GENERATING STATISTICAL TABLES MEETING NDA GUIDELINES THE LAZY WAY

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Introduction

Generating statistical tables that will satisfy Food and Drug Administration (FDA) guidelines for a New Drug Application (NDA) can be an onerous, time-consuming task. According to the guidelines (FDA), the statistical tables summarizing the following analyses of the main efficacy variable(s) are required:

1. An overall analysis including p-values for the drug and drug-by-investigator interaction effect.
2. 95% confidence intervals
3. Power calculations
4. Statistical analysis variable broken down by investigators.
5. Analysis of variance tables
6. Intent-to-treat analysis

This is only a portion of the NDA application and does not include the safety section.

The purpose of this paper is to present a way of generating statistical tables quickly eliminating much of the drudgery by utilizing SAS and SAS/STAT. This paper discusses:

1. Past and present procedures in generating statistical tables.
2. Producing a table which includes p-values for the drug and drug-by-investigator effects for a two-arm parallel trial.
3. Producing a table for a two-arm parallel trial table with statistics broken down by investigator.
4. What you can do with an output of least squares means.
5. Generating tables for a combination drug trial.
7. Generating tables with least squares means, confidence intervals, and power calculations.
8. Comment on preferred and intent-to-treat analysis.

This paper is restricted to the case where the main efficacy variable is continuous, normally distributed, and analysis of variance is the statistical method of choice.

Statistical Tables, Past and Present

In the past and possibly the present, statistical tables were produced by the following procedures:

1. Produce tables by writing own procedure in FORTRAN, BASIC, PL/I, etc.
2. Produce printouts utilizing SAS, BMDP, SPSS, etc. and then photocopy the printouts.
3. Use SAS's PROC PRINTTO in which one transfers certain statistics from an electronic printout to a SAS data set, and output a hard copy in the format you want.
4. Generate tables using PROC TABULATE and have an administrative person type the p-values and perform other cosmetic work to this electronic table.

The disadvantage of #3 is that when a new version of SAS comes out, the program may need to be rewritten to accommodate the possible shift in columns on the printout. The disadvantage of #4 is that it is very time consuming and potentially disastrous if errors in the data set warrant reanalysis.

Generating Tables in Version 5 vs. 6

In version 5 of SAS, the process of generating statistical tables might involve the use of PROC TABULATE. Tables are transferred electronically to a word processor (e.g., WORDPERFECT, etc.), p-values produced by GLM are transcribed to the table by a secretary (very time consuming) to produce a final product.

In using version 6, the process of generating tables might look like the following:

1. Descriptive statistics are produced by PROC MEANS.
2. P-values are produced by GLM and merged to a table produced by PROC MEANS. The result?
   - no transcription
   - minimal use of administrative support

Example #1: Two Arm Parallel Trial

A typical pivotal study for a NDA will usually have multiple investigators, two treatment groups (drug and placebo), subjects randomized to one of the treatment groups, baseline period, and follow-up visits. One wants to produce a statistical table in the format as shown in Table 1. To do this, the following is suggested:

data step (select protocol specific data preferred analysis)
create data set with baseline data (dsnBL)
create data set with changes from baseline (dsnCHNG)
append data sets BL and CHNG
compute descriptive statistics (dsnDATA1)
compute p-values via GLM (dsnPVALUE)

PROC GLM OUTSTAT=PVVALUE NOPRINT;
CLASS DRUG INVD BY WEEK;
MODEL DIFF = DRUG INVD DRUG INVD AS 3;
(DIFF is the dependent variable, invid is the investigator effect.)
merge DATA1 and PVVALUE data sets
output table (procPRINT, PUT, etc.)

Appendix 1 presents a suggested SAS code for this example.

Example #2: By Investigator Analysis

In breaking down the analysis by investigator the following strategy was carried out:

- compute descriptive statistics by investigator, drug, time
- compute Levene's test (see Appendix 3 for the SAS code) for the test of homogeneity of variances (Milliken and Johnson)
- use PROC GLM with the outstat option to compute the p-values, degrees of freedom and other statistics

i.e. (SAS CODE)

```sas
PROC GLM OUTSTAT = STAT2 NOPRINT; 
   BY INVID WEEK;
   MODEL DIFF = DRUG / SS3;
```

from data sets TA12, compute t-statistic

Table 2 presents the desired statistical table summarizing the analysis broken down by investigator. Appendix 3 presents the source code to produce the table.

Example #3: LSM's, Confidence Intervals, Power Calculations:

Since most clinical trials are unbalanced because of missing data, drop-outs, disqualifications, etc., a table of least squares means (LSM) is necessary (see Milliken and Johnson).

In creating a table of LSMs, the following source code was used in which a SAS data set of LSM's (PUT=SUGIA.LSM) is created.

```sas
PROC GLM OUTSTAT = VALUE NOPRINT;
   CLASS DRUG INVID~Y WEEK;
   MODEL DIFF = DRUG INVID AS 3;
   LSMEANS DRUG / DIFF STOERR OUT=SUG1A.LSM;
```

The following statistics is contained in a least squares means data set:

```
   OBS  WEEK  _NAME_  DRUG  LSMEAN  STDERR
   3   0     DIFF  1   190.952  0.20708
   6   1     DIFF  2   -21.948  0.45822
   7   4     DIFF  1   -22.665  0.29601
```

From the above, one can create a table as shown in Table 3.

Tables summarizing confidence interval and power calculations can also be created from the statistics contained in a least squares means data set output. A source code describing how to create a table is shown in Appendix 4. For power calculations one can use the following algorithm (or an equivalent) to compute the power of the test (Dixon and Massey):

\[
d = \frac{(Z_{1-\alpha} + Z_{1-\beta}) \times (1 + (1.21\times Z_{1-\alpha} \times 1.06)/df)}
\]

where 
- \(d = \Delta / \text{standard error}\)
- \(\Delta = \text{clinical difference}\)
- \(df = \text{degrees of freedom}\)

(The normal approximation can be replaced by the t-distribution for small sample sizes.)

The power is based on the probability associated with \(Z_{1-\beta}\).

A source code is presented in Appendix 4.

Example #4: Three Treatment Groups or More

There are times when there are three treatment groups involved in a pivotal study. For instance, in an adjuvant drug trial, the sponsoring company must show that the combination drug must be significantly better than the individual components. To generate a statistical table summarizing this type of trial, the following strategy is suggested:

- compute descriptive statistics (PROC MEANS)
- utilize GLM and output p-values and least squares mean estimates as discussed before
- perform data steps to get data in usable format (i.e. PROC TRANSPOSE)
- compute t-statistics from output of LSM's using the strategy suggested in Example #3.
- merge data sets
- output

Table 4 presents a statistical table where the degrees of freedom from the ANOVA, t-statistic of the pair-wise comparisons along with the p-values and other statistics. Appendix 5 presents the source code.

Example #5: ANOVA tables

Lastly, if ANOVA is performed, an ANOVA table should also be presented. In creating analysis of variance tables, one should use output from outstat = option in GLM. The data set created by outstat contains statistics shown in Appendix 6. With this data set, one can manipulate the numbers to produce tables shown in Tables 5 and 6 which describes ANOVA at each visit for a two-way analysis of variance and a table for repeated measures ANOVA, respectively.

Intent-To-Treat Analysis

Two types of analyses are most likely presented in an NDA: preferred analysis and an intent-to-treat analysis (ITT). A preferred analysis focuses on data that is protocol-specific. An intent-to-treat analysis may include all data or may data specific...
to definitions described by Gillings and Koch.

Using the strategies already discussed, one can produce tables quickly for both types of analyses by utilizing one of the following strategies:

1. Create a SAS program that hardcodes data that is to be excluded due to protocol violations and use a %INCLUDE in the main body of a program described above. For instance:

   /* subjects deleting from the statistical analysis */
   /* exclude INVEST # 1 */
   if invid = 1438 then delete;
   /* disqualified */
   if patid = 404 then delete;
   /* never received drug */
   if patid = 200 then delete;
   /* changed mind re participation */
   if patid = 512 then delete;
   /* change of bp medication */
   if (patid = 202 and visit >= 4) then delete;
   /* multiple visits within a study period */
   if (patid = 409 and visit = 6) then delete;

   OR

Create a code for each protocol violation in a SAS data set.

I.E.

   value code
   0 = 'Data Analyzed';
   1 = 'BPS < 140/90 mm Hg'
   2 = 'Short Washout'
   3 = 'PM Exam'
   4 = 'AM Drops'
   5 = 'Multiple Visit'
   6 = 'Change Meds'
   7 = 'Interim Visit'
   8 = 'PM BL Exam'
   9 = 'Improper Entry'
  10 = 'Not Enter Study'
  11 = 'Disqualified'

Insert IF CODE = 0; for the preferred analysis in the program. For the ITT analysis, if the codes 8 and 9 do not meet the definition of an ITT, just insert IF (code=8 or code=9) then delete in the programs. Tables should be quickly generated.

SUMMARY

UTILIZING PROCS MEANS AND GLM WITH THE OUTSTAT AND OUT=LSM OPTIONS, TABLES CAN BE EASILY GENERATED TO MEET NDA GUIDELINES REQUIRING TABLES WITH:

A. DESCRIPTIVE STATISTICS WITH P-VALUES
B. ANALYSIS BY INVESTIGATORS
C. CONFIDENCE INTERVALS
D. POWER CALCULATIONS
E. ANALYSIS OF VARIANCE TABLES

The result is minimal use of administrative support, cuts down the amount of time in generating tables of analyses of patient subsets, and saves time.

REFERENCES


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APPENDICES

APPENDIX 1: Two-Arm Parallel Trial

DATA ALL; SET SUGI.IOP2;
DATA BASE; SET ALL; IF WEEK = 0; /*MERGE BASEUNE WITH
CHANGE FROM */
DATA DIFF; DROP DIFF; /*BASEUNE */
DATA BASE;
DATA SET; SET ALL;
IF WEEK = 0 THEN DELETE;
PROC APPEND BASE =SET DATA =IOP;
/*APPEND BASEUNE WITH
CHANGES */
PROC SORT DATA = ALL3; "CALCULATE DESCRIPTIVE STATISTICS 1</
PROC SORT DATA =ALL3; SY DRUG WEEK;
PAOC MEANS N MEAN STD TO NOPRINT DATA = ALL3; SY DRUG WEEK; VAR
DIFF;
OUTPUT OUT =STATS N =N MEAN =MEAN STD =SID;
OUTPUT OUT =STATS N =N MEAN =MEAN STD =SID;
DATA DRG1; SET STATS;
IF DRUG = 1; /*CAN MODIFY TO SUIT FORMAT OF TABLE */
N1=N;
MEAN1=MEAN;
STD1=STD;
KEEP WEEK N1 MEAN1 STD1;
DATA DRG2; SET STATS;
IF DRUG = 2;
N2=N;
MEAN2=MEAN;
STD2=STD;
KEEP WEEK N2 MEAN2 STD2;
DATA ALLST; MERGE DRG1 DRG2; BY WEEK;
/*CALCULATE THE T-STATISTIC */
IF _TYPE_ = 'SS3';
/*CALCULATE THE T-STATISTIC */
IF _TYPE_ = 'SS3';
/*CREATING DATA SETS WITH P-VALUES AND DEGREES OF FREEDOM */
DATA LEVENE; MERGE IOP2 STATS1; BY INVID DRUG WEEK;
Z =ABS PIFF -MEAN);
PROC SORT; BY INVID WEEK;
PROC GLM NOPRINT OUTSTAT=SUGIA.STAT2 NOPRINT; CLASS DRUG INVID;
MODEL Z = DRUG INVID DRUG;
LSMEANS DRUG /3S3;
DATA LEV2; SET LEV;
IF _SOURCE_ = 'ORUG';
LEVENE = PROB;
KEEP INVID WEEK LEVENE;
/*LEVENE TEST END *
Appendix 2 - levene's Test:
*/
CALCULATE LEVENE'S TEST FOR HOMOGENEITY OF VARIANCES */
PROC SORT DATA =STATS1; BY INV1D DRUG WEEK;
PROC SORT DATA =IOP2; BY INV1D DRUG WEEK;
DATA LEVENE; MERGE IOP2 STATS1; BY INVID DRUG WEEK;
Z =ABS(DIFF-MEAN);
PROC SORT BY INV1D;
PROC GLM NOPRINT OUTSTAT =LEV2; CLASSES DRUG BY INV1D WEEK;
MODEL Z = DRUG AS3;
DATA LEV2; SET LEV;
IF _SOURCE_ = 'DRUG';
LEVENE = PROB;
KEEP INV1D WEEK LEVENE;
/*LEVENE TEST END *
Appendix 3: Analysis By Investigator
*/
/*GENERATE P-VALUES FOR EACH INVESTIGATOR */
PROC GLM OUTSTAT=STAT2 NOPRINT; CLASS DRUG BY INV1D WEEK;
MODEL DIFF = DRUG AS3;
DATA OF; SET STAT2;
IF _SOURCE_ = 'ERROR';
PVALUE = PROB;
KEEP INVID WEEK OF;
DATA PVAL; SET STAT2;
IF _TYPE_ = 'SS3';
/*CALCULATE THE T-STATISTIC */
PVALUE = PROB;
KEEP INVID WEEK PVALUE;
DATA ALL; MERGE OF PVAL1; BY INVID WEEK;
PROC SORT DATA =LEV2; BY INVID;
DATA ALLST; MERGE ALLST ALL LEV2; BY INV1D WEEK;
PROC SORT BY INV1D;
PROC PRINT SPUT = '*DATA =ALLST';
TITLE 6 'TABLE 9.6';
TITLE 7 'SYSTOLIC BLOOD PRESSURE (MM Hg)';
TITLE 8 'ANALYSIS BY INVESTIGATOR';
APPENDIX 4: CONFIDENCE INTERVALS AND POWER CALCULATIONS:
*/
/*calculate confidence intervals */
diff1 = Ism3-ism1;
var1 = (se1*se1) + (se3*se3);
stderr1 = sqrt(var1);
diff2 = Ism2-ism1;
var2 = (se2*se2) + (se1*se1);
stderr2 = sqrt(var2);
t13 = (diff1)/stderr1;
t12 = (diff2)/stderr2;
P13 = (1-PROBT(ABS(T13),DF))*2;
P12 = (1-PROBT(ABS(T12),DF))*2;
P12 = (1 - PROBT(ABS(T12),DF))^2;  
\[ f = \text{finv}(0.95,1,\text{df}); \]
\[ t = \text{sqrt}(f); \]
\[ \text{LOW13} = \text{DIFF} + \text{T*STDERR1}; \]
\[ \text{UP13} = \text{DIFF} + \text{T*STDERR2}; \]
\[ \text{LOW12} = \text{DIFF} + \text{T*STDERR1}; \]
\[ \text{UP12} = \text{DIFF} + \text{T*STDERR2}; \]

Appendix 5: Combination drug trial

GROUP 1 vs 3*/  
GROUP 1 is the least squares mean of GROUP 3* */  
\[ \text{SE} 1 \text{ is the standard error of GROUP 1 */}\]
\[ \text{VAR 1 is the variance of the difference of */}\]

\[ \text{DIFF} 1 = \text{LSM 3} - \text{LSM 1}; \]
\[ \text{VAR 1} = (\text{SE}^2 1 + \text{SE}^2 3); \]
\[ \text{LSM1} = \text{MULT (VAR 1); } \]
\[ \text{DIFF} 2 = \text{LSM 2} - \text{LSM 1}; \]
\[ \text{VAR 2} = (\text{SE}^2 2 + \text{SE}^2 1); \]
\[ \text{LSM2} = \text{MULT (VAR 2); } \]
\[ \text{DIFF} 3 = \text{DIFF} 1 / \text{DIFF} 2; \]
\[ \text{DIFF} 4 = \text{DIFF} 1 / \text{DIFF} 2; \]
\[ \text{VAR 3} = (\text{SE}^2 1)^2; \]
\[ \text{LSM3} = \text{MULT (VAR 3); } \]
\[ \text{DIFF} 5 = \text{DIFF} 4 / \text{DIFF} 3; \]
\[ \text{VAR 4} = (\text{SE}^2 1)^2; \]
\[ \text{LSM4} = \text{MULT (VAR 4); } \]
\[ \text{DIFF} 6 = \text{DIFF} 5 / \text{DIFF} 4; \]

\[ \text{POWER} 12 = \text{PROBT(ABS(TBETAI2),DF)}; \]
\[ \text{POWER} 13 = \text{PROBT(ABS(TBETAI3),DF)}; \]

Appendix 6: Raw ANOVA Results From an OUTSTAT data set

<table>
<thead>
<tr>
<th>OBS</th>
<th>WEEK</th>
<th><em>NAME</em></th>
<th><em>SOURCE</em></th>
<th><em>TYPE</em></th>
<th>DF</th>
<th>SS</th>
<th>F</th>
<th>PROB</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0</td>
<td>DIFF</td>
<td>ERROR</td>
<td>ERROR</td>
<td>160</td>
<td>634.76</td>
<td>2</td>
<td>0.003</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>DIFF</td>
<td>DRUG</td>
<td>SS3</td>
<td>2</td>
<td>2.08</td>
<td>0.2617</td>
<td>0.77010</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>DIFF</td>
<td>INVID</td>
<td>SS3</td>
<td>5</td>
<td>9.46</td>
<td>0.4767</td>
<td>0.79324</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>DIFF</td>
<td>DRUG*INVID</td>
<td>SS3</td>
<td>10</td>
<td>58.10</td>
<td>1.4645</td>
<td>0.15723</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>DIFF</td>
<td>ERROR</td>
<td>ERROR</td>
<td>143</td>
<td>1023.44</td>
<td>2</td>
<td>0.003</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>DIFF</td>
<td>DRUG</td>
<td>SS3</td>
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<td>13.29</td>
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<td>0.39748</td>
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<td>11</td>
<td>1</td>
<td>DIFF</td>
<td>INVID</td>
<td>SS3</td>
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<td>12</td>
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<td>DRUG*INVID</td>
<td>SS3</td>
<td>10</td>
<td>46.15</td>
<td>0.6448</td>
<td>0.1633</td>
</tr>
</tbody>
</table>

TABLE 1

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>TWO-ARM PARALLEL TRIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
<td>B</td>
</tr>
<tr>
<td>-3</td>
<td>92</td>
</tr>
<tr>
<td>0</td>
<td>92</td>
</tr>
<tr>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>75</td>
</tr>
</tbody>
</table>

TABLE 2

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>ANALYSIS BROKEN DOWN BY INVESTIGATOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator</td>
<td>WEEK</td>
</tr>
<tr>
<td>99</td>
<td>-3</td>
</tr>
<tr>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
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</tr>
<tr>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>0</td>
<td>14</td>
</tr>
</tbody>
</table>
### Table 3

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo Least Squares Mean</th>
<th>Standard Error</th>
<th>Drug Least Squares Mean</th>
<th>Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3</td>
<td>-27.3</td>
<td>0.22</td>
<td>-21.0</td>
<td>0.34</td>
</tr>
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<td>0</td>
<td>191.0</td>
<td>0.21</td>
<td>190.5</td>
<td>0.32</td>
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<td>-21.0</td>
<td>0.46</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th>Week</th>
<th>Gp A/B Mean</th>
<th>Standard Error</th>
<th>Gp A Mean</th>
<th>Standard Error</th>
<th>Gp B Mean</th>
<th>Standard Error</th>
<th>A/B vs A P-Value</th>
<th>A/B vs B P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3</td>
<td>191.06</td>
<td>2.83</td>
<td>170.87</td>
<td>2.71</td>
<td>171.00</td>
<td>2.76</td>
<td>0.07</td>
<td>0.206</td>
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<tr>
<td>0</td>
<td>0.00</td>
<td>2.20</td>
<td>0.00</td>
<td>2.20</td>
<td>0.00</td>
<td>2.20</td>
<td>1.00</td>
<td>0.000</td>
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<tr>
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<td>0.00</td>
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<td>0.00</td>
<td>2.20</td>
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<tr>
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<td>0.00</td>
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<td>0.00</td>
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<td>2.20</td>
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<td>2.20</td>
<td>1.00</td>
<td>0.000</td>
</tr>
</tbody>
</table>

### Table 5

<table>
<thead>
<tr>
<th>Week</th>
<th>Source</th>
<th>Mean Square</th>
<th>Degrees of Freedom</th>
<th>F</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3</td>
<td>Drug</td>
<td>3.3765</td>
<td>2</td>
<td>0.067</td>
<td>0.432</td>
</tr>
<tr>
<td></td>
<td>Inv 1</td>
<td>36.2551</td>
<td>5</td>
<td>0.132</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Drug*Inv 1</td>
<td>12.3516</td>
<td>10</td>
<td>2.673</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Error</td>
<td>4.4734</td>
<td>150</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Drug</td>
<td>1.6951</td>
<td>2</td>
<td>0.752</td>
<td>0.403</td>
</tr>
<tr>
<td></td>
<td>Inv 1</td>
<td>1.9013</td>
<td>5</td>
<td>0.477</td>
<td>0.733</td>
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<tr>
<td></td>
<td>Drug*Inv 1</td>
<td>5.8192</td>
<td>10</td>
<td>1.465</td>
<td>0.157</td>
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<td>Error</td>
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<td>1</td>
<td>Drug</td>
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<td>0.929</td>
<td>0.397</td>
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<tr>
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### Table 6

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<th>Source</th>
<th>Mean Square</th>
<th>Degrees of Freedom</th>
<th>F</th>
<th>P-Value</th>
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<td>36.001</td>
<td>&lt;0.001</td>
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<td>1.593</td>
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<td>11.679</td>
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<td>15.785</td>
<td>91.2</td>
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Heywood adjustment factor = 1.00

Test of Homogeneity of within covariance matrices:
Chi-sq = 13.81, 10 df, p-value = 0.223

† Investigator
‡ Error mean square and df for drug effect. DF based on Satterthwaite approximation.
§ Error mean square and df for investigator effect. DF based on Satterthwaite approximation.
¶ Error mean square and df for investigator-by-drug effect. DF based on Satterthwaite approximation.