Modelling and Exact Testing for A (4 × 4) Cross-Over Trial with Binary Data

نمذجة (انشاء نموذج) واجراء اختبارات دقيقة (غير تقريبية) لتجربة تلقي متواليات علاجية (تبادلية) رباعية (4 × 4) تحتوي على بيانات ثنائية

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Abstract

A method of analyzing binary data from a four-treatment, four-period cross-over trial is described. This method is based on a log-linear model, and on computing exact tests using different techniques proposed by *StatXact* and *LogXact*. Here we deal with the problem of establishing therapeutic equivalence of four treatments. This method is illustrated using an example of unstructured binary data (Williams Design) where responses are recorded for the selected order of treatments.

Keywords: Association; Binary data; Cross-over trial; Hypothesis Testing; Log-Linear Model; *LogXact*; *StatXact*.

ملخص

وصف لطريقة رياضية لتحليل بيانات ثنائية ماخوذة من تجربة تلقي متواليات علاجية (تبادلية) من فئة اربع علاجات (ادوية او جرعات) معطاة على اربع فترات. الطريقة الموصوفة هنا اسست على نموذج لوغارتمي- خطي، حيث اتيح اجراء اختبارات (احصائية) دقيقة (غير تقريبية) باستخدام عدة طرائق مقترحة ومستخدمة عبر رزمتين (احصائيتين) حديثتين *LogXact* و*StatXact*. وفي هذه المخطوطة فاننا نعالج مسالة تحقيق التعادل (التكافؤ) العلاجي لاربع علاجات (ادوية). وقد تم تجلية هذه الطريقة الموصوفة بالاستعانة بمثال من بيانات ثنائية غير

منظمة (تصميم وليامز). حيث تسجل الاستجابات (للعلاج) لكل من الترتيب المختار للدواء (او الجرعة الدوائية).

الكلمات المفتاحية: الارتباط، بيانات ثنائية، تجربة تلقي متواليات علاجية مختلفة، اختبار فرضيات، نموذج لوغارتمي-خطي، رزم احصائية.

Introduction

In this article we construct a new model that deals with a four-treatment, four-period cross-over design, and, in addition, exact tests will be performed. Our model is an extension of the log-linear model developed by Jones and Kenward (1987) for analyzing binary data from a three-treatment, three-period cross-over trial, (3×3 K-J model). In this extension of the 3×3 K-J model we shall follow the same approach, and we shall use, almost, the same system of parameterization. Exact tests are performed on data in Table (1), (see below), using *StatXact* (StatXact, 1991) and *LogXact* (LogXact, 1992).

Cross-over trials are an important class of designs used in the pharmaceutical industry and medical management research. This type of clinical trials is most commonly used in early drug development, especially in Phase I, bioequivalence, dose-proportionality and dose escalation studies, and in phase II pharmacodynamics studies. Cross-over designs are suitable for many trials that involve relatively stable conditions, to compare effects of treatments on patients of chronic diseases, such as asthma, cancer, hypertension, rheumatism, migraine, and blood pressure as well. Cross-over trials require smaller samples since the same subject is given several treatments over time, thus increase the efficiency and precision of treatment comparisons, if they are properly designed. Cross-over trials play also an important role in agricultural experiments, biological assays, behavioral experiments, and in statistical research in other fields. (For more on cross-over trials and their applications, see also, Senn, 2002, and, Jones and Kenward, 2014).

In this sort of trials, each patient (subject) receives some or all of the treatments in a pre-determined sequence for the same period of time long enough to evaluate the treatment effect. Treatment periods are separated

by washout time periods. Baseline measurements play a role to improve design efficiency. Liang and Carriere (2010) have examined the impact of baseline on designs and found that baseline observations improve design efficiency considerably for two-period design model while the improvement is rather modest for three or four-period designs. Furthermore, they found little additional benefits for measuring baselines at each treatment period as compared to measuring baselines only in the first period.

There are many cross-over trials concerned with the analysis of continuous data responses, such as blood pressure and heart rate, but often 2 × 2 (two-treatments over two-periods) designs are used. Recently a greater attention has been given to the analysis of binary responses (relief/no relief, or improvement/no improvement), (see, for example, Jones and Kenward, 1989, and Farewell, 1985). Huitson (1982) provided a review of cross-over trials and Jones and Kenward (1989) provided a very good coverage of the statistical aspects of the design and analysis of cross-over trials. Diaz-Uriarte (2002) emphasized the importance of constructing models for binary data from cross-over designs, and performing different statistical research and tests as a growing field.

Most of the tests performed on binary data in cross-over trials were in parallel to those tests performed on continuous data.

Agresti (1992) surveyed theoretical and computational developments of exact methods for multidimensional contingency tables, and suggested the need for additional research that would make exact methods more widely applicable.

Kenward and Jones (1987) proposed a method for the construction of log-linear models for binary data from a 2×2 cross-over design and developed conditional and likelihood ratio tests for comparisons of interest. Mainland (1963) derived a test for direct treatment effect, using a heuristic argument based on the randomization of subjects to groups. Gart (1969) modified the test by giving a rigorous derivation of a test for a treatment difference that is valid in the presence of a period difference. The exact test derived by Gart was based, in fact, on an extension of the

logistic model of Cox (1958). Gart showed that his test was equivalent to Fisher's exact test for 2×2 contingency table. Mainland-Gart test, (M-G test), as termed in Kenward and Jones (1987), was not a model-based test. M-G test, for treatment difference, is valid in the presence of a period difference (i.e., contrary to McNemar test, (McNemar, 1974)), and is thus valid in the absence of a treatment-by-period interaction (Kenward and Jones, 1987). Almost all of the previous tests used in cross-over trials were non model-based tests. In this article we develop a log-linear model that is valid for analyzing binary data from a four-treatment, four-period cross-over trial.

In this manuscript we construct a new model that deals with a four-treatment, four-period cross-over design, and, perform exact tests. In this new model, we extend the 3×3 K-J log-linear model, and apply it to real binary data Table (1). In this extension of the K-J model we follow the same approach, but slightly modified parameterization. Exact tests are performed on data in Table (1), using two new softwares, *StatXact* (StatXact, 1991) and *LogExact* (LogXact, 1992).

Kenward and Jones (1992) presented the following example for binary data from a 4×4 cross-over trial, (see Table 1). In this 4×4 cross-over trial, based on Williams Design, 80 subjects (patients) were randomly assigned to four sequences of treatment groups: ABCD, BDAC, CADB & DCBA (Group 1, Group 2, Group 3 & Group 4, respectively). The binary response recorded on each subject as 0 for no relief and 1 for relief. Therefore, each subject provided one of 16 possible outcomes (0, 0, 0, 0), (0, 0, 0, 1), … , (1, 1, 1, 1). The number of subjects who responded with each of these 16 outcomes in each of the four periods (π_1, π_2, π_3, π_4) is given in Table (1). We use the data from this example to illustrate our method.

The model derived here is an extension of the log-linear model proposed by Kenward and Jones (1987). The same known exact tests of independence, such as Likelihood ratio exact test, Fisher's exact test, and Chi–squared exact test, will be performed together with the traditional asymptotic methods, but two new packages, *StatXact* and *LogXact* are used. Exact tests will be calculated for the 4×4 trial using data from

Table (1). *Monte Carlo* simulations are performed in *StatXact* to sample from the resulting sparse table of the data itself. *Monte Carlo* simulation is used as a substitute for the ordinary techniques to calculate *p*-values.

Table (1): Number of patients for each treatment sequence and response pattern.

Outcome	**Treatment Sequence**			
(π_1, π_2, π_3, π_4)	ABCD	BDAC	CADB	DCBA
(0, 0, 0, 0)	1	0	1	1
(0, 0, 0, 1)	0	1	1	0
(0, 0, 1, 0)	1	1	0	1
(0, 0, 1, 1)	1	0	0	0
(0, 1, 0, 0)	1	1	1	0
(0, 1, 0, 1)	1	1	1	2
(0, 1, 1, 0)	1	1	1	2
(0, 1, 1, 1)	0	1	1	0
(1, 0, 0, 0)	1	0	1	0
(1, 0, 0, 1)	1	1	0	0
(1, 0, 1, 0)	1	0	1	0
(1, 0, 1, 1)	2	0	0	1
(1, 1, 0, 0)	1	1	1	0
(1, 1, 0, 1)	0	2	2	4
(1, 1, 1, 0)	2	3	3	0
(1, 1, 1, 1)	4	9	5	10
Total	**18**	**22**	**19**	**21**

For the data in Table (1), two general approaches will be used: a model-based analysis, and a non-model based analysis and tests. So, first we start with establishing a log-linear model for this data and then execute the said tests. This framework will extend Jones and Kenward work and develop an extension to Mainland-Gart test.

2. Derivation of the log-linear model

2.1 Recent log-linear models

Kenward and Jones (1987) developed a log-linear model for binary 2×2 cross-over data (2×2 K-J model). For a pair of two correlated binary random variables (X_1, $X_{2)}$, their model takes the general form:

$$P(X_1 = x_1, X_2 = x_2)=\exp(\beta_0 +\beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2) \quad (1)$$

The parameter β_0 is a normalizing term, chosen so that the probabilities sum to 1.0 over the (four) joint outcomes. There is an expression like that in (1) for the other group in the cross-over design, and therefore the overall model has six independent parameters. The parameter β_{12} determines the statistical dependence of the pair of random variables. The remaining four parameters determine, respectively, the probability of success, differences in period and treatment effect, and the treatment-by-period interaction.

Jones and Kenward (1987) extended their 2×2 K-J model to a new log-linear model to cope with analyzing binary data from a three-treatment, three-period cross-over trial, and mirrors the analysis of continuous data, (3×3 K-J model).

Jones and Kenward (1987) suggested the following model:

$$Y_{ijk} = \mu+s_{ik} + \pi_j + \tau_{d[i,j]}+ \lambda_{d[i,j-1]} +e_{ijk} \quad (2)$$

Where

y_{ijk} is the observed value of a random variable on the *k*th subject in period *j* of group *i*.

μ= general mean,

s_{ik} =the effect of subject *k* in group *i*, *i*=1, 2, … , *s*, *k*=1, 2,…,n_i ,

π_j =the effect of period *j*, *j*=1, 2, …, *p*,

$\tau_{d[i,j]}$ = the direct effect of the treatment administered in period *j* of group *i*, (note that, here, there are *s* different groups of subjects; each group receives the *t* treatments in a different order).

$\lambda_{d[i,j-1]}$ = the effect of the carry-over of the treatment administered in period *j*-1 of group *i* where $\lambda_{[i,0]}$ is equal to 0,

e_{ijk}= a random error for subject *k* in period *j* in group *i*. (See, Jones and Kenward, 1989).

Based on the multivariate logistic model of Cox (1972), the model for *p* correlated binary random variables (X_1, …, X_p) would take the form (Kenward and Jones, 1987):

$$P(X_1=x_1, X_2=x_2, \dots, X_p=x_p)= \exp(\beta_0 +\sum_{i=1}^{p} x_i \beta_i+\sum_{i=2}^{p} \sum_{j=1}^{i-1} x_i x_j \beta_{ij}) \quad (3)$$

The binary responses are coded as 1 and -1 rather than 1 and 0. Both K-J models (1) and (2) in their final forms were written for each group in detailed expansion formulas. (See, Kenward and Jones, 1987, and Jones and Keward,1987).The most interesting features of the 2×2 K-J model are as follows: (i) the possibility of performing most of the standard relevant tests frequently used in the field of binary cross-over data, such as Mainland-Gart test and Prescott's test (which are valid only in the absence of a treatment-by- period interaction, and Armitage and Hills test, (which is valid for treatment-by-period interaction but based on the non-preference responses), (Kenward and Jones,1987). Indeed, the system of parameterization used in K-J models is workable for most of these mentioned tests, despite some (solvable) problems of over parameterization; (ii) the possibility of generalization (extension) of K-J model to higher cross-over designs, such as, three-treatment, three-period trials as done by Jones and Kenward, (1987), and to four-treatment, four-period (4×4) trials, as done herein.

2.2 A new log-linear model for four-treatment, four-period (4 × 4) trials

We'll follow a step-by-step approach to develop constructing this model.

Let Y_{ijk} be the observation on the kth subject in group (treatment sequence) i in period j, and $i = 1, 2, 3, 4$; $j = 1, 2, 3, 4$; $k = 1, 2, \ldots, n_i$. Then, for our new model, the sixteen logits (log odds) of the probabilities of a success for the kth subject, are obtained from (4) and (5) below:

$$\text{logit}[P(Y_{ijk}=1)] = \ln[P(Y_{ijk}=1)/1-P(Y_{ijk}=1)] = \alpha + \pi_j + \tau_i \quad (4)$$

Here α is the basic probability of success (relief, or improvement), π_j is the associated period effect, τ_i is the associated treatment effect, and,

$$\text{logit}[P(Y_{ijk}=0)] = \ln\{P(Y_{ijk}=0)/ [1-[P(Y_{ijk}=0)]]\} = \ln[P(Y_{ijk}=0) /P(Y_{ijk}=1)]$$

$$= 1/\text{logit}[P(Y_{ijk}=1)]$$

$= [\alpha + \pi_j + \tau_i + (\lambda_i)]^{-1}$; λ_i is the associated (first-order) carry-over effect from treatment i, that is the effect of treatment i which persists into the next period. This implies that

$$P(Y_{ijk}=0) = [1+\exp(\alpha + \pi_j + \tau_i + (\lambda_i))]^{-1} \quad (5)$$

For 4×4 cross-over trial, we have a total of 16 logits, (see, Appendix 1).

From Equation (5) we get:

$$P(Y_{ijk}= 1) = 1 - P(Y_{ijk}= 0) = 1-[1 + \exp(\alpha + \pi_j + \tau_i + (\lambda_i))]^{-1}$$

$$= \exp(\alpha + \pi_j + \tau_i + (\lambda_i))/[1 + \exp(\alpha + \pi_j + \tau_i + (\lambda_i))] \quad (6)$$

Now for the ith group, let $\rho_{i.}$ be the joint probability of the jth outcome, then ρ_{ij} is the probability of observing jth outcome in group i, where i=1, 2, 3, 4, j=1, 2, 3, ... ,16.

So, we define

$\rho_{i1} = P(Y_{11k}= 0, Y_{12k}= 0, Y_{13k}= 0, Y_{14k}= 0)$,

$\rho_{i2} = P(Y_{11k}= 0, Y_{12k}= 0, Y_{13k}= 0, Y_{14k}= 1)$,

$\rho_{i3} = P(Y_{11k} = 0, Y_{12k}=0, Y_{13k}= 1, Y_{14k} = 0)$, and so forth up to

$\rho_{i16} = P(Y_{11k}= 1, Y_{12k}= 1, Y_{13k} = 1, Y_{14k}= 1)$.

Similar to the K-J model, we assume here that the observations from each subject are independent. That is, we can treat each row of the 16×4

table (in Table (1) of counts $\{n_{ij}\}$ as independent observations from a multinomial distribution. Associated with each entry n_{ij} is a corresponding probability ρ_{ij} of a subject producing this outcome, i.e, we have $\{\rho_{ij}\}$ probabilities. Therefore, the probability of the joint outcome from a subject is simply the product of the probabilities obtained in the above expressions (4), (5), (6), and the rest. Moreover, we can construct expressions for the probabilities in terms of effects of interest through a new logistic model.

Now for a 4-tuples of correlated binary random variables (X_1, X_2, X_3, X_4), our model takes the general form**:**

$P(X_1=x_1, X_2=x_2, X_3=x_3, X_4=x_4)=$

$$\exp\left[\mu + \sum_{i=1}^{4}\left(\frac{x_i+1}{2}\right)(\tau_i + \pi_i + \alpha) + \sum_{\substack{j=2 \\ (i<j)}}^{4} \sum_{i=1}^{3} x_i\, x_j\, \sigma_{ij}\right] \qquad (7)$$

Where, for this expression only, we code the binary responses as 1 and -1 rather than usual coding of 1 and 0, (Kenward and Jones, 1987).

Now for the group i =1, say, the treatment sequence ABCD, (Group1) and for the outcome (0, 0, 0, 0) which is equivalent in Equation (7) to P(-1, -1, -1, -1), we have for ρ_{ij}; i, j= 1, 2, 3, 4 the following probabilities:

$P(Y_{11k} = 0, Y_{12k}=0, Y_{13k}=0, Y_{14k}=0)=$

$P(Y_{11k}=0).\ P(Y_{12k}=0).P(Y_{13k}=0).P(Y_{14k}=0)=\exp(\xi_1)$; ξ_1 is a normalizing term.

And similarly, for the outcome (1, 1, 1, 1), which is equivalent in Equation (7) to P(1, 1, 1, 1), we'll have:

$P(Y_{11k}=1, Y_{12k}=1, Y_{13k}=1, Y_{14k}=1)=\exp(\xi_1 + 4\alpha + \pi_1 + \pi_2 + \pi_3 + \pi_4 + \tau_1 + \tau_2 + \tau_3 + \tau_4 + \lambda_1 + \lambda_2 + \lambda_3)$. We proceed in the same manner for the rest of the other three groups, i.e., the treatment sequences: BDAC, CADB and DCBA. (Group2, Group3 & Group 4, respectively), for details, see Appendix 3.

Abu-Solqan (1994) found for this set of data in Table (1), that the change in Deviance for interaction term was relatively small so that it can be neglected when tested for inclusion in the model. Hence, the λ_i's will

be omitted out of our current model. To model the within-subject structure in the 3×3 K-J model, Jones and Kenward (1987) introduced three additional (extra to the 2×2 model) parameters: σ_{12}, σ_{13} and σ_{23}. These parameters are such that if the response in periods 1 and 2 are the same, then σ_{12} is included in the model, whereas if the responses are different - σ_{12} is included instead, and so on for the rest of the periods. In our model, three more parameters; namely σ_{14}, σ_{24} and σ_{34} will be used to be able to model the new within-subject structure, with similar indication, i.e., if the response in periods 1 and 4 are the same, then σ_{14} is included in the model, whereas if the responses are different -σ_{14} is included instead, and so on for the rest of the periods.

Thus, we have the following probability expressions:

For group i=1, for the outcome (0, 0, 0, 0), and for simplicity we shall write,

$P(0, 0, 0, 0)$ for $P(Y_{11k}=0, Y_{12k}=0, Y_{13k}=0, Y_{14k}=0)$. So,

$P(0,0,0,0)=\exp(\mu_1+ \sigma_{12}+ \sigma_{13}+ \sigma_{14}+ \sigma_{23} + \sigma_{24}+ \sigma_{34})$.

And, for the outcome (0, 0, 0, 1) we have:

$P(0, 0, 0, 1)$ for $P(Y_{11k}=0, Y_{12k}=0, Y_{13k}=0, Y_{14k}=1)$. So,

$P(0,0,0,1)=\exp(\mu_1 + \sigma_{12}+ \sigma_{13}- \sigma_{14}+ \sigma_{23}- \sigma_{24}- \sigma_{34}+(\alpha + \pi_4+ \tau_4))$, and so forth, up to the outcome (1, 1, 1, 1) where:

$P(1,1,1,1)=\exp(4\alpha + \pi_1+ \pi_2+ \pi_3+ \pi_4+ \tau_1+ \tau_2+ \tau_3+ \tau_4+ \mu_1+ \sigma_{12}+ \sigma_{13}+ \sigma_{14}+ \sigma_{23}+ \sigma_{24}+ \sigma_{34})$.

Here μ_1 is a normalizing term, which replaced ξ_1, as a consequence of including the dependency parameters. (Finally, this is replaced by μ in our model in Equation (7)). We do the same for the other three groups. (See, Table (3A) in Appendix 3). Finally, the overall model for probability of the joint outcome is conveniently expressed in logarithmic form, i.e., we let $l_{ij}=\ln(\rho_{ij})$. Consequently, our model becomes, say, for group i=1 as shown in Table (2 A), (see Appendix 1). Models for groups 2, 3 and 4 were done similarly. To make our model simpler (with less parameters),

we substitute ε_1 for $\sigma_{12} + \sigma_{13} + \sigma_{14} + \sigma_{23} + \sigma_{24} + \sigma_{34}$ and, ε_2 for $\sigma_{12} + \sigma_{13} - \sigma_{14} + \sigma_{23} - \sigma_{24} - \sigma_{34}$ and so forth, as they appear in different groups from $P(0, 0, 0, 0)$ up to $P(1, 1, 1, 1)$. (See, Tables (1A) and (2A), in Appendix 3). Thus, we have our model in its final structure; for Group1 as displayed in Table (2A); for Groups 2, 3 and 4 as displayed in Table (3A) in Appendix 3, w1here μ_2, μ_3 and μ_4 are normalizing terms. (This 16×4 contingency table is combined from the previously mentioned four tables, where the four treatments group will be the four columns. This will be referred to as the full model, which is displayed in Table (3A), in Appendix 3.

3. Hypothesis Testing

The null hypothesis of equal treatment effects, to be tested here, which means that there is no association between treatments, is H_o: $\boldsymbol{\tau} = \mathbf{0}$, or equivalently $\tau_1 + \tau_2 = -(\tau_3 + \tau_4)$.

For an $r \times c$ contingency table, independence (of treatments' effects) is equivalent to log odds ratios equals zero i.e,

Log $(p_{ij}.p_{rc}/p_{rj}.p_{ic})=0$; $i = 1, \ldots, r-1$; $j=1,\ldots, c-1$; $r=16$, $c=4$. (See, Agresti, 1984). So,

$$\log p_{ij} + \log p_{rc} - \log p_{rj} - \log p_{ic} = 0 \qquad (8)$$

Since our model in its final structure was expressed in terms of logarithms, then Equation (7) is applicable directly to it, should we choose to find or to calculate the odds ratios. Now under the null hypothesis, for the full model, one can easily calculate each of the resulting odds ratios with any two adjacent outcomes in any of these groups. We get the following expressions, as examples:

$\mu_1 + 2\alpha + \pi_2 + \pi_4 + \tau_2 + \tau_4 + \varepsilon_6 + \mu_4 + 4\alpha + \pi_1 + \pi_2 + \pi_3 + \pi_4 + \tau_1 + \tau_2 + \tau_3 + \tau_4 + \varepsilon_{16} - \mu_1 - 4\alpha - \pi_1 - \pi_2 - \pi_3 - \pi_4 - \tau_1 - \tau_2 - \tau_3 - \tau_4 - \varepsilon_{16} - \mu_4 - 2\alpha - \pi_2 - \pi_4 - \tau_1 - \tau_3 - \varepsilon_6 = 0 \rightarrow \tau_2 + \tau_4 = -\tau_1 - \tau_3$, and so forth. (See, Appendix 2, for more examples).

Finally, we get the following:

$$\tau_1 + \tau_2 = -(\tau_3 + \tau_4) \quad (9)$$

4. Data Analysis

4.1 Testing for Treatment-by-Period interaction

As a valid alternative to computing either the exact or asymptotic *p*-values, *Monte Carlo* simulations will be used here. (See, StatXact, 1992). Under the null hypothesis of no interaction (between treatment effect and period), and using *Monte Carlo* sampling from *StatXact* to generate 20,000 simulated tables from Table (1), which consists of sparse data, it is found that the exact results for *p*-values for the three tests are indeed indicative, showing no interaction between treatment and period**.** On the other hand, as shown in Table (2), the asymptotic results are unreliable, since the sampled table is a sparse one. It is interesting to remark here that applying the same tests on the 14×4 table which is resulted by deleting first row (consists of zeros; nothing has changed) and the last row (consists of ideal sought change; i.e., all relieved) from Table (1), has produced very close results to those obtained from the whole table. On sampling of 34,000 tables from the resulting 14×4 table we get 0.930, 0.949 and 0.899 as Monte Carlo (exact) *p*-values for Fisher's, Likelihood ratio and Chi-squared tests, respectively.

Table (2): Three *StatXact* tests of independence between treatments and periods for data in Table (1).

Three Tests of Independence			
***p*-value**	**Fisher**	**Likelihood Ratio**	**Chi – squared**
Asymptotic	0.875	0.563	0.918
Exact	0.881	0.940	0.972

4.2 Testing for Treatment Effect

We first study the effect of each of the four treatments separately. Therefore, the four treatments are displayed, in Table (3), as if they were different. On testing for association, i.e., H_o: treatments are not independent (i.e., associated). We found, using *StatXact*, that Fisher's exact test had given no indication of association (*p*-value= 0.379). It is

interesting to note here that the calculated mid *p*-value (=0.375), for Table (3), is almost the same as asymptotic value. The mid *p*-value is used, generally, because it is less conservative (i.e, more powerful). (For more details on mid p-value see, for example, LogXact, 1992, and, Gene Hwang, & Yang, 2001).

Similar results were found with the Likelihood ratio and Chi-squared exact tests.

Table (3): Relieved and non-relieved patients due to direct effect of each treatment for data in Table (1).

Response	**Treatment**				**Total**
	A	B	C	D	
Relief 1	59	50	58	53	220
No Relief 0	21	30	22	27	100
Total	80	80	80	80	320

4.3 Testing for Period Effect

We study here, separately, relationship between treatment and period effect, and relationship between order of treatment and patient's response, as well. Table (4) was formulated for the purpose of studying the period effect in analogous way to that used for treatment effect above. On testing for association between treatment and period effect, under the null hypothesis H_o: there is association (between treatment and period effects); it was found that *p*-value was 0.07 as displayed in Table (5). These readings show insignificant effect of period on the type of response of the patient.

Table (4): Relieved and non-relieved patients due to period allocation for data in Table (1).

Response	**Period**				**Total**
	π_1	π_2	π_3	π_4	
Relief 1	57	63	50	50	220
No Relief 0	23	17	30	30	100
Total	80	80	80	80	320

Table (5): Three *StatXact* tests of independence for the period effect from response for data in Table (4).

p-value	Three Tests of Independence		
	Fisher	**Likelihood Ratio**	**Chi-squared**
Asymptotic	0.073	0.070	0.076
Exact	0.072	0.071	0.078
Mid *p*-value	0.071	0.071	0.076

Now we contrast treatment A followed by treatment B, (B|A), *vs*. treatment A followed by treatment C, (C|A) to investigate the effect of this order on response. Table (6) is derived for this purpose. This table also shows no association, *p*-value=0.7. That is, treatment order has no effect on the patient's response. Regardless approximate equal values obtained here for three measures for the *p*-value, the mid *p*-value is used, generally, because it is less conservative (i.e, more powerful).

Table (6): Effect of treatment order on the subject's response for data in Table (1).

Response	B|A	C|A	**Total**
Relief 1	7	7	14
No Relief 0	11	15	26
Total	18	22	40

On contrasting the rest of treatments according to their order: B|A *vs*. D|A, D|B *vs*. C|B, D|B *vs*. A|B, A|C *vs*. B|C, A|C *vs*. D|C, A|D *vs*. B|D and A|D *vs*. C|D, and formulating the appropriate tables for each pair of the above, we obtained the same result, i.e., no association between treatment order and the patient's response.

4.4 Testing for Carry-over Effect

This effect is aliased with the period effect. That is, the carry-over effect from a treatment τ_i, which is carried into the next period, is confounded with the effect of this period itself. Therefore, we get the same results as in Table (4). That is, the carry-over effect from the *i*th treatment is independent from the type of response recorded by patients. However,

this does not necessarily mean that there were no carry-over effects between the treatment sequences. On contrasting carry-over effect from one period to another, we get, for example, the following table, (see, Table (7).

Table (7): Patients due to effects of treatment A in period 1 and in period 2, respectively for data in Table (1).

Response	$A \rightarrow \pi_2$	$A \rightarrow \pi_3$	**Total**
Relief 1	7	9	16
No Relief 0	11	10	21
Total	18	19	37

To study the effect of treatment A in both period 1 and period 2, we test data of Table (7). Here also we found that treatment A (or dose A) did not contribute to type of responses of patients regardless of the period in which it was administered, (p-value = 0.07). Same results were obtained for $A \rightarrow \pi_3$ *vs.* $A \rightarrow \pi_4$ and also for $B \rightarrow \pi_3$ *vs.* $B \rightarrow \pi_4$. That is, administering this treatment A (or dose A) in the shown periods was found to be independent from type of response recorded for the patients who received that treatment.

4.5 Testing for Sequence Effect

Here we study the effect of each treatment within a sequence, and the effect of treatment sequence on the patient's response. For the first purpose, we formulated Table (8).

Table (8): Patients for data in Table (1) due to effects of each treatment within a sequence.

Response	**Sequence**				**Total**
	A	B	C	D	
Relief 1	12	11	11	9	43
No Relief 0	6	7	7	9	29
Total	18	18	18	18	**72**

In this table, the reading 12, for example, represents the number of patients who responded positively i.e., on taking treatment A (or dose A) in the sequence ABCD shown in the table itself, and so forth. On testing for association we found, using *StatXact*, that exact *p*-value = 0.382 showing no indication for association. That is, the design (or structure) of the sequence ABCD had no effect on the type of response recorded by subjects. The same conclusion was found for the other three sequences. In conclusion, we can say that the design (or structure) of the treatment sequences in general has no effect on the response of the subjects. Secondly, we continued testing for the effect of treatments sequences on patients' responses. To this end, we formulated Table (9).

Table (9): Patients for data in Table (1) due to the effect of treatments sequences on the patient's response.

Response	**Sequence**				**Total**
	[ABCD]	[BDAC]	[CADB]	[DCBA]	
Relief 1	43	65	48	64	220
No Relief 0	29	23	28	20	100
Total	72	88	76	84	320

Here, we can notice a match between Table (9) and Table (3). Similarly, the calculated *p*-value for Table (9), from *StatXact*, (0.07 for both asymptotic and exact tests of Fisher's, Likelihood and Chi-square), failed to show association between sequence and type of response. Indeed, no association was found (*p*-value=0.07) for the following table of extremes, Table (1).

Table (10): Relieved and non-relieved patients of Table (1) due to the extreme effects of the treatment sequence.

Response	**Sequence**				**Total**
	[ABCD]	[BDAC]	[CADB]	[DCBA]	
Relief 1 (1,1,1,1)	4	9	5	10	28
No Relief 0 (0,0,0,0)	1	0	1	1	3
Total	5	9	6	11	31

4.6 Contrasting Treatments vs. Periods

For this purpose, we formulated Table (11), where in this table $A_{(\pi 1)}$ denotes treatment A, as given in period (π_1), and so forth. 0, for example, in the entry (1,1) of this table represents the number of patients with "positive" carry-over from A to A, and 11 in the entry (1,2) represents number of patients with "positive" or active carry-over from A in to B, i.e., from the first period into the second. On testing for association, using *StatXact*, for data in Table (11), we found that *p*-value (asymptotic=exact) =0.000; i.e., there exists a significant sign of association between a treatment allocation in a period with positive carry-over effect (yields a relief) from another treatment (or dose) of the previous period. We may remark here that it was not surprising to get *p*-value equal to zero, (or tends to zero). This is because the diagonal of Table (11), all consist of zeros, structural zeros.

Table (11): Patients with "positive" carry-over after administering a treatment for data in Table (1).

	Treatment				**Total**
	$A_{(\pi 1)}$	$B_{(\pi 2)}$	$C_{(\pi 3)}$	$D_{(\pi 4)}$	
A	0	11	10	15	36
B	0	0	11	17	28
C	15	11	0	15	41
D	15	9	9	0	33
Total	30	31	30	47	138

Table (12): Relieved patients with each treatment in each sequence for data in Table (1).

Response	**Sequence**				**Total**
	[ABCD]	[BDAC]	[CADB]	[DCBA]	
relief with A	12	16	13	15	65
relief with B	10	19	15	18	62
relief with C	12	15	11	14	52
relief with D	9	15	10	17	51
Total	43	65	49	64	221

4.7 Contrasting Treatment Sequence vs. Relief with Each Treatment as a Distinct One

For the purpose of contrasting treatment sequence *vs*. relief with each treatment as a distinct one, we constructed Table (12). On sampling 20,000 tables, using *Monte Carlo* from *LogXact*, for Table (12), we got *p*-value = 0.99 (exact and asymptotic corrected to 2 decimal places). This means that no relationship was found between a treatment which gave a relief and the sequence in which this treatment was administered.

5. Discussion

It has been shown, in this paper, that modeling binary data from 4×4 cross-over trials is possible and useful. The main approach used here is the same of the 3×3 K-J model, with its considerations regarding parameters and tests for cross-over trials. Although such models contain a large number of parameters, which is one of the modeling drawbacks, we can under certain assumptions make a great deal of reduction amongst these parameters, particularly, on conditioning on the nuisance parameters (their sufficient statistics), and thus getting exact distributions for our model. In the example which we used here, to perform all the calculations, we treated the four treatments as unstructured. However, these treatments can be easily tackled in a special way when we test for the effect of order of treatments. For example, if we choose the first and the fourth sequences, we would get Table (13), in which **1**= (1, 1, 1, 1) and **0** = (0, 0, 0, 0).

Table (13): Relieved and non- relieved patients with selected two treatment sequences for data in Table (1).

	Sequence		
Response	[ABCD]	[DCBA]	**Total**
ALL Relief **1**	12	15	27
No Relief **0**	10	18	28
Total	22	33	55

We found from exact tests, using *StatXact*, that there was no interaction between treatments order in the sequences and type of response. Same result was obtained for the other remaining sequences. In

performing exact tests, *StatXact* and *LogXact* have shown a reliable capability. These two packages can perform both asymptotic and exact tests together. This saves a great deal of time. On analyzing Table (8), for example, we may get more than the following on one screen of *LogXact*. Table (14) illustrates this.

Table (14): *LogXact* screen results for confidence intervals (C.I) of odds ratios for data of Table (8).

Treatment Odds Ratio	95% C.I for odds ratios	
	Asymptotic	**Exact**
A Baseline	Baseline	Baseline
B 0.8143	(0.5328 , 1.242)	(0.5163 , 1.266)
C 0.6616	(0.2839 , 1.542)	(0.2666 , 1.604)
D 0.5382	(0.1513 , 1.915)	(0.1377 , 2.031)

These results emphasize the previous findings, and encourage doing more research. *StatXact* and *LogXact* have shown a great reduction in time used to perform different tests and simulation. For example, to find *p*-value for Table (1) through simulating 20,000 tables and to find the Likelihood ratio statistic (which is equal to 42.85), among other things, it took *StatXact* only 0: 9: 25.18 of time. Time elapsed for simulating 20,000 tables to find the Chi-squared statistics (Which is equal to 32.52) was 0: 9: 23.81. (These two packages can be easily run on any IBM-PC, with at least 512 KB of RAM and at least 2 MB of Hard Drive). Finally, it is recommended to do some more work on fitting our full model, and its goodness-of-fit.

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Appendix (1)

For example,

Logit$[P(Y_{11k}= 0)] = 1/(\alpha + \pi_1 + \tau_1)$,from which we get

$[P(Y_{11k}= 0)] = [1 + \exp(\alpha + \pi_1 + \tau_1)]^{-1}$, and

logit$[P(Y_{44k}= 0)] = 1/(\alpha + \pi_4 + \tau_1)$ from which we get

$[P(Y_{44k}= 0)] = [1 + \exp(\alpha + \pi_4 + \tau_1)]^{-1}$, (here the first 4 in Y_{44k} stands for the fourth treatment, or dose, in the treatment sequence DCBA). We note also here that this expression contains no carry-over, not because it is null, but rather because it is aliased with other previous carry-over effects, which makes trials design and protocol unpractical, and so difficult to be mathematically modeled), and so forth.

Also, from (6), we have, for example,

$P(Y_{12k}=1) = 1-P(Y_{11k}=0) =1-[1+ \exp(\alpha + \pi_1 + \tau_1)]^{-1}$

$=\exp(\alpha + \pi_1 + \tau_1)/\exp(\alpha + \pi_1 + \tau_1)$ and,

$P(Y_{44k} = 1) = \exp(\alpha + \pi_4 + \tau_1)/[1 + \exp(\alpha + \pi_4 + \tau_1)]$, and so forth.

Appendix (2)

$\mu_2+ 2\alpha + \pi_2+ \pi_4+ \tau_3+ \tau_4+ \varepsilon_6+\mu_4+ 4\alpha + \pi_1+ \pi_2+ \pi_3+ \pi_4+ \tau_1+ \tau_2+ \tau_3+ \tau_4+ \varepsilon_{16}- \mu_2- 4\alpha - \pi_1- \pi_2- \pi_3- \pi_4- \tau_1- \tau_2- \tau_3- \tau_4- \varepsilon_{16}- \mu_4- 2\alpha - \pi_2- \pi_4- \tau_1- \tau_3 - \varepsilon_6 = 0 \rightarrow \tau_4 = -\tau_1$ and,

$\mu_3 + 2\alpha + \pi_1+ \pi_3+ \tau_3+ \tau_4+ \varepsilon_{11}+\mu_4+ 4\alpha + \pi_1+ \pi_2+ \pi_3+ \pi_4+ \tau_1+ \tau_2+ \tau_3+ \tau_4+ \varepsilon_{16}- \mu_3- 4\alpha - \pi_1- \pi_2- \pi_3- \pi_4- \tau_1- \tau_2- \tau_3- \tau_4- \varepsilon_{16}- \mu_4- 2\alpha - \pi_1- \pi_3- \tau_2- \tau_4- \varepsilon_{11}= 0\rightarrow \tau_2 = -\tau_3$

Appendix 3

Table (1A): The logarithms l_{1j} of the outcome probabilities of Group1.

Outcome	Group (1)
(0,0,0,0)	$(\mu_1 + \sigma_{12} + \sigma_{13} + \sigma_{14} + \sigma_{23} + \sigma_{24} + \sigma_{34})$
(0,0,0,1)	$(\mu_1 + \sigma_{12} + \sigma_{13} - \sigma_{14} + \sigma_{23} - \sigma_{24} - \sigma_{34} + (\alpha + \pi_4 + \tau_4)$
(0,0,1,0)	$(\alpha + \pi_3 + \tau_3 + \mu_1 + \sigma_{12} - \sigma_{13} + \sigma_{14} - \sigma_{23} + \sigma_{24} - \sigma_{34})$
(0,0,1,1)	$(2\alpha + \pi_3 + \pi_4 + \tau_3 + \tau_4 + \mu_1 + \sigma_{12} - \sigma_{13} - \sigma_{14} - \sigma_{23} - \sigma_{24} + \sigma_{34})$
(0,1,0,0)	$(\alpha + \pi_2 + \tau_2 + \mu_1 + \sigma_{12} - \sigma_{13} - \sigma_{14} - \sigma_{23} - \sigma_{24} + \sigma_{34})$
(0,1,0,1)	$(2\alpha + \pi_2 + \pi_4 + \tau_2 + \tau_4 + \mu_1 - \sigma_{12} + \sigma_{13} - \sigma_{14} - \sigma_{23} + \sigma_{24} - \sigma_{34})$
(0,1,1,0)	$(2\alpha + \pi_2 + \pi_3 + \tau_2 + \tau_3 + \mu_1 - \sigma_{12} - \sigma_{13} + \sigma_{14} + \sigma_{23} - \sigma_{24} - \sigma_{34})$
(0,1,1,0)	$(2\alpha + \pi_2 + \pi_3 + \tau_2 + \tau_3 + \mu_1 - \sigma_{12} - \sigma_{13} + \sigma_{14} + \sigma_{23} - \sigma_{24} - \sigma_{34})$
(0,1,1,1)	$(3\alpha + \pi_2 + \pi_3 + \pi_4 + \tau_2 + \tau_3 + \tau_4 + \mu_1 - \sigma_{12} - \sigma_{13} - \sigma_{14} + \sigma_{23} + \sigma_{24} - \sigma_{34})$
(1,0,0,0)	$(\alpha + \pi_1 + \tau_1 + \mu_1 - \sigma_{12} - \sigma_{13} - \sigma_{14} + \sigma_{23} + \sigma_{24} + \sigma_{34})$
(1,0,0,1)	$(2\alpha + \pi_1 + \pi_4 + \tau_1 + \tau_4 + \mu_1 - \sigma_{12} - \sigma_{13} + \sigma_{14} + \sigma_{23} - \sigma_{24} - \sigma_{34})$
(1,0,1,0)	$(2\alpha + \pi_1 + \pi_3 + \tau_1 + \tau_3 + \mu_1 - \sigma_{12} + \sigma_{13} - \sigma_{14} - \sigma_{23} + \sigma_{24} - \sigma_{34})$
(1,0,1,1)	$(3\alpha + \pi_1 + \pi_3 + \pi_4 + \tau_1 + \tau_3 + \tau_4 + \mu_1 - \sigma_{12} + \sigma_{13} + \sigma_{14} - \sigma_{23} - \sigma_{24} + \sigma_{34})$
(1,1,0,0)	$(2\alpha + \pi_1 + \pi_2 + \tau_1 + \tau_2 + \mu_1 + \sigma_{12} - \sigma_{13} - \sigma_{14} - \sigma_{23} - \sigma_{24} + \sigma_{34})$
(1,1,0,1)	$(3\alpha + \pi_1 + \pi_2 + \pi_4 + \tau_1 + \tau_2 + \tau_4 + \mu_1 + \sigma_{12} - \sigma_{13} + \sigma_{14} - \sigma_{23} + \sigma_{24} - \sigma_{34})$
(1,1,1,0)	$(3\alpha + \pi_1 + \pi_2 + \pi_3 + \tau_1 + \tau_2 + \tau_3 + \mu_1 + \sigma_{12} + \sigma_{13} - \sigma_{14} + \sigma_{23} - \sigma_{24} - \sigma_{34})$
(1,1,1,1)	$(4\alpha + \pi_1 + \pi_2 + \pi_3 + \pi_4 + \tau_1 + \tau_2 + \tau_3 + \tau_4 + \mu_1 + \sigma_{12} + \sigma_{13} + \sigma_{14} + \sigma_{23} + \sigma_{24} + \sigma_{34})$

Table (2A): The logarithms l_{1j} of the outcome probabilities of Group1, replacing $\sum\sigma_{ij}$ by ε_i

Outcome	Group (1)
(0,0,0,0)	$(\mu_1 + \varepsilon_1)$
(0,0,0,1)	$(\mu_1 + \alpha + \pi_4 + \tau_4 + \varepsilon_2)$
(0,0,1,0)	$(\mu_1 + \alpha + \pi_3 + \tau_3 + \varepsilon_3)$
(0,0,1,1)	$(\mu_1 + 2\alpha + \pi_3 + \pi_4 + \tau_3 + \tau_4 + \varepsilon_4)$
(0,1,0,0)	$(\mu_1 + \alpha + \pi_2 + \tau_2 + \varepsilon_5)$
(0,1,0,1)	$(\mu_1 + 2\alpha + \pi_2 + \pi_4 + \tau_2 + \tau_4 + \varepsilon_6)$
(0,1,1,0)	$(\mu_1 + 2\alpha + \pi_2 + \pi_3 + \tau_2 + \tau_3 + \varepsilon_7)$
(0,1,1,1)	$(\mu_1 + 3\alpha + \pi_2 + \pi_3 + \pi_4 + \tau_2 + \tau_3 + \tau_4 + \varepsilon_8)$
(1,0,0,0)	$(\mu_1 + \alpha + \pi_1 + \tau_1 + \varepsilon_9)$
(1,0,0,1)	$(\mu_1 + 2\alpha + \pi_1 + \pi_4 + \tau_1 + \tau_4 + \varepsilon_{10})$
(1,0,1,0)	$(\mu_1 + 2\alpha + \pi_1 + \pi_3 + \tau_1 + \tau_3 + \varepsilon_{11})$
(1,0,1,1)	$(\mu_1 + 3\alpha + \pi_1 + \pi_3 + \pi_4 + \tau_1 + \tau_3 + \tau_4 + \varepsilon_{12})$
(1,1,0,0)	$(\mu_1 + 2\alpha + \pi_1 + \pi_2 + \tau_1 + \tau_2 + \varepsilon_{13})$
(1,1,0,1)	$(\mu_1 + 3\alpha + \pi_1 + \pi_2 + \pi_4 + \tau_1 + \tau_2 + \tau_4 + \varepsilon_{14})$
(1,1,1,0)	$(\mu_1 + 3\alpha + \pi_1 + \pi_2 + \pi_3 + \tau_1 + \tau_2 + \tau_3 + \varepsilon_{15})$
(1,1,1,1)	$(\mu_1 + 4\alpha + \pi_1 + \pi_2 + \pi_3 + \pi_4 + \tau_1 + \tau_2 + \tau_3 + \tau_4 + \varepsilon_{16})$

Table (3A): The Full Model.

Outcome	Group1	Group2	Group3	Group4
(0,0,0,0)	$(\mu_2 + \varepsilon_1)$	$(\mu_2 + \varepsilon_1)$	$(\mu_3 + \varepsilon_1)$	$(\mu_4 + \varepsilon_1)$
(0,0,0,1)	$(\mu_2+\alpha_4+\pi_4+\tau_3+\varepsilon_2)$	$(\mu_2+\alpha_4+\pi_4+\tau_3+\varepsilon_2)$	$(\mu_3+\alpha_4+\pi_4+\tau_3+\varepsilon_2)$	$(\mu_4+\alpha_4+\pi_3+\tau_3+\varepsilon_3)$
(0,0,1,0)	$(\mu_2+\alpha_3+\pi_3+\tau_2+\varepsilon_3)$	$(\mu_2+\alpha_3+\pi_3+\tau_2+\varepsilon_3)$	$(\mu_3+\alpha_3+\pi_3+\tau_2+\varepsilon_3)$	$(\mu_4+\alpha_3+\pi_3+\tau_2+\varepsilon_3)$
..	.....	.....	.....	.....
(0,1,0,0)	$(\mu_2+\alpha_2+\pi_2+\tau_1+\varepsilon_5)$	$(\mu_2+\alpha_2+\pi_2+\tau_1+\varepsilon_5)$	$(\mu_3+\alpha_2+\pi_2+\tau_1+\varepsilon_5)$	$(\mu_4+\alpha_2+\pi_2+\tau_1+\varepsilon_5)$
..	.....	.....	.....	.....
..	.....	.....	.....	.....
..	.....	.....	.....	.....
(1,0,0,0)	$(\mu_2+\alpha_1+\pi_1+\tau_1+\varepsilon_8)$	$(\mu_2+\alpha_1+\pi_1+\tau_1+\varepsilon_8)$	$(\mu_3+\alpha_1+\pi_1+\tau_1+\varepsilon_8)$	$(\mu_4+\alpha_1+\pi_1+\tau_1+\varepsilon_8)$
..	.....	.....	.....	.....
..	.....	.....	.....	.....
..	.....	.....	.....	.....
..	.....	.....	.....	.....
(1,1,1,1)	$(\mu_2+4\alpha_1+\pi_1+\pi_2+\pi_3+\pi_4+\tau_1+\tau_2+\tau_3+\tau_4+\varepsilon_{16})$	$(\mu_2+4\alpha_1+\pi_1+\pi_2+\pi_3+\pi_4+\tau_1+\tau_2+\tau_3+\tau_4+\varepsilon_{16})$	$(\mu_3+4\alpha_1+\pi_1+\pi_2+\pi_3+\pi_4+\tau_1+\tau_2+\tau_3+\tau_4+\varepsilon_{16})$	$(\mu_4+4\alpha_1+\pi_1+\pi_2+\pi_3+\pi_4+\tau_1+\tau_2+\tau_3+\tau_4+\varepsilon_{16})$