

Modified data analysis in two period cross-over design

Abstract

This paper proposes and presents a chi-square statistical method for the analysis of response from one period cross over design for two sample data in which the sampled populations may be measurements that are numeric (assuming real values) and non-numeric assuming only values on the nominal scale. Test statistics are developed for testing the null hypothesis that subjects who receive each of the treatments first do not differ in their response as well as the null hypothesis that subjects exposed to one of the treatment or experimental conditions first do not on the average differ in their responses with those exposed to the other treatment or experimental condition first. Estimates of the proportions responding positive; experiencing no change in response or responding negative are provided for subjects exposed to each treatment first as well as for the two treatments together. The proposed method which is illustrated with some sample data can be used with either numeric or non-numeric data and is shown to be at least as powerful as the traditional two sample small 't' test.

Keywords: cross over, treatment, chi-square, design, patients

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Introduction

Suppose subjects for a clinical trial are first matched on characteristics associated with the outcome under study such as a disease and randomly assigned the treatments T_1 and T_2 . In particular, suppose as in a cross over design each subject serves as his own control, that is, each patient receives each treatment. One half of the sample of $2n$ patients or subjects is randomly selected to be given the two treatments in one order and the other half to be given the treatments in the reversed order. That is n of the random sample of the $2n$ patients or subjects is given treatment T_2 first and treatment T_1 later and the remaining n subjects is given treatment T_1 first and treatment T_2 later.

A number of factors must be guarded against in analyzing the data from such studies. However, the order in which the treatments are given may affect the response.¹ A test that is valid when order effects are present has been described by Gart.² Another factor to be guarded against is the possibility that a treatment's effectiveness may be long lasting and hence may affect the response to the treatment given after it. When this so-called carry over effect operates and when it is unequal for the two treatments, then for comparing their effectiveness, only the data from the first period may be used.³ Specifically, the responses by the subjects given one of the treatments first must be compared with the responses by the subjects given the other treatment first. In this paper we present a method for analyzing data from a crossover design in which each subjects serves as his own control and analysis is based on responses by patients given one of the treatments first and responses by patients given the other treatment first. Here allowance is made for the possibility that patients or subjects may die or drop out of the study.

The proposed method

In the regular two crossover design were subjects served as own control in controlled clinical trials or diagnosis screening test to study the differential effects of two procedures such as drugs or treatments. Random samples of matched pairs might in terms of some

demographic characteristics such as age, gender or body mass index are used. A randomly selected subject from each of the matched pairs of subjects is given or administered one of the 2 treatments or drugs first, while the remaining subjects in the matched pair of subjects is given or administered the remaining test drug or treatment first. This procedure is later repeated in the reverse order. That is the randomly selected subject in each matched pair of subjects given one of the two days first is now given the other drug or treatments while the remaining subject in the pair earlier given the 2nd treatment first is now given the first treatment or drug. Because of some of the problems that may often arise in these type of clinical trials in which the effects of the drugs may be long lasting, each having carry-over effects with long dry out periods, the usual practice is often to base statistical analysis and comparison of subject responses to the two treatments on only subject responses to treatments, tests or drug administered first, while treating responses obtained during the second administration of the drugs perhaps only to gauge the pattern of responses.

We here however propose a modification of this approach. Here only those subjects in each matched pairs of subjects who failed to respond positive when administered one of the treatments or tests will be administered a second treatment or test later. Similarly only those subjects in each matched pair of subjects who respond negative when administered the second drug or treatment first will later be administered the other treatment. This approach would enable the researcher not only compare the differential effects of the 2 drugs or treatment when they are administered to subjects in the matched pairs of subjects with one of the treatments given one of the subjects first and the other treatments given to the remaining subjects in the pair first. The procedure will also enable the researcher determine whether on the average the proportion of matched pairs of subjects who fail to respond positive when administered one of the 2 treatment first but respond positive when administered the other treatment later are equal to a proportion of subjects in a matched pairs of subjects who respond negative when administered the second treatment first but respond positive when administered the first treatment later.

To develop a statistical method to compare the proportion of subjects in the matched pairs of subjects who respond positive when

administered the test, drug or treatment T_2 say first with the proportion of subjects in the matched pairs of subjects who test or respond positive when administered test, drug, or treatment T_2 first we may proceed as follows:

Suppose n is a number of randomly selected matched pairs of subjects to be used in a screening test or clinical trials. Suppose further one subject in a randomly selected matched pairs of subjects is administered treatment T_2 say and the remaining subjects in the matched pair of subject is administered treatment T_2 say first.

Let

$$u_{il1} = \begin{cases} 1, & \text{if in the } i\text{th pair of match subjects, a randomly selected} \\ & \text{subject is administered test drug treatment } T_1 \text{ first} \\ 0, & \text{otherwise} \end{cases}$$

for $i = 1, 2, \dots, n$ th pairs; $l = 1, 2, \dots, \text{treatments}$.

Let

$$\pi_{l1}^+ = P(u_{il1}) = 1$$

And

$$W_{l1} = \sum_{i=1}^n u_{il1}$$

Now the expected value and variance of u_{il1} are respectively

$$E(u_{il1}) = \pi_{l1}^+; \text{Var}(u_{il1}) = \pi_{l1}^+(1 - \pi_{l1}^+)$$

Similarly the expected value and variance W_{l1} are respectively

$$E(W_{l1}) = \sum_{i=1}^n E(u_{il1}) = n\pi_{l1}^+; \text{Var}(W_{l1}) = \sum_{i=1}^n \text{Var}(u_{il1}) = n\pi_{l1}^+(1 - \pi_{l1}^+)$$

Now T_l is the proportion of the probability that a subject in randomly selected matched pair of subjects test or responds positive when administered test, or treatment T_l first in a two period controlled trial or diagnostic screening test, for $l=2$ its sample estimate is

$$\hat{\pi}_{l1}^+ = P_{l1} = \frac{f_{l1}^+}{n} = \frac{W_{l1}}{n}$$

Where $f_{l1}^+ = W_{l1}$ is the total number of subjects in the matched pairs of subjects who test or respond positive when administered treatment T_l first in a diagnostic screening test or controlled clinical trial. In

other words, $f_{l1}^+ = W_{l1}$ is the total number of 1's in the frequency distribution of the n values of 0s and 1s in u_{il1} , for $l=1, 2, \dots, n; i=1, 2, \dots, n$.

The corresponding sample estimate of the variance of $\hat{\pi}_{l1}^+$ is

$$\text{Var}(\hat{\pi}_{l1}^+) = \text{Var}\left(\frac{W_{l1}}{n}\right) = \frac{\hat{\pi}_{l1}^+(1 - \hat{\pi}_{l1}^+)}{n} = \frac{P_{l1}(1 - P_{l1})}{n}$$

A null hypothesis that is usually of interest in two period cross over design is that the proportion of subjects in the period populations of subjects administered test, drug, or treatment T_l first is the same as the proportion of subjects in the paired populations of subjects administered test, drug, or treatment T_2 first in a control clinical trial, or the null hypothesis

$$H_0: \pi_{l1}^+ = \pi_{l2}^+ \text{ versus } H_1: \pi_{l1}^+ \neq \pi_{l2}^+$$

(1) Now the sample estimate of the difference in proportion, $\pi_{l1}^+ - \pi_{l2}^+$ is

$$(2) \quad \hat{\pi}_{l1}^+ - \hat{\pi}_{l2}^+ = p_{l1} - p_{l2} = \frac{f_{l1}^+ - f_{l2}^+}{n} = \frac{W_{l1} - W_{l2}}{n}$$

Whose estimated variance is

$$(3) \quad \text{Var}(\hat{\pi}_{l1}^+ - \hat{\pi}_{l2}^+) = \text{Var}(p_{l1} - p_{l2}) = \text{Var}\left(\frac{W_{l1} - W_{l2}}{n}\right)$$

Now it is easily shown using the specifications of equations 1-3 that $\text{Cov}(W_{l1}, W_{l2}) = 0$

Hence

$$(4) \quad \text{Var}(\hat{\pi}_{l1}^+ - \hat{\pi}_{l2}^+) = \text{Var}(p_{l1} - p_{l2}) = \frac{\text{Var}(W_{l1}) + \text{Var}(W_{l2})}{n^2} = \frac{\hat{\pi}_{l1}^+(1 - \hat{\pi}_{l1}^+) + \hat{\pi}_{l2}^+(1 - \hat{\pi}_{l2}^+)}{n}$$

Hence the chi-square test statistic for the null hypothesis H_0 of equation 8 is

$$\chi^2 = \frac{(\hat{\pi}_{l1}^+ - \hat{\pi}_{l2}^+)^2}{\text{Var}(\hat{\pi}_{l1}^+ - \hat{\pi}_{l2}^+)} = \frac{(W_{l1} - W_{l2})^2}{\text{Var}(W_{l1}) + \text{Var}(W_{l2})} = \frac{n(\hat{\pi}_{l1}^+ - \hat{\pi}_{l2}^+)^2}{\hat{\pi}_{l1}^+(1 - \hat{\pi}_{l1}^+) + \hat{\pi}_{l2}^+(1 - \hat{\pi}_{l2}^+)}$$

Which under the null hypothesis of equation 8 has approximately the chi-square distribution with 1 degree of freedom for sufficiently large n ?

Where $\hat{\pi}_{l1}^+ = p_{l1}$, for $l=1, 2$

The null hypothesis H_0 of equation 8 is rejected at the α level of significant if $\chi^2 \geq \chi_{1-\alpha;1}^2$, otherwise the null hypothesis H_0 is accepted. As earlier noted above an additional and modified method of or approach to the analysis of data obtained in a two period cross over design is to also compare the responses of those subjects in the

matched paired populations of subjects who failed to test or respond positive to one of the two treatment when administered first but respond positive when the other treatment is administered to them later with the responses of the remaining subjects who failed to respond positive when administered the second test or treatment first but respond positive when administered the first test or treatment later that is at the second trial. In these cases interest is then only in the

$n_{l_1} = n - f_{j_1}^+$ subjects who failed to respond positive when administered test or treatment T_l first but respond positive when administered test or treatment T_l later, that is at the second clinical trial or diagnostic screening test, for $l, j=1, 2; l \neq j$. To conduct this additional and modified analysis of response data, we may let

$$u_{il_2;j} = \begin{cases} 1, & \text{if for the } i\text{th night pair of subjects, the subject} \\ & \text{administered treatment } T_j \text{ first fails to respond} \\ & \text{positive but respond positive when the same subset is administered} \\ & \text{treatment } T_l \text{ later that is at the second trial} \\ 0, & \text{otherwise} \end{cases} \tag{13}$$

for $i = 1, 2, \dots, n_{l_2} = n - f_j^+; l, j = 1, 2; l \neq j$.

Let $\pi_{l_2}^+ = P(u_{il_2;j}=1)$ (14)

And $W_{l_2} = \sum_{i=1}^{n_{l_2}} u_{il_2;j}$ (15)

Now the expected value and variance of $u_{il_2;j}$ are respectively

$$E(u_{il_2;j}) = \pi_{l_2}^+, \text{Var}(u_{il_2;j}) = \pi_{l_2}^+(1 - \pi_{l_2}^+) \tag{16}$$

Similarly the expected value and variance of W_{l_2} are respectively

$$E(W_{l_2}) = \sum_{i=1}^{n_{l_2}} E(u_{il_2;j}) = n_{l_2} \pi_{l_2}^+, \text{Var}(W_{l_2}) = \sum_{i=1}^{n_{l_2}} \text{Var}(u_{il_2;j}) = n_{l_2} \pi_{l_2}^+(1 - \pi_{l_2}^+) \tag{17}$$

Now T_l is the proportion or the probability that a randomly selected subject in the matched pairs of subjects administered test or treatment T_l first fail to respond positive but this same subject respond positive when administered test or treatment T_l later, that is at the second trial. Its sample estimate is

$$\hat{\pi}_{l_2}^+ = P_{l_2} = \frac{f_{l_2}^+}{n_{l_2}} = \frac{W_{l_2}}{n_{l_2}} \tag{18}$$

Where $f_{l_2}^+ = W_{l_2}$ are the total number of subjects in the matched pairs of subjects who failed to respond positive when administered test for treatment T_j first but respond positive when administered test or treatment T_l later, that at the second trial. In other words, $f_{l_2}^+ = W_{l_2}$ is the total number of 1s in the frequency distribution of the n_{l_2} values of 0s and 1s in $u_{il_2;j}$, for $i=1, 2, \dots, n_{l_2} = n - f_{l_1}^+; (l, j=1, 2; l \neq j)$.

The sample estimate of the variance of $\pi_{l_2}^+$ is

$$\text{Var}(\hat{\pi}_{l_2}^+) = \frac{\text{Var}(P_{l_2})}{n_{l_2}} = \frac{\text{Var}(W_{l_2})}{n_{l_2}^2} = \frac{\pi_{l_2}^+(1 - \pi_{l_2}^+)}{n_{l_2}} \tag{19}$$

As noted above, an additional null hypothesis that may be of further research interest when expressed in terms of the difference between population proportions is

$$H_0: \pi_{12}^+ = \pi_{22}^+ \text{ versus } H_1: \pi_{12}^+ \neq \pi_{22}^+ \tag{20}$$

Now the sample estimate of the difference in population proportion is

$$\hat{\pi}_{12}^+ - \hat{\pi}_{22}^+ = P_{12} - P_{22} = \frac{f_{12}^+}{n_{12}} - \frac{f_{22}^+}{n_{22}} = \frac{W_{12}}{n_{12}} - \frac{W_{22}}{n_{22}} \tag{21}$$

The corresponding sample estimate of the variance of $\hat{\pi}_{12}^+ - \hat{\pi}_{22}^+$ is

$$\text{Var}(\hat{\pi}_{12}^+ - \hat{\pi}_{22}^+) = \text{Var}(P_{12} - P_{22}) = \text{Var}\left(\frac{W_{12}}{n_{12}} - \frac{W_{22}}{n_{22}}\right) \tag{22}$$

It is easily shown using the specification of equations 13-15 that $\text{Cov}(W_{12}, W_{22}) = 0$.

Hence

$$\text{Var}(\hat{\pi}_{12}^+ - \hat{\pi}_{22}^+) = \text{Var}\left(\frac{W_{12}}{n_{12}}\right) + \text{Var}\left(\frac{W_{22}}{n_{22}}\right) = \frac{\hat{\pi}_{12}^+(1 - \hat{\pi}_{12}^+)}{n_{12}} + \frac{\hat{\pi}_{22}^+(1 - \hat{\pi}_{22}^+)}{n_{22}} \tag{23}$$

The null hypothesis H_0 in equation 20 may now be treated using the chi-square test statistic

$$\chi^2 = \frac{(\hat{\pi}_{12}^+ - \hat{\pi}_{22}^+)^2}{Var(\hat{\pi}_{12}^+ - \hat{\pi}_{22}^+)} = \frac{\left(\frac{W_{12}}{n_{12}} - \frac{W_{22}}{n_{22}}\right)^2}{Var(\hat{\pi}_{12}^+ - \hat{\pi}_{22}^+)} = \frac{n_{12} \cdot n_{22} (\hat{\pi}_{12}^+ - \hat{\pi}_{22}^+)^2}{n_{22} \cdot \hat{\pi}_{12}^+ (1 - \hat{\pi}_{12}^+) + n_{12} \cdot \hat{\pi}_{22}^+ (1 - \hat{\pi}_{22}^+)} \tag{24}$$

Which under the null hypothesis H_0 of equation 20 has approximately the chi-square distribution with 1 degree of freedom for sufficiently large values of n_{12} . $\hat{\pi}_{12}^+ = p_{12}$, for $l=1,2$ and n_{22} . The null hypothesis H_0 of equation 20 is rejected at the α level of significance if equation 12 is satisfied; otherwise H_0 is accepted.

Illustrative example

A researcher clinician is interested in comparing the effectiveness of two malaria drugs, D_1 and D_2 in the treatment of malaria using two period crossover designs in a controlled clinical trial. She collected 40 random samples of matched pairs of malaria patients, matched by age, sex and body weight. She administered treatment D_1 first to a randomly selected patient in each pair of patients and also administered the remaining drug D_2 first to the other patient in the pair. After the dry out period she repeated a drug administration in the reverse order. But this time she administered drug D_1 to only those

patients who fail to improve, that is who fail to respond positive when administered drug D_2 first, and also administered drug D_2 now to only those patients who fail to recover when administered drug D_1 first. The results are presented in Table

Now from Table 1 we have that $f_{11}^+ = 20; f_{11}^- = 20; f_{21}^+ = 15$ and $f_{21}^- = 25$.

Hence

$$\hat{\pi}_{11}^+ = P_{11} = \frac{20}{40} = 0.50; \hat{\pi}_{11}^- = 1 - P_{11} = 1 - \frac{20}{40} = 1 - 0.50 = 0.50;$$

$$\hat{\pi}_{21}^+ = P_{21} = \frac{15}{40} = 0.375; \text{ and } \hat{\pi}_{21}^- = 1 - P_{21} = \frac{25}{40} = 0.625$$

To test the null hypothesis H_0 of equation 8 we have from equation 11 that

$$\chi^2 = \frac{40(0.50 - 0.375)^2}{(0.50)(0.50) + (0.375)(0.625)} = \frac{0.625}{0.250 + 0.234} = 1.291 (P\text{-value} = 0.1208)$$

Which with 1 degree of freedom is not statistical significant ($P\text{-value} = 0.1208$). Further research interest would now be to administer treatment T_1 (drug D_2) to subject who fail to respond positive when administered treatment T_2 (drug D_2) first, and also to administer treatment T_2 (drug D_2) to subjects who fail to respond positive when administered treatment T_1 (drug D_1) first and compare the positive responds rates for the two groups of subjects. The results are shown in Table 2.

Table 1 Responses (+,-) by subjects in Randomly Selected Matched pairs Administered Treatment T_l first (u_{il})

Pair(i)	$u_{i1} u_{i2l}$	Pair(i)	$u_{i1} u_{i2l}$	Pair(i)	$u_{i1} u_{i2l}$
1	$T_1^+ \quad T_2^-$	15	$T_2^+ \quad T_2^+$	29	$T_2^- \quad T_2^-$
2	$T_2^- \quad T_2^-$	16	$T_2^- \quad T_2^+$	30	$T_2^+ \quad T_1^-$
3	$T_2^+ \quad T_1^+$	17	$T_1^+ \quad T_2^-$	31	$T_2^- \quad T_2^-$
4	$T_1^- \quad T_2^-$	18	$T_1^- \quad T_1^-$	32	$T_2^- \quad T_1^+$
5	$T_1^- \quad T_1^-$	19	$T_1^- \quad T_1^-$	33	$T_1^- \quad T_2^+$
6	$T_2^- \quad T_2^-$	20	$T_2^- \quad T_1^-$	34	$T_2^+ \quad T_1^-$
7	$T_2^+ \quad T_2^+$	21	$T_2^- \quad T_1^+$	35	$T_1^+ \quad T_2^+$

Table Continued

Pair(i)	$u_{i1} u_{i2}$	Pair(i)	$u_{i1} u_{i2}$	Pair(i)	$u_{i1} u_{i2}$
8	$T_1^+ T_2^-$	22	$T_2^- T_1^+$	36	$T_2^- T_2^-$
9	$T_2^- T_1^+$	23	$T_2^+ T_2^+$	37	$T_1^- T_2^-$
10	$T_2^+ T_2^+$	24	$T_2^+ T_1^-$	38	$T_1^- T_1^-$
11	$T_1^- T_1^-$	25	$T_1^- T_2^-$	39	$T_1^- T_2^-$
12	$T_2^- T_1^+$	26	$T_2^- T_2^-$	40	$T_2^- T_1^-$
13	$T_1^- T_1^-$	27	$T_1^+ T_2^-$		
14	$T_2^+ T_2^+$	28	$T_2^- T_1^+$		

Table 2 Responses (+,-) to treatment T_j by Randomly Selected subjects from Matched Pairs of Subjects who fail to Respond positive when Treated with Treatment T_j first (u_{i12})

S/N of Subjects Responding Negative When Given Treatment T_2 First	Subject Response to Treatment T_1 When Given Later	u_{i12}	S/N of Subjects Responding Negative When Given Treatment T_1 First	Subject Response to Treatment T_2 When Given Later	T_2^-
1	T_2^-	T_1^+	1	T_1^-	T_2^-
2	T_2^-	T_1^+	3	T_2^+	T_2^+
4	T_2^-	T_1^-	4	T_2^+	T_2^+
5	T_2^-	T_1^+	5	T_2^-	T_2^-
6	T_2^-	T_1^-	11	T_2^-	T_2^-
8	T_2^-	T_1^-	13	T_1^-	T_2^+
9	T_2^-	T_1^-	15	T_2^+	T_2^+
11	T_2^-	T_1^-	16	T_1^-	T_2^+
12	T_2^-	T_1^-	18	T_1^-	T_2^-
16	T_1^-	T_1^-	20	T_1^-	T_2^-

Table Continued

S/N of Subjects Responding Negative When Given Treatment T ₂ First	Subject Response to Treatment T ₁ When Given Later	<i>u_{i12}</i>	S/N of Subjects Responding Negative When Given Treatment T ₁ First	Subject Response to Treatment T ₂ When Given Later	<i>T₂⁻</i>
17	<i>T₁⁺</i>	<i>T₁⁺</i>	24	<i>T₁⁻</i>	<i>T₂⁻</i>
19	<i>T₁⁻</i>	<i>T₁⁻</i>	25	<i>T₁⁻</i>	<i>T₂⁻</i>
20	<i>T₁⁻</i>	<i>T₁⁻</i>	30	<i>T₁⁻</i>	<i>T₂⁻</i>
21	<i>T₂⁻</i>	<i>T₁⁺</i>	31	<i>T₁⁻</i>	<i>T₂⁻</i>
22	<i>T₂⁻</i>	<i>T₁⁻</i>	33	<i>T₂⁻</i>	<i>T₂⁻</i>
25	<i>T₂⁻</i>	<i>T₁⁺</i>	34	<i>T₂⁺</i>	<i>T₂⁺</i>
26	<i>T₂⁻</i>	<i>T₁⁺</i>	37	<i>T₂⁻</i>	<i>T₂⁻</i>
27	<i>T₂⁻</i>	<i>T₁⁻</i>	38	<i>T₂⁻</i>	<i>T₂⁻</i>
28	<i>T₂⁻</i>	<i>T₁⁻</i>	39	<i>T₂⁺</i>	<i>T₂⁺</i>
29	<i>T₂⁻</i>	<i>T₁⁻</i>	40	<i>T₂⁺</i>	<i>T₂⁺</i>
31	<i>T₁⁻</i>	<i>T₁⁻</i>			
32	<i>T₁⁺</i>	<i>T₁⁺</i>			
37	<i>T₂⁻</i>	<i>T₁⁺</i>			
38	<i>T₁⁺</i>	<i>T₁⁺</i>			
40	<i>T₂⁻</i>	<i>T₁⁺</i>			

Now from Table 2 we have that $f_{12}^+ = 13, f_{12}^- = 12, f_{22}^+ = 12$ and $f_{22}^- = 8$.

Hence

$$\hat{\pi}_{12}^+ = P_{12} = \frac{13}{25} = 0.52; \hat{\pi}_{12}^- = 1 - P_{12} = \frac{12}{25} = 0.48; \hat{\pi}_{22}^+ = P_{22} = \frac{12}{20} = 0.60 \text{ and } \hat{\pi}_{22}^- = 1 - P_{22} = \frac{8}{20} = 0.40$$

Therefore the resulting difference in positive response rates by those two populations of subjects is estimated as

$$\hat{\pi}_{12}^+ - \hat{\pi}_{22}^+ = P_{12} - P_{22} = 0.52 - 0.60 = -0.08$$

To test the null hypothesis H_0 of equation 20 that subjects who fail to respond positive when administered treatment $T_2(D_2)$ first but respond positive when administered treatment $T_1(D_1)$ first are equally likely to experience the same level of positive responds this time around as subject who fail to respond positive when administered treatment $T_1(D_1)$ first but respond positive when administered treatment $T_2(D_2)$ later, we obtain from equation 24 that the required chi-square test statistics as

$$\chi^2 = \frac{(25)(20)(0.08)^2}{20(0.52)(0.48) + 25(0.60)(0.40)} = \frac{3.20}{10.992} = 0.291$$

Which with 1 degree of freedom is not statistically significant again leading to an acceptance of the null hypothesis of equal population proportions of positive responds by subjects or patients?

Conclusion

We have in this paper proposed and presented a chi-square statistical method for the analysis of response from one period cross over design for two sample data in which the sampled populations may be measurements that are numeric (assuming real values) and non-numeric assuming only values on the nominal scale. Test statistics developed were used in testing the null hypothesis that subjects who receive each of the treatments first do not differ in their response leading to the acceptance of the null hypothesis of no difference as well as the null hypothesis that subjects exposed to one of the treatment or experimental conditions first do not on the average differ in their responses with those exposed to the other treatment or

experimental condition first also leading to the acceptance of the null hypothesis of no difference. Estimates of the proportions responding positive; experiencing no change in response or responding negative are provided for subjects exposed to each treatment first as well as for the two treatments together.

The proposed method was illustrated with some sample non-numeric data here and is shown to be at least as powerful as the traditional two sample small 't' test.

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None.

Conflict of Interest

None.

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