

Calculation and Assessment of Inferential Test Statistics for Meta-Analyses of Crossover Clinical Trials

Hurley, G.J., Procter and Gamble Pharmaceuticals, Inc., Mason, OH

ABSTRACT

Meta-analysis is the process of combining two or more similar data sets in order to make inference on the combined data set. In the case of clinical trials, this methodology is often used to increase the amount of data available and thereby increase the power to detect a difference between treatment groups. Meta-analysis is generally used to combine data sets from studies of similar design with similar end points. Traditionally, meta-analysis is used to combine data from two or more parallel designed data sets. However, it is often desirable to combine two or more crossover data sets or a number of crossover and parallel data sets with each other. Methodologies to do this, as defined by Curtin F, Elbourne D, and Altman DG in 2002, will be reviewed. A SAS macro written to simulate two cross-over trials and assess the results with respect to power and type I error rate of the test statistics defined by Curtin, et.al. will then be described. Results of this simulation will then be presented and discussed.

INTRODUCTION

In the realm of clinical trials, meta-analysis has generally been used to combine data sets only from clinical trials that have had a parallel design [4] however it is possible to implement the methodologies of meta-analysis on a number of two-period, two-sequence cross-over clinical trials or on a combination of parallel and two-period, two-sequence cross-over clinical trials. Although this methodology is not as straight forward as those involving only studies of parallel design, it is in fact quite tractable, and easily implemented in practice using a SAS[®] macro language. This methodology applies to both continuous [1] and binary [2] outcomes, although for the purposes of this paper, only continuous outcomes will be considered. Furthermore, methods exist of assessing meta-analytic carry-over effect across studies [3]. One thousand data sets have been simulated under a large number of scenarios by this author using a SAS macro. These data sets are simulated as if they come from two cross-over clinical trials. From these datasets, four test statistics described by Curtin, et.al. [3]. are calculated for each of the one thousand meta-analyses per scenario. From these results, error rates are calculated for these statistics.

METHODS

As the simulation assumes two cross-over trials, the methodology of Curtin, et.al. [3] is simplified to this case.

Assume the two two-period ("1" and "2"), two-sequence ("AB" and "BA") cross-over trials are evaluating the same treatment effect, θ , with a balanced number of subjects on each sequence and each period of each cross-over study, that is there are an equal number of subjects on each treatment-period combination on each study. The mean outcome obtained in trial i , sequence j , in period k can be written $\bar{y}_{ijk}$. $\bar{y}_{ijk}$ has variance v_{ijk} and covariance between the mean outcomes obtained in periods 1 and 2, cov_{ij12} . Define the average sequence difference in period 1 as $g_{i1} = \bar{y}_{i11} - \bar{y}_{i21}$. Likewise define the average sequence difference in period 2 as $g_{i2} = \bar{y}_{i22} - \bar{y}_{i12}$. Treatment effect on study i can be estimated by using the first period only, with the estimator $F_i = \bar{y}_{i11} - \bar{y}_{i21}$, or it can be estimated using both periods, with the estimator

$D_i = \frac{1}{2}(g_{i1} + g_{i2})$. However, this second estimator potentially contains bias from carry-over effect. Carry-over effect on

the i^{th} trial is defined as λ_i , and estimated by $S_i = s_{i1} - s_{i2}$, where $s_{ij} = \bar{y}_{ij1} + \bar{y}_{ij2}$, that is the sum of the average period outcome in sequence j . From the properties of variances and covariances, it follows that $v(F_i) = v_{i11} + v_{i21}$,

$v(D_i) = \frac{1}{4}(v_{i11} + v_{i12} + v_{i21} + v_{i22} - 2\text{cov}_{i112} - 2\text{cov}_{i212})$, and $v(S_i) = v_{i11} + v_{i12} + v_{i21} + v_{i22} + 2\text{cov}_{i112} + 2\text{cov}_{i212}$.

Define the weight estimators $w(F_i) = v(F_i)^{-1}$, $w(D_i) = v(D_i)^{-1}$, and $w(S_i) = v(S_i)^{-1}$. Curtin, et. al. [3] now propose the following pooled estimates of first period treatment effect, both period treatment effect, and carry-over effect, respectively:

$$\bar{Y}_{XOFirst} = \frac{\sum_{i=1}^k w(F_i)F_i}{\sum_{i=1}^k w(F_i)}$$

$$\bar{Y}_{XOCross} = \frac{\sum_{i=1}^k w(D_i)D_i}{\sum_{i=1}^k w(D_i)}, \text{ and}$$

$$\bar{C}_{XO} = \frac{\sum_{i=1}^k w(S_i) S_i}{\sum_{i=1}^k w(S_i)}.$$

Consider, $v(\bar{Y}_{XOCross}) = v\left(\frac{\sum_{i=1}^k w(D_i) D_i}{\sum_{i=1}^k w(D_i)}\right) = \frac{\sum_{i=1}^k w(D_i)^2 v(D_i)}{\left(\sum_{i=1}^k w(D_i)\right)^2}$ noting that $w(D_i) = v(D_i)^{-1}$,

$$\frac{\sum_{i=1}^k w(D_i)^2 v(D_i)}{\left(\sum_{i=1}^k w(D_i)\right)^2} = \frac{\sum_{i=1}^k w(D_i)}{\left(\sum_{i=1}^k w(D_i)\right)^2} = \frac{1}{\sum_{i=1}^k w(D_i)}.$$

Similarly,

$$v(\bar{Y}_{XOFirst}) = \frac{1}{\sum_{i=1}^k w(F_i)} \text{ and } v(\bar{C}_{XO}) = \frac{1}{\sum_{i=1}^k w(S_i)}.$$

One can now consider a number of hypotheses for any meta-analysis of a number of cross-over studies:

H_{00} : $\theta = \lambda^* = 0$, where θ is treatment effect and λ^* is one definition of meta-analytic carry-over effect (which can be defined in different ways [3]),

H_{01} : $\theta = 0$,

H_{02} : $\theta - \lambda^{**}/2 = 0$, where λ^{**} is another definition of meta-analytic carry-over effect [3], and

H_{03} : $\lambda^* = 0$.

Note that $\lambda^* = 0 \Leftrightarrow \lambda^{**} = 0$ [3]. For H_0 , the test statistic $T^2 = \begin{pmatrix} \bar{Y}_{XOCross} \\ \bar{C}_{XO} \end{pmatrix}^T S^{-1} \begin{pmatrix} \bar{Y}_{XOCross} \\ \bar{C}_{XO} \end{pmatrix}$ is considered [3], where

$$S = \begin{pmatrix} v(\bar{Y}_{XOCross}) & 0 \\ 0 & v(\bar{C}_{XO}) \end{pmatrix}. \text{ Hence, } T^2 = \frac{\bar{Y}_{XOCross}^2}{v(\bar{Y}_{XOCross})} + \frac{\bar{C}_{XO}^2}{v(\bar{C}_{XO})}. \text{ Using Hotelling-T}^2 \text{ distribution,}$$

$\frac{(n-p)T^2}{p(n-1)} \sim F_{p, n-p}$, where n is the sample size and p is the dimension of the random vectors. The current practice of

meta-analysis is to let n tend to infinity with approximate normal distribution [3]. Hence, we get $\frac{1}{2} T^2 \sim F_{2, \infty}$. Furthermore,

for H_1 , H_2 , and H_3 , Curtin, et. al., give the test statistics as $Z = \frac{\bar{Y}_{XOFirst}}{\sqrt{v(\bar{Y}_{XOFirst})}} \sim N(0,1)$, $Z = \frac{\bar{Y}_{XOCross}}{\sqrt{v(\bar{Y}_{XOCross})}} \sim N(0,1)$, and

$Z = \frac{\bar{C}_{XO}}{\sqrt{v(\bar{C}_{XO})}} \sim N(0,1)$, respectively. It is noted that in practice, H_{00} should be tested, followed by simultaneously testing

H_{01} , H_{02} , and H_{03} [3]. This will not inflate Type I Error rate [3].

SIMULATION MACRO

A SAS macro has been written to simulate data from two hypothetical trials, both having a cross-over design. The macro creates these data based upon means for each trial, sequence, and period based upon user input. The macro generates 1000 such two trial combinations and counts the number of times the four null hypotheses are rejected under each scenario. The goal of this is to assess the power and Type I Error rates of these statistics under each scenario. These hypothetical trials have 100 subjects each with 50 subjects on each leg.

In order to generate the data on the first trial, the following data step was used within the macro (a similar data step was used to simulate the second trial):

```
data one;
  length patno $8;
  %do i=1 %to 50;
    patno="&i";
    treatment="A";
    period="1";
    sequence="AB";
    outcome=rannor(&simulate+&cnt+1112200000)+&a1;
    output;
  %end;
  %do i=1 %to 50;
    patno="&i";
    treatment="B";
    period="2";
    sequence="AB";
    outcome=rannor(&simulate+&cnt+1613000000)+&b2;
    output;
  %end;
  %do i=51 %to 100;
    patno="&i";
    treatment="B";
    period="1";
    sequence="BA";
    outcome=rannor(&simulate+&cnt+1705000000)+&b1;
    output;
  %end;
  %do i=51 %to 100;
    patno="&i";
    treatment="A";
    period="2";
    sequence="BA";
    outcome=rannor(&simulate+&cnt+1112900000)+&a2;
    output;
  %end;
run;
```

Although most of this code should be understandable to readers familiar with macro, there are a couple points of interest regarding the seed of the rannor function. It should first be noted that the macro variables a1, a2, b1, and b2 represent the mean of each sequence and period within this study and the rannor function is adding a random variable from the standard normal distribution, $N(0,1)$, to each variable. As mentioned previously, it was determined to use a seed in order to replicate the generation of data. Hence the 10-digit numbers seen in the code above were chosen. However, as 1000 **different** sets of two trials were desirable, the addition of the macro variable simulate, which is a counter of the 1000 iterations is added to this 10-digit number, so a new data set will be generated with each iteration. Without this addition, the same data set would have been created 1000 times. Furthermore, the macro variable cnt is added there to get a different set of random variables added to each iteration of the macro. This macro variable is specified when the user calls the macro.

Following the generation of the first set of two trials, the statistics $\frac{1}{2}T^2 = \frac{1}{2} \left(\frac{\bar{Y}_{XOCros}^2}{v(\bar{Y}_{XOCross})} + \frac{\bar{C}_{XO}^2}{v(\bar{C}_{XO})} \right)$, $Z = \frac{\bar{Y}_{XOFirst}}{\sqrt{v(\bar{Y}_{XOFirst})}}$,

$Z = \frac{\bar{Y}_{XOCross}}{\sqrt{v(\bar{Y}_{XOCross})}}$, and $Z = \frac{\bar{C}_{XO}}{\sqrt{v(\bar{C}_{XO})}}$ are calculated as they are described above in the methods section. Means and

standard errors are generated using Proc SQL, while correlations are calculated using Proc Corr. These are then loaded into macro variables to use in calculating the aforementioned statistics. Macro variables are used for this purpose to reduce processing time in the simulation, as the data step appears to consume more resources than the macro facility.

SIMULATION RESULTS

Table 1 lists the results from this simulation, under a large number of simulated conditions. It should be noted that means were chosen between 7 and 16 to simulate responses that either show treatment, period, carryover, some combination of, or none of these effects. All data were generated using the Standard Normal distribution around these theoretical means. Some results are easily apparent from this table. First, it is noted that these test statistics, for the majority of cases have adequate Power or Type I Error rates. Hence, only those cases that are interesting will be discussed. The first of these is the case where the carryover effect is exactly twice that of the treatment effect for both studies. Under this scenario, one may note that H_{02} is actually true. Hence, what is seen in the table under this scenario is a Type I Error Rate near 0.05, as would be expected for a true null hypothesis. These scenarios are marked with the superscript b in the table. It is noted that this particular null hypothesis seems to be sensitive to carryover being twice treatment effect in only one study or to when the combination of the two studies may be close to this number. In those cases marked by the superscript c, it is seen that in the case where on study 1, $\theta=2$ and $\lambda=2$, while on study 2, $\theta=2$ and $\lambda=4$, H_{02} was rejected only 111 times. Likewise, when $\theta=0$ and $\lambda=4$ on study 1 and $\theta=2$ and $\lambda=0$ on study 2, H_{02} was rejected 278 times. Finally, in the case where on study 1, $\theta=4$ and $\lambda=4$, while $\theta=2$, with $\lambda=4$ on study 2, H_{02} was rejected only 268 times. Hence, H_{02} appears to lack power in these circumstances. Another interesting note is that these test statistics seem to be able to differentiate between period effect and other effects. There are several examples of period effect illustrated in the table. For these examples, the test statistics generally behave well. For the five cases where only Period effect is present, Type I Error may be slightly inflated, since 16 of 20 estimated values were above 0.05, while only 3 were below 0.05 (one was exactly 0.05). However, it should be noted that these values were bounded from above by 0.082 and from below by 0.045. Those 16 values above 0.05 were fairly evenly distributed among the four null hypotheses. When period effect was considered in the presence of treatment effect, the first three null hypotheses (H_{00} , H_{01} , and H_{02}) were rejected with power=1.00. H_{03} , which tested carryover effect, showed no more rejection than expected with Type I Error. In general, then, these test statistics had good behavior with respect to Period Effect. A quick review of the table clearly shows that, in general, these test statistics have large power and acceptable Type I Error rates with respect to treatment effect and carryover effect.

TABLE 1: SIMULATION RESULTS / TYPE I ERROR RATE AND POWER

Condition								$H_{00}: \theta = \lambda^* = 0$		$H_{01}: \theta = 0$		$H_{02}: \theta - \lambda^{**}/2 = 0$		$H_{03}: \lambda^* = 0$	
S1 T1 P1 a	S1 T1 P2 a	S1 T2 P1 a	S1 T2 P2 a	S2 T1 P1 a	S2 T1 P2 a	S2 T2 P1 a	S2 T2 P2 a	Number of times rejected	Estimated Power or Type I Error Rate	Number of times rejected	Estimated Power or Type I Error Rate	Number of times rejected	Estimated Power or Type I Error Rate	Number of times rejected	Estimated Power or Type I Error Rate
7	7	7	7	7	7	7	7	61	$\alpha=0.061$	67	$\alpha=0.067$	55	$\alpha=0.055$	50	$\alpha=0.050$
7	7	9	9	7	7	9	9	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	68	$\alpha=0.068$
7	7	11	11	7	7	11	11	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	43	$\alpha=0.043$
7	9	7	9	7	9	7	9	63	$\alpha=0.063$	67	$\alpha=0.067$	51	$\alpha=0.051$	62	$\alpha=0.062$
7	11	7	11	7	11	7	11	49	$\alpha=0.049$	61	$\alpha=0.061$	45	$\alpha=0.045$	49	$\alpha=0.049$
7	9	7	7	7	9	7	7	1000	$1-\beta=1.000$	54	$\alpha=0.054$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$
7	11	7	7	7	11	7	7	1000	$1-\beta=1.000$	64	$\alpha=0.064$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$
7	9	9	11	7	9	9	11	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	48	$\alpha=0.048$
7	9	11	13	7	9	11	13	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	45	$\alpha=0.045$
7	11	11	15	7	11	11	15	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	56	$\alpha=0.056$
7	9	9	9	7	9	9	9	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$
7	9	11	11	7	9	11	11	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$
7	11	9	9	7	11	9	9	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	48 ^b	$\alpha=0.048$	1000	$1-\beta=1.000$
7	11	11	11	7	11	11	11	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$
7	9	9	9	8	10	8	8	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	111 ^c	$1-\beta=0.111$	1000	$1-\beta=1.000$
7	9	9	9	8	10	10	10	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$
7	9	9	9	8	8	10	10	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	999	$1-\beta=0.999$
7	9	7	9	8	12	8	12	76	$\alpha=0.076$	82	$\alpha=0.082$	68	$\alpha=0.068$	71	$\alpha=0.071$
7	9	7	9	8	10	8	10	55	$\alpha=0.055$	65	$\alpha=0.065$	53	$\alpha=0.053$	50	$\alpha=0.050$
7	9	11	13	8	12	12	16	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	46	$\alpha=0.046$
7	9	11	13	8	12	10	14	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	51	$\alpha=0.051$
7	9	11	13	8	10	12	14	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	58	$\alpha=0.058$
7	9	11	13	8	10	10	12	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	54	$\alpha=0.054$
7	9	9	11	8	12	10	14	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	46	$\alpha=0.046$
7	9	9	11	8	10	10	12	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	46	$\alpha=0.046$
7	7	9	9	9	9	11	11	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	61	$\alpha=0.061$
7	11	7	7	8	12	8	8	1000	$1-\beta=1.000$	74	$\alpha=0.074$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$
7	11	7	7	8	8	12	12	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$
7	11	7	7	8	8	10	10	1000	$1-\beta=1.000$	1000	$1-\beta=1.000$	278 ^c	$1-\beta=0.278$	1000	$1-\beta=1.000$

^a S – Study T – Treatment P – Period

^b This result is expected as carry-over effect is twice treatment effect.
^c These results are described in detail in the text.
 α = Type I Error Rate (Estimated Probability of Incorrectly Rejecting the Null Hypothesis at the 0.05 Level)
 $1-\beta$ = Power (Estimated Probability of Correctly Rejecting the Null Hypothesis at the 0.05 Level)

TABLE 1 CONTINUED: SIMULATION RESULTS / TYPE I ERROR RATE AND POWER

Condition								$H_{00}: \theta = \lambda^* = 0$		$H_{01}: \theta = 0$		$H_{02}: \theta - \lambda^{**}/2 = 0$		$H_{03}: \lambda^* = 0$	
7	11	11	11	8	12	12	12	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000
7	11	11	11	8	12	8	8	1000	1- β =1.000	1000	1- β =1.000	268 ^c	1- β =0.268	1000	1- β =1.000
7	11	11	11	8	12	10	10	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000
7	11	11	11	8	8	12	12	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000
7	11	11	11	8	10	12	12	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000
7	11	11	11	8	10	8	8	1000	1- β =1.000	1000	1- β =1.000	977	1- β =0.977	1000	1- β =1.000
7	11	11	11	8	10	10	10	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000
7	11	11	11	8	8	10	10	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000
7	11	7	7	9	13	9	9	1000	1- β =1.000	49	α =0.049	1000	1- β =1.000	1000	1- β =1.000
7	11	7	7	9	11	9	9	1000	1- β =1.000	61	α =0.061	1000	1- β =1.000	1000	1- β =1.000
7	11	9	9	8	12	8	8	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000
7	11	9	9	8	12	10	10	1000	1- β =1.000	1000	1- β =1.000	62 ^b	α =0.062	1000	1- β =1.000
7	11	9	9	8	8	12	12	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000
7	11	9	9	8	10	8	8	1000	1- β =1.000	1000	1- β =1.000	998	1- β =0.998	1000	1- β =1.000
7	11	9	9	8	8	10	10	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000
7	11	7	11	8	12	8	12	64	α =0.064	69	α =0.069	60	α =0.060	68	α =0.068
7	7	7	7	9	9	9	9	64	α =0.064	68	α =0.068	55	α =0.055	59	α =0.059
7	11	11	15	8	12	12	16	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	60	α =0.060
7	11	11	15	8	12	10	14	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	45	α =0.045
7	11	9	13	8	12	10	14	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	45	α =0.045
7	7	11	11	9	9	13	13	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	49	α =0.049
7	7	11	11	9	9	11	11	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	49	α =0.056
7	9	7	7	8	12	8	8	1000	1- β =1.000	50	α =0.050	1000	1- β =1.000	1000	1- β =1.000
7	9	7	7	8	8	12	12	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	997	1- β =0.997
7	9	7	7	8	10	8	8	1000	1- β =1.000	65	α =0.065	1000	1- β =1.000	1000	1- β =1.000
7	9	7	7	8	8	10	10	1000	1- β =1.000	1000	1- β =1.000	980	1- β =0.980	999	1- β =0.999
7	9	11	11	8	12	8	8	1000	1- β =1.000	1000	1- β =1.000	928	1- β =0.928	1000	1- β =1.000
7	9	11	11	8	12	10	10	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000
7	9	11	11	8	8	12	12	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	998	1- β =0.998
7	9	11	11	8	10	12	12	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000
7	9	11	11	8	10	8	8	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000
7	9	11	11	8	10	10	10	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000

MWSUG 15-P4

7	9	11	11	8	8	10	10	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	999	1- β =0.999
7	9	9	9	8	12	8	8	1000	1- β =1.000	1000	1- β =1.000	986	1- β =0.986	1000	1- β =1.000
7	9	9	9	8	12	10	10	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000
7	9	9	9	8	8	12	12	1000	1- β =1.000	1000	1- β =1.000	1000	1- β =1.000	998	1- β =0.998
^a S – Study T – Treatment P – Period ^b This result is expected as carry-over effect is twice treatment effect. ^c These results are described in detail in the text. α = Type I Error Rate (Estimated Probability of Incorrectly Rejecting the Null Hypothesis at the 0.05 Level) 1- β = Power (Estimated Probability of Correctly Rejecting the Null Hypothesis at the 0.05 Level)															

CONCLUSION:

These statistics clearly have good properties with regard to Type I Error Rate and Power. H_{02} is the hardest of these hypotheses to interpret, due to the fact that it is a contrast between treatment and carryover effect. However, it may still be of interest for certain applications or for academic interest. This paper did not address the issue of simultaneously testing the last three hypotheses.

Additionally, it must be noted that with these statistics, while derived theoretically [1, 3], were tested here programmatically via simulation. This is often of great value to determine Power and Type I Error Rate of test statistics. This type of simulation is very simple to write using the SAS System, as the code presented here has illustrated.

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CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

George J. Hurley
Procter and Gamble Pharmaceuticals, Inc.
Health Care Research Center, Box 594
8700 Mason Montgomery Road
Mason, OH 45040
Phone: (513) 622-3020
Fax: (513) 622-0987
Email: hurley.gj@pg.com