Oyeka and Okeh, 2:2
http://dx.doi.org/10.4172/scientificreports.643

Open Access Scientific Reports

Research Article Open Access

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

Oyeka ICA[1] and Okeh UM[2]*

[1]Department of Applied Statistics, Nnamdi Azikiwe University, Awka, Nigeria
[2]Department of Industrial Mathematics and Applied Statistics, Ebonyi State University, Abakaliki, Nigeria

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 understudy 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_1 first and treatment T_2 later and the remaining n subjects is given treatment T_2 first and treatment T_1 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 die or drop out of the study.

The Proposed Method

In general, let n_j subjects or patients be randomly assigned for treatment with T_j first: for j=1,2 when n_1 and n_2 are not necessarily equal. Let y_{ij} be the response by the i^{th} subject administered treatment T_j first for i=1,2,…, n_j, j=1,2.

Two possibilities present themselves here namely: y_{ij} 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 y_{ij} is the numeric, assuming responses or values in the range (c_1,c_2) where c_1 and c_2 are real numbers ($c_1<c_2$) that indicate that the subject test normal, condition of interest absent, response is negative, etc. Values of y_{ij} that are less than or equal to c_1 and values that are greater than or equal to c_2 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 y_{ij} are on the nominal scale of measurement then y_{ij} may assume values such are positive, non-definitive or negative: present, non definitive or absent; yes, non-definitive or no, etc.

If y_{ij} is numeric, let

$$U_{ij}=\begin{Bmatrix} 1\ if\ either\ y_{ij}<c_1\ or\ y_{ij}>c_2 \\ 0\ if\ either\ y_{ij}=c_1\ or\ y_{ij}=c_2 \\ -1\ if\ c_1<y_{ij}<c_2 \end{Bmatrix} \quad (1)$$

for i=1,2,...,n_j; j=1,2

If y_{ij} is non-numeric but assumes values on a nominal scale of measurement, let

$$U_{ij}=\begin{Bmatrix} 1\ if\ y_{ij}\ indicate\ condition\ that\ is\ positve, present, yes, not\ improved\ etc \\ 0\ if\ y_{ij}\ indicates\ condition\ that\ is\ non-definitive, non\ specific, uncertain\ etc \\ -1\ if\ y_{ij} indicate\ condition\ that\ is\ negative, absent, no, improved\ etc \end{Bmatrix} \quad (2)$$

for i=1,2,...,n_j; 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 $n_j=n$ for j=1,2.

For both equations 1 and 2, let

***Corresponding author:** Okeh UM, Department of Industrial Mathematics and Applied Statistics, Ebonyi State University Abakaliki, Nigeria, E-mail: uzomaokey@ymail.com

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

$$\pi_j^+ = P(U_{ij} = 1); n_j^0 = P(U_{ij} = 0) \text{ and } \pi_j^- = P(U_{ij} = -1) \quad (3)$$

Where

$$\pi_j^+ + \pi_j^0 + \pi_j^- - 1 \quad (4)$$

Let $w_j = \sum_{i=1}^{n_i} U_{ij}$ (5)

Now

$$E(U_{ij}) = \pi_j^+ - \pi_j^- \quad (6)$$

and

$$Var(U_{ij}) = E(U_{ij}^2) - (EU_{ij})^2 \quad (7)$$

That is

$$Var(U_{ij}) = \pi_j^+ + \pi_j^- - (\pi_j^+ - \pi_j^-)^2 \quad (8)$$

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

That is

$$E(W_j) = n_j(\pi_j^+ - \pi_j^-) \quad (9)$$

$$Also\ Var(W_j) = E(W_j^2) - (EW_j)^2$$

Which when simplified and evaluated using equations (8) and (9) yields

$$Var(W_j) = n_j(\pi_j^+ - \pi_j^-) - (\pi_j^+ - \pi_j^-)^2) \quad (10)$$

Note that the sample estimates of π_j^+, π_j^0 *and* π_j^- are respectively $\hat{\pi}_j^+, \hat{\pi}_j^0$ *and* $\hat{\pi}_j^-$ given as

$$\hat{\pi}_j^+ = \frac{f_j^+}{n_j}; = \hat{\pi}_j^0 = \frac{f_j^0}{n_j}; = \hat{\pi}_j^- = \frac{f_j^-}{n_j} \quad (11)$$

Where f_j^+, f_j^0 *and* f_j^- are respectively the numbers of $1^s, 0^s$ *and* -1^s in the frequency distribution of these values in U_{ij}. The sample estimate of the difference between π_j^+ and π_j^- namely $\pi_j^+ - \pi_j^-$ is

$$\hat{\pi}_j^+ - \hat{\pi}_j^- = \frac{f_j^+ - f_j^-}{n_j} = \frac{W_j}{n_j} \quad (12)$$

Where i=1,2,...,n_j; j=1,2

or equivalently using equation (12), we have that the estimated variance of W_j is from equations 10 and 11

$$Var(W_j) = n_j(\hat{\pi}_j^+ + \hat{\pi}_j^- - (\hat{\pi}_j^+ - \hat{\pi}_j^-)^2) \quad (13)$$

$$Var(W_j) = n_j(\hat{\pi}_j^+ + \hat{\pi}_j^-) - \frac{W_j^2}{n_j} \quad (14)$$

The null hypothesis that the subjects or patients who take treatment T_j first are as likely to test positive (abnormal, yes) do not differ in their response which is as negative (normal, no) that is equivalent to testing of null hypothesis

$$H_{0j} : \pi_j^+ = \pi_j^- \text{ or } H_{0j} : \pi_j^+ - \pi_j^- = 0$$

vs

$$H_{1j} : \pi_j^+ - \pi_j^- \neq 0 \text{ For } j = 1, 2 \quad (15)$$

Under H_{0j} the test statistic:

$$\chi_j^2 = \frac{W_j^2}{Var(W_j)} = \frac{W_j^2}{n_j(\hat{\pi}_j^+ + \hat{\pi}_j^-) - \frac{W_j^2}{n_j}} = \frac{\left(n_j(\hat{\pi}_j^+ + \hat{\pi}_j^-)\right)^2}{n_j(\hat{\pi}_j^+ + \hat{\pi}_j^-) - \frac{W_j^2}{n_j}} \quad (16)$$

for j=1,2 has approximately the chi-square distribution with 1 degree of freedom for sufficiently large sample size n_j. H_{0j} is rejected at a specified α level of significance $\chi_j^2 \geq \chi_{1-\alpha;1}^2$ otherwise H_0 is accepted where $\chi_{1-\alpha;1}^2$ is obtained from an appropriate chi-square table with 1 degree of freedom at α 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

$$H_0 : \pi_1^+ - \pi_1^- = \pi_2^+ - \pi_2^- \text{ or } (\pi_1^+ - \pi_1^-) - (\pi_2^+ - \pi_2^-) = 0$$

vs

$$H_1 : (\pi_1^+ - \pi_1^-) - (\pi_2^+ - \pi_2^-) \neq 0 \quad (17)$$

The null hypothesis may be tested using the test statistics

$$\chi^2 = \frac{(W_1 - W_2)^2}{Var(W_1 - W_2)} = \frac{\left(n_1(\hat{\pi}_1^+ - \hat{\pi}_2^-) + n_2(\hat{\pi}_2^+ - \hat{\pi}_2^-)\right)^2}{Var(W_1 - W_2)} \quad (18)$$

Which under H_0 has a chi-square distribution with 1 degree of freedom for sufficiently large values of n_1 and n_2 where

$$Var(W_1 - W_2) = VarW_1 + VarW_2 - 2\text{cov}(W_1, W_2) \quad (19)$$

Now

$$\text{cov}(W_1, W_2) = E(W_1W_2) = E(W_1)E(W_2)$$
$$= E\sum_{r=1}^{n_1}\sum_{s=1}^{n_2} U_{r1}U_{s2} - E\sum_{r=1}^{n_1} U_{r1} E\sum_{s=1}^{n_2} U_{s2}$$
$$= \sum_{r=1}^{n_1}\sum_{s=1}^{n_2} E(U_{r1}U_{s2}) - \sum_{r=1}^{n_1} E(U_{r1}) \sum_{s=1}^{n_2} E(U_{s2})$$

Now $U_{r1}U_{s2}$ can only assume the values 1,0 and -1. It assumes the value 1 if U_{r1} and U_{s2} both assume the value 1 or both assume the value 1 or both assume the value -1 with probability $\pi_1^+.\pi_2^- + \pi_1^-.\pi_2^+$; It assumes the value 0 if U_{r1} and U_{s2} both assume the value 0 or U_{r1} assume the value 0, no matter the value assumed by U_{s2} or U_{s2} assumes the value 0 no matter the value assumed by U_{r1} with probability.

$\pi_1^+.\pi_2^0 + \pi_1^0(\pi_2^+ + \pi_2^-) + \pi_2^0(\pi_1^+ + \pi_1^-)$; $U_{r1}U_{s2}$ assumes the value -1 if U_{r1} assumes the value 1 and U_{s2} assumes the value -1 or vice versa with probability $\pi_1^+.\pi_2^- + \pi_1^- + \pi_2^+$.

Hence using these values, evaluating and simplifying we have

$$\text{cov}(W_1, W_2) = n_1n_2(\pi_1^+.\pi_2^+ + \pi_1^-.\pi_2^- - (\pi_1^+.\pi_2^- + \pi_1^-.\pi_2^+)) - n_1n_2(\pi_1^+ - \pi_1^-) + (\pi_2^+ - \pi_2^-) = 0$$

Using these values in Equation 19 with Equation 10, we have that

$$Var(W_1 - W_2) = Var(W_1) + Var(W_2)$$
$$= n_1(\pi_1^+ + \pi_1^- - (\pi_1^+ - \pi_1^-)^2) + n_2(\pi_2^+ + \pi_2^- - (\pi_2^+ - \pi_2^-)^2) \quad (20)$$

Or equivalently

$$Var(W_1 - W_2) = n_1(\pi_1^+ + \pi_1^-) - \frac{W_1^2}{n_1} + n_2(\pi_2^+ + \pi_2^-) - \frac{W_2^2}{n_2} \quad (21)$$

Therefore, the test statistic of equation 18 may be written as

$$\chi^2 = \frac{(W_1 - W_2)^2}{n_1(\pi_1^+ + \pi_1^-) - \frac{W_1^2}{n_1} + n_2(\pi_2^+ + \pi_2^-) - \frac{W_2^2}{n_2}} = \frac{\left(n_1(\hat{\pi}_1^+ - \hat{\pi}_2^-) + n_2(\hat{\pi}_2^+ - \hat{\pi}_2^-)\right)^2}{n_1(\pi_1^+ + \pi_1^-) - \frac{W_1^2}{n_1} + n_2(\pi_2^+ + \pi_2^-) - \frac{W_2^2}{n_2}} \quad (22)$$

which has a chi-square distribution with 1 degree of freedom for

sufficiently large n_1 and n_2. The null hypothesis of equation 17 is rejected at the α level of significance if $\chi^2 \geq \chi^2_{1-\alpha;1}$.

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

$$\chi^2 = \frac{n_1 n_2 \left((\hat{\pi}_1^+ - \hat{\pi}_1^-) - (\hat{\pi}_2^+ - \hat{\pi}_2^-)\right)^2}{n_2\left(\hat{\pi}_1^+ + \hat{\pi}_1^- - (\hat{\pi}_1^+ - \hat{\pi}_1^-)^2\right) + n_1\left(\hat{\pi}_2^+ + \hat{\pi}_2^- - (\hat{\pi}_2^+ - \hat{\pi}_2^-)^2\right)} \quad (23)$$

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_1=14 subjects are screened with procedure T_1 first and the remaining sub-sample of n_2=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 plus sign (+) indicates conditions present or positive response; 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; +; -; +; +; +; +;

We here use these data to illustrate the proposed method.

Results

Now using equation 1 with the data we have that $f_1^+ = 6; f_1^0 = 5; f_1^- = 3; f_2^+ = 10; f_2^0 = 5 \text{ and } f_2^- = 5$

Hence from equation 11, we have that

$$\hat{\pi}_1^+ = \frac{6}{14} = 0.429; \hat{\pi}_1^0 = \frac{5}{14} = 0.357; \hat{\pi}_1^- = \frac{3}{14} = 0.214,$$

$$\hat{\pi}_2^+ = \frac{10}{20} = 0.500; \hat{\pi}_2^0 = \frac{5}{20} = 0.250 \text{ and } \hat{\pi}_2^- = \frac{5}{20} = 0.250$$

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

Var (W_1)=14(0.429+0.214-(0.429-0.214)^2)=14(0.597)=8.358

and

Var (W_2)=20(0.500+0.250-(0.500-0.250)^2)=20(0.687)=13.740.

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

$\hat{\pi}_1 = \hat{\pi}_1^+ - \hat{\pi}_1^- = \frac{W_1}{n_1} = \frac{6-3}{14} = \frac{3}{14} = 0.214$ with estimated variance

$$Var(\hat{\pi}_1) = \frac{0.429 + 0.214 - (0.429 - 0.214)^2}{14} = \frac{0.643 - 0.046}{14} = \frac{0.597}{14} = 0.043$$

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

$\hat{\pi}_2 = \hat{\pi}_2^+ - \hat{\pi}_2^- = \frac{W_2}{n_2} = \frac{10-5}{20} = \frac{5}{20} = 0.250$ with estimated variance

$$Var(\hat{\pi}_2) = \frac{0.500 + 0.250 - (0.500 - 0.250)^2}{20} = \frac{0.750 - 0.063}{20} = \frac{0.687}{20} = 0.034$$

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

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

$Var(\hat{\pi}) = Var.(\hat{\pi}_1) + Var\,(\hat{\pi}_2) = 0.043 + 0.034 = 0.077$

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 $\chi^2 = \frac{(-0.036)^2}{0.077} = \frac{0.072}{0.077} = 0.935$ which 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 $P_1 = \frac{f_1^+}{n_1} = \frac{6}{14} = 0.429$ with the proportion of subjects who test positive when screened with test T_2 first namely $P_2 = \frac{f_2^+}{n_2} = \frac{10}{20} = 0.500$

The corresponding Chi-square test statistic is $\chi^2 = \frac{(p_1 - p_2)^2}{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} = \frac{(0.429 - 0.500)^2}{\frac{(0.429)(0.571)}{14} + \frac{(0.500)(0.500)}{20}} = \frac{0.005}{0.030} = 0.167$ which 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

1. Meiser P, Free SM, Jackson GL (1958) Re-moderation of methodology in studies of pains relief. Biometrics 14: 330-342.
2. Gart JJ (1969) An exact test for comparing matched proportions in crossover designs. Biometrika 56: 75-80.
3. Grizzle JE (1965) The two-period change-over design and its use in clinical trials. Biometrics 21: 467-480.