_1+n_2-4,m_1+m_2-4}(1-\alpha)
\]

where \( F_{n_1+n_2-4,m_1+m_2-4}(1-\alpha) \) is the \((1-\alpha)\)th quantile of an \( F \)-distribution with \( n_1 + n_2 - 4 \) and \( n_1 + m_1 + n_2 + m_2 - 4 \) degrees of freedom, and

\[
s_e^2 = \sum_{k=1}^{m_1} \sum_{i=1}^{n_k} (z_{ki} - \bar{z}_k)^2 / \left( n_k - m_k \right)
\]

\[
s_k^2 = \sum_{k=1}^{m_1} \sum_{i=m_k+1}^{n_k} (z_{ki} - \bar{z}_k)^2 / \left( n_k - m_k \right)
\]

3. The SAS Program

A SAS program using SAS version 6.08 is developed for the methods described in section 2 for a two-sequence, three-period crossover design with unbalanced data. The following variables are the key variables which should be included in the data set.

(a). seq: a variable presenting sequence, i.e. 1 or 2
(b). pd1: a response variable of the first period. (e.g. AUC, \( C_{max} \), etc...)
(c). pd2: a response variable for the 2nd period
(d). pd3: a response variable for the 3rd period

After the above 4 variables are defined in the data set, the SAS program can be executed by using the following macro statement.

\%analyze(2, indata)

where: \( \text{indata} \) = the name of the input data set

The SAS macro is given below:

```sas
options ls=132 cs=cr nodate nonumber;
%macro analyze(number, indata);
data all cmpl miss;
  infile "&indata"
  l1;
  input subj seq pd1-pd3;
  n~l; dl~pd1-pd2; d2~pd2-pd3;
  t1=(d1**2)+(d2**2)+(d1*d2);
  t2=d1**2;
  zb=mean(ofpd1-pd3);
  if pd3 A=. then m=1;
  else m=0;
  if n then output all;
  if m then output cmpl;
  if n and not m then output miss;
  proc means data=all noprint nway;
  class seq;
  var pd1 pd2 pd3 dl d2;
  output out=allm mean = ylb y2b y3b d1b d2b
  n = n;
  proc means data=cmpl noprint nway;
  class seq;
  var dl d2 m t1 zb;
  output out = cmplm mean = d1h d2h
  sum =
  css = sd1 sd2 sm st1 ussc;
  proc means data=miss noprint nway;
  class seq;
  var t2 zb;
  output out = missm
  sum =
  css = usst ussm;
data results;
  merge allm cmplm missm end=
  last;
  by seq;
%do n=1 %to &number;
  retain y&n.1b y&n.2b y&n.3b
d&n.1b d&n.2b n&n
d&n.1h d&n.2h m&n t&n.1
t&n.2 s&n.1c s&n.1m;
```

1422
if seq=&n then do;
y&n.lb=yJb; y&n.2b=y2b;
y&n3b=y3b; d&n.lb=dlb;
d&n.2b=d2b; n&n=n; m&n=m;
d&n.lh=dlh; d&n.2h=d2h;
I&n.l=tl; I&n.2=12; s&n.lc=usse;
s&n.lm=ussm;
end;
end;

if last then do;
lsrx=1/2*yllb-1/4*yI2b-1/4*y21b+
1/2*y22b+ 1/4*y23b;
lsr = 1/2*y12b-1/2*y13b-
1/2*y22b+1/2*y23b;
mlrx = 3/8*dllb+1/8*dllh+1/4*d12b-
3/8*d21b-1/8*d2lh+1/4*d22b;
mlcr = 1/2*(-(1/2*dllb+1/2*dllh+d12b+
1/2*d21b-1/2*d2lh+d22b);
ndf = n1+n2-4; ddf=nl+n2+m1+m2-4;
sig_e = 1/ddf((2/3)t11+1/2*t12-n1/2*
d11b)**2+(m1/6*(d11h+2*d12h)**2))
+(2/3)*t21+1/2*T22-n2/2*d21b**2-
((m2/6)*d21h+2*d22h)**2));

f_stat = (6/5*(sllc+s2lc)+
(sllc+s2lc))/ndf*sig_e);
p_value = 1-probf(f_stat, ndf, ddf);
t_qnt = tinv(0.975, ddf);
rx = 3/32*(3/m1+3/n2+1/m1+1/m2);
ct = 1/8*(1/n1+1/n2+3/m1+3/m2);
mlrx = mlrx-t_qnt*(sig_e*rx)**0.5;
mlrx_u = mlrx+t_qnt*(sig_e*rx)**0.5;
mlcr = mlcr-t_qnt*(sig_e*cr)**0.5;
mlcr_u = mlcr+t_qnt*(sig_e*cr)**0.5;
output;
end,

if last then do;
lsrx=1/2*yllb-1/4*yI2b-1/4*y21b+
1/2*y22b+ 1/4*y23b;
lsr = 1/2*y12b-1/2*y13b-
1/2*y22b+1/2*y23b;
mlrx = 3/8*dllb+1/8*dllh+1/4*d12b-
3/8*d21b-1/8*d2lh+1/4*d22b;
mlcr = 1/2*(-(1/2*dllb+1/2*dllh+d12b+
1/2*d21b-1/2*d2lh+d22b);
ndf = n1+n2-4; ddf=nl+n2+m1+m2-4;
sig_e = 1/ddf((2/3)t11+1/2*t12-n1/2*
d11b)**2+(m1/6*(d11h+2*d12h)**2))
+(2/3)*t21+1/2*T22-n2/2*d21b**2-
((m2/6)*d21h+2*d22h)**2));

f_stat = (6/5*(sllc+s2lc)+
(sllc+s2lc))/ndf*sig_e);
p_value = 1-probf(f_stat, ndf, ddf);
t_qnt = tinv(0.975, ddf);
rx = 3/32*(3/m1+3/n2+1/m1+1/m2);
ct = 1/8*(1/n1+1/n2+3/m1+3/m2);
mlrx = mlrx-t_qnt*(sig_e*rx)**0.5;
mlrx_u = mlrx+t_qnt*(sig_e*rx)**0.5;
mlcr = mlcr-t_qnt*(sig_e*cr)**0.5;
mlcr_u = mlcr+t_qnt*(sig_e*cr)**0.5;
output;
end,

4. AN EXAMPLE

A two-sequence, three-period crossover experiment was conducted to compare two treatments of a drug product in women who have a diagnosis of late luteal phase dysphoric disorder. Thirty-two subjects were randomly assigned to sequence 1 which received three treatments in the order of A, B, and B. There were 36 subjects in sequence 2 and received three treatments in the order of B, A, and A. The analysis of efficacy was based on the depression score which was the sum of the responses to 13 symptoms in each symptom checklist completed at each treatment period. Table 1 lists the depression scores for each subject by three periods. The dropout rates of the third period were 75% and 50% for sequence 1 and sequence 2, respectively.

To illustrate the developed SAS program, we create a data set, named depress, as follows:

data depress;
input subj seq pd1 pd2 pd3;
cards;
1 1 20 22 26
2 1 18 38 22
3 1 49 49 53
4 1 26 41 35
run;

%analyze(2, depress)
SAS OUTPUT

(a) Ordinary Least Squares Methods:

<table>
<thead>
<tr>
<th>Treatment Effect</th>
<th>Carry-Over Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate</td>
<td>-3.727</td>
</tr>
<tr>
<td></td>
<td>-2.090</td>
</tr>
</tbody>
</table>

(b) Maximum Likelihood Method Based on Difference:

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<th>Carry-Over Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate</td>
<td>-3.654</td>
</tr>
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</tr>
<tr>
<td>95% C.I.</td>
<td>(-6.130, -1.179)</td>
</tr>
<tr>
<td>Sigma_e_sq</td>
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</tr>
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</table>

(c) The Comparison of Two Methods:

H0: 2*[(Sigma_a)**2 <= (Sigma_e)**2
H1: 2*[(Sigma_a)**2 > (Sigma_e)**2

F-Statistics = 1.417
D.F. = (64, 106)
P_Value = 0.056

REFERENCES


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c/o E-Mail: CHOW@BMS.COM
Table 1. Depression Scores

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