Statistical Analysis of Response from One Period Cross Over Design in Clinical Trial

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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

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 T1 and T2. 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 T1 first and treatment T2 later and the remaining n subjects is given treatment T2 first and treatment T1 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 [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 drop out of the study.

The Proposed Method
In general, let nj subjects or patients be randomly assigned for treatment with Tj first; for j=1,2 when nj and n1 are not necessarily equal. Let yij be the response by the ith subject administered treatment Tj first for i=1,2,…,nj, j=1,2.

Two possibilities present themselves here namely: yij may be numeric assuming real values or it may be non-numeric assuming only values on the nominal scale of measurement. If the test score yij is the numeric, assuming responses or values in the range (c1,c2) where c1 and c2 are real numbers (c1<c2) that indicate that the subject test normal, condition of interest absent, response is positive, negative, etc. Values of yij that are less than or equal to c1 and values that are greater than or equal to c2 indicate the opposite conclusion; i.e., the patient tests are positive, the condition is present, response is abnormal, there is no improvement, etc. If the response yij are on the nominal scale of measurement then yij may assume values such as positive, non-definitive or negative: present, non definitive or absent; yes, non-definitive or no, etc.

If yij are numeric, let

\[ U_i = \begin{cases} 1 & \text{if } y_{ij} < c_1 \text{ or } y_{ij} > c_2, \\ 0 & \text{if } y_{ij} = c_1 \text{ or } y_{ij} = c_2, \\ -1 & \text{if } c_1 < y_{ij} < c_2 \end{cases} \]  

for i=1,2,…,nj, j=1,2

If yij are non-numeric but assumes values on a nominal scale of measurement, let

\[ U_i = \begin{cases} 1 & \text{if } y_{ij} \text{ indicates condition that is positive, present, yes, not improved etc} \\ 0 & \text{if } y_{ij} \text{ indicates condition that is non-definitive, non specific, uncertain etc} \\ -1 & \text{if } y_{ij} \text{ indicates condition that is negative, absent, no, improved etc} \end{cases} \]  

for i=1,2,…,nj, j=1,2

Note that by specification allowance has been made for the possibility that patients or subjects may drop out that is, they are lost to the study. If patients do not drop out of the study then nj=n for j=1,2.

For both equations 1 and 2, let

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Received February 05, 2013; Published March 22, 2013

Citation: Oyeka ICA, Okeh UM (2013) Statistical Analysis of Response from One Period Cross Over Design in Clinical Trial. 2: 643 doi:10.4172/scientificreports.643

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\[ \pi_j^* = P(U_j = 1); n_j^0 = P(U_j = 0) \text{ and } \pi_j^* = P(U_j = -1) \] (3)

Where
\[ \pi_j^* + \pi_j^0 + \pi_j^- = 1 \] (4)

Let \( w_j = \sum_{i=1}^{n} U_{ij} \)

Now
\[ E(U_{ij}) = \pi_j^* - \pi_j^- \] (6)

and
\[ Var(U_j) = E(U_{ij}^2) - (E(U_{ij}))^2 \] (7)

That is
\[ Var(U_j) = \pi_j^* + \pi_j^0 - (\pi_j^* - \pi_j^-)^2 \] (8)

Also, \( E(W_j) = E(\sum_{i=1}^{n} U_{ij}) = \sum_{i=1}^{n} E(U_{ij}) \)

That is
\[ E(W_j) = n_j(\pi_j^* - \pi_j^-) \] (9)

Also \( Var(W_j) = E(W_{ij}^2) - (E(W_{ij}))^2 \)

Which when simplified and evaluated using equations (8) and (9) yields
\[ Var(W_j) = n_j(\pi_j^* - \pi_j^-) \] (10)

Note that the sample estimates of \( \pi_j^* \), \( \pi_j^0 \) and \( \pi_j^- \) are respectively \( \hat{\pi}_j^*, \hat{\pi}_j^0 \) and \( \hat{\pi}_j^- \) given as
\[ \hat{\pi}_j^* = \frac{\sum_{i=1}^{n} U_{ij}}{n_j} \]

Where \( j = 1,2 \) has approximately the chi-square distribution with 1 degree of freedom for sufficiently large sample size \( n \). \( \pi_j^* \) is rejected at a specified level of significance \( \chi_j^2 \geq \chi^2_{1,\alpha} \) otherwise \( \pi_j^* \) is accepted where \( \chi_j^2 \) is obtained from an appropriate chi-square table with 1 degree of freedom at a level of significance.

Of greater interest however is testing the null hypothesis \( H_0 \) that patients or subjects who take treatment \( T_1 \) first have the same positive response rate as patients who take treatment \( T_2 \) first. This is equivalent to testing the null hypothesis
\[ H_0: \pi_j^* - \pi_j^- = \pi_j^0 - \pi_j^- \quad \text{or} \quad (\pi_j^* - \pi_j^-) - (\pi_j^0 - \pi_j^-) = 0 \]

vs
\[ H_1: (\pi_j^* - \pi_j^-) - (\pi_j^0 - \pi_j^-) \neq 0 \] (17)

The null hypothesis may be tested using the test statistics
\[ \chi^2 = \frac{(W_j^2 - W_j^-)^2}{Var(W_j)} \] (18)

Which under \( H_0 \) has a chi-square distribution with 1 degree of freedom for sufficiently large values of \( n_j \) and \( n \).

Now \( Var(W_j) = Var(W_{ij} + Var(W_j) - 2 \text{ cov}(W_{ij}, W_j) \) (19)

Now \( \text{ cov}(W_{ij}, W_j) = E(W_{ij}W_j) - E(W_{ij})E(W_j) \)

Using these values in Equation 19 with Equation 10, we have that
\[ Var(W_j) = \frac{n_j(\pi_j^* - \pi_j^-)}{n_j} \] (20)

Or equivalently
\[ Var(W_j) = \frac{n_j(\pi_j^* - \pi_j^-) - (\pi_j^0 - \pi_j^-)^2}{n_j} \] (21)

Therefore, the test statistic of equation 18 may be written as
\[ \chi^2 = \frac{(W_j^2 - W_j^-)^2}{n_j(\pi_j^* + \pi_j^-) \frac{W_j^2}{n_j} + n_j(\pi_j^0 + \pi_j^-) \frac{W_j^2}{n_j}} \]

for \( j = 1,2 \) has approximately the chi-square distribution with 1 degree of freedom for sufficiently large sample size \( n_j \). \( H_0 \) is rejected at a specified level of significance.
sufficiently large $n_{1}$ and $n_{2}$. The null hypothesis of equation 17 is rejected at the a level of significance if $x^2 > \chi^2_{1,a}$. 

Otherwise the null hypothesis is accepted. Also the test statistic of equation 22 may equivalently be expressed in terms of sample proportions as:

$$x^2 = \frac{n_{1}p_{1}}{\hat{\pi}_1^2} - \hat{\pi}_1 + \frac{n_{2}p_{2}}{\hat{\pi}_2^2} - \hat{\pi}_2$$

(23)

If the null hypothesis $H_0$ of equation 17 is rejected, then each $H_{0j}$ for $j=1,2$ is tested to determine which of the groups treated first with treatment $T_j; j=1,2$ may have led to the rejection of the overall null hypothesis of equation 17.

**Illustrative Example**

A clinician is interested in determining whether or not a certain condition is present in a population. He collected a random sample of 'n'=34 subjects from this population and exposed each of them to two types of diagnostic procedures $T_1$ and $T_2$ at two different points in time. A sub-sample of $n=14$ subjects are screened with procedure $T_1$ first and the remaining sub-sample of $n=20$ subjects are at the same time screened with procedure $T_2$ first. This process is repeated with the same subjects in the reverse order a little while later. The results for the tests administered first on the subjects are as follows where a minus sign (-) indicates condition absent or negative response; and a zero (0) indicates condition indeterminate or non-specific:

- Test $T_1$: -; +; 0; +; -; 0; 0; +; 0; 0; +; -; +; +;
- Test $T_2$: 0; -; +; 0; +; 0; 0; +; 0; 0; +; +; -; +; +;

We here use these data to illustrate the proposed method.

**Results**

Now using equation 1 with the data we have that $f_1=6; f_2=5; f_3=3; f_4=5 and f_5=5$.

Hence from equation 11, we have that

- $\hat{\pi}_1 = \frac{6}{14} = 0.429, \hat{\pi}_2 = \frac{5}{14} = 0.357, \hat{\pi}_3 = \frac{3}{14} = 0.214,$
- $\hat{\pi}_4 = \frac{5}{20} = 0.250 and \hat{\pi}_5 = \frac{5}{20} = 0.250.$

$W_1=6-3=3; W_2=10-5=5$.

Now from equation 13, we have that the variances of $W_1$ and $W_2$ are respectively

$$\text{Var}(W_1)=\frac{14}{n_1}(0.429+0.214-0.036)^2=8.358$$

and

$$\text{Var}(W_2)=\frac{20}{n_2}(0.500+0.250-0.077)^2=13.740.$$ 

The difference between the sample proportions of subjects responding positive and negative when screened with test $T_1$ first is

$$\hat{\pi}_1 - \hat{\pi}_2 = \frac{W_1}{n_1} = \frac{6-3}{14} = 0.214$$

with estimated variance

$$\text{Var}(\hat{\pi}_1) = \frac{0.429+0.214-0.036)^2}{14} = \frac{0.643}{14} = 0.046$$

Similarly, the difference between the proportion of sample subject responding positive and negative when screened with test $T_2$ first is

$$\hat{\pi}_2 - \hat{\pi}_3 = \frac{W_2}{n_2} = \frac{10-5}{20} = 0.250$$

with estimated variance

$$\text{Var}(\hat{\pi}_2) = \frac{0.250+0.250-0.036)^2}{20} = \frac{0.687}{20} = 0.034.$$ 

Hence, the difference in the proportions of sample subjects responding positive when screened with test $T_1$ first compared with when screened with test $T_2$ first is

$$\hat{\pi}_1 - \hat{\pi}_2 = 0.214 - 0.250 = -0.036$$

with estimated variance

$$\text{Var}(\hat{\pi}_1) + \text{Var}(\hat{\pi}_2) = 0.046 + 0.034 = 0.080$$

Now notice that the estimated value of $\hat{\pi} = -0.036$ seem to indicate that test $T_2$ may have greater tendency of revealing positive responses by subjects more than test $T_1$. To ascertain whether this tendency is statistically significant, we have from equation 23 that

$$x^2 = \frac{(-0.036)^2}{0.072} = \frac{0.935}{0.077} = 9.35$$

with 1 degree of freedom is not statistically significant, leading to a non-rejection of the null hypothesis of equation 17. It would be instructive to compare the results obtained using the proposed method with what would have been obtained if the traditional two-sample method of analysis had been used with the data.

To do this, we would compare the sample proportion of subjects who test positive when screened with test $T_1$ first namely $p_1 = \frac{6}{14}$, with the sample proportion of subjects who test positive when screened with test $T_2$ first namely $p_2 = \frac{10}{20}$.

The corresponding Chi-square test statistic is

$$x^2 = \frac{(p_1-p_2)^2}{\frac{6}{14}+\frac{10}{20}} = \frac{(0.429-0.500)^2}{0.687} = \frac{0.030}{14} = 0.021$$

with 1 degree of freedom is also not statistically significant again leading to a non-rejection of the null hypothesis.

**Discussions**

However, although the proposed method and the traditional method here both lead to a non-rejection of the null hypothesis, the relative sizes of the corresponding chi-square values nonetheless suggest that the traditional method is likely to lead to an acceptance of the null hypothesis (Type II Error) more frequently and hence is likely to be less powerful than the proposed method. Furthermore, the proposed method unlike the traditional method enables the statistical comparisons of subjects' responses under each treatment in the event that the overall or initial null hypothesis is rejected. It also enables the simultaneous estimation of the proportions of subjects under each treatment and overall, whose response in the tests is either positive, indeterminate or negative which provide additional useful information for policy purposes.

**Conclusion**

We have here proposed and developed a method for the analysis of data generated from a cross-over type study design in which analysis is based only on the sample subjects exposed to the two experimental or treatment conditions first. 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.

Reference