VALIDITY AND APPLICABILITY OF TESTS FOR ORDERED ALTERNATIVES WITH BINARY RESPONSE FOR A CLINICAL DOSE-RESPONSE STUDY

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ABSTRACT

This paper examines type I error rates and powers of several tests for ordered alternatives of a clinical dose-response study of a drug with dichotomous responses. The tests are analogues of tests for ordered alternatives for means of normal populations with known common variances. The tests are derived assuming asymptotic normality of estimates of response rates and are called large sample approximate tests. Type I error rates and powers of these tests are investigated through exact enumeration of the product binomial probabilities. The results show that Bartholomew's chi-bar test and Williams type test can be used in relatively small samples and also give high power for broad ordered alternatives.

1. Introduction

In clinical development of a new drug, a dose-response study is conducted to confirm existence of dose-response relationship. In general, efficacy rate of a drug increases with dose in a certain dose range of the drug and reaches to the maximum response. Some considers it to be important that the minimum effective dose and/or the maximum effective dose should be statistically identified. However, the minimum effective dose is usually defined as the lowest dose which shows statistically significant difference from the placebo. When a large placebo effect exists or when there are many non-responders, the difference of response rate between the lowest and highest doses may not be large enough to statistically identify the minimum effective dose in samples of moderate sizes.

In a dose response study of a drug on an efficacy variable, first of all it should be proved that there is statistically significant dose-dependent changes in the efficacy variable among several doses. When there are four or more dose levels, it is possible to estimate a dose-response curve by fitting a sigmoid curve and estimate the dose giving a specific amount of response which is clinically meaningful. Thus we are primarily interested in tests having high powers for broad ordered alternatives. Many authors have discussed tests against ordered alternatives in quantitative responses. Among them, Berenson (1982) and Shirley (1979),(1985) compared several tests with respect to powers and reported that, in general, Bartholomew's test and its nonparametric counterpart, which is proposed by Chacko (1963) and discussed by Shorack (1967), are recommendable. Budde and Bauer (1989) discuss multiple test procedures for dose-finding studies. Kuriki, Hirotsu and Hayter (1989) and Hirotsu, Kuriki and Hayter (1992) propose a test to find change point, which is referred to as the max-t test. Ruberg (1989) discusses use of contrasts to identify the minimum effective dose in animal experiments. As far as the author knows, there are only a few authors, Armitage (1955), Cochran(1955) and Bartholomew (1959a), who discussed testing ordered alternatives for binomial populations. This is why the Cochran-Armitage test is so widely used in clinical trials in parallel group comparisons of several doses of a drug.

In the present paper, we develop several tests for ordered alternatives for binomial populations and examine their type I error rates and power properties of several tests against ordered alternatives.

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The tests examined are analogues of tests for ordered alternatives for means of normal distributions with common known variances. The tests are derived from asymptotic normality of sample response rates, and the distribution of any test statistic examined is an unconditional approximate distribution derived from the asymptotic normal theory. The same test statistic is used to define conditional tests for the same alternative. Conditional tests are useful when sample sizes are small. In section 2, several types of ordered alternatives are discussed. In section 3, tests against the ordered alternatives described in section 2 are discussed. Some of the tests are obtained by modifying tests derived for quantitative responses. In later sections, we examine type I error rates and powers of the tests by computing exact unconditional distributions. Before that in section 4 useful formulae for computing the distribution function of a test statistic are derived. Type I error rates and powers are examined in section 5 and 6, respectively. In the final section 7 we illustrate sample size determination for a dose-response study.

2. Situation and hypotheses

Let $D_1, \dots, D_K$ be K doses of a drug to be tested, where $D_1 < \dots < D_K$. The lowest dose D_1 may be a placebo. Suppose n subjects are randomly divided into K subgroups and the k th dose D_k is administered to n_k subjects of the k th group. Let r_k be the number of subjects who respond in the k th group, $k = 1, \dots, K$ and let $r = r_1 + \dots + r_K$. The results are summarized in a $2 \times K$ contingency table. Let p_k be the population response rate at dose D_k , and assume that r_k has the binomial distribution with index n_k , $k = 1, \dots, K$. For convenience, we write K -tuples of p_k 's, n_k 's and r_k 's as $\mathbf{p} = (p_1, \dots, p_K)$, $\mathbf{n} = (n_1, \dots, n_K)$ and $\mathbf{r} = (r_1, \dots, r_K)$, respectively. If there is no drug effect,

$$H_0: p_1 = \dots = p_K$$

holds. Let us assume that the drug effect monotonically increases and this is represented as

$$K_0: p_1 \leq \dots \leq p_K, \text{ where at least one of the inequalities is strict.}$$

We further consider more restricted hypotheses as follows:

$$K_1: p_1 = \dots = p_k < p_{k+1} = \dots = p_K \text{ for some } k \text{ } (1 \leq k < K-1),$$

$$K_2: p_1 = \dots = p_k < p_{k+1} \leq \dots \leq p_K \text{ for some } k \text{ } (1 \leq k < K-1),$$

where K_1 is an analogue of a hypothesis discussed for normal means by Kuriki, Hirotsu and Hayter (1989), and K_2 is implicitly considered by Williams (1972). Next, let us consider a model $p_k = \alpha + \beta\theta(D_k)$, $k = 1, \dots, K$ where α and β are unknown constants and $\theta(x)$ is a monotonically increasing function of $x > 0$. Then H_0 implies that $\beta = 0$ and an alternative K_3 is defined by $\beta > 0$. This hypothesis is implied by Cochran-Armitage test. Let us consider further a hypothesis

$$K_4: p_1 < p_k \text{ at least one } k \text{ } (1 < k \leq K).$$

Note that K_4 neither is implied by K_0 nor implies K_0 . Therefore this is not a dose-response hypothesis.

Let us denote the observed response rate r_k/n_k by R_k , $k = 1, \dots, K$, $\mathbf{R} = (R_1, \dots, R_K)$ and $\mathbf{R} = \mathbf{r}/\mathbf{n}$. We call $\mathbf{R}$ the raw estimate of $\mathbf{p}$. The sums $r_u + \dots + r_v$ and $n_u + \dots + n_v$ are denoted by $r_{[u,v]}$ and $n_{[u,v]}$, respectively, for $1 \leq u \leq v \leq K$. An estimate of p_k under K_0 is given by well-known amalgamation procedure described by Bartholomew (1959a) and Barlow et al. (1972). The formula is

$$R_k^* = \max_{1 \leq u \leq k} \min_{k \leq v \leq K} r_{[u,v]} / n_{[u,v]}, \quad k = 1, \dots, K.$$

We call $\mathbf{R}^* = (R_1^*, \dots, R_K^*)$ max-min estimate of $\mathbf{p} = (p_1, \dots, p_K)$ under K_0 .

3. Tests for ordered alternatives of binomial populations

In this section, we briefly define statistical tests for testing ordered alternatives described in section 2. Some of these tests are originally proposed for testing ordered alternative of mean values of normal populations with common known variances. When we apply these tests to dichotomous variables, we assume that the response variable R_k has a binomial distribution with index n_k and

response probability $p_k, k = 1, \dots, K$. Then from the asymptotic normality of $R_k, k = 1, \dots, K$, any test statistics for testing H_0 against K^* , which will be discussed below, asymptotically has the distribution function of the corresponding test statistic defined for normal populations. Thus any test can be defined by using a critical point for the corresponding normal theory test. We will refer to these tests as large sample approximate tests in the subsequent discussion.

On the other hand, it is easy to define a test conditional on the observed total number of response R . This type of test which is defined by the same test statistic as the large sample approximate test can be performed by calculating exact conditional p values using multivariate hypergeometric distribution. When sample sizes are small, the exact approach may be applied. Conditional tests are briefly discussed in a later section. However, in the subsequent sections, we examine only large sample approximate tests.

3.1 Bartholomew's chi-bar square test

Bartholomew (1959a) proposed a likelihood ratio test of means of normal populations under order restriction. He gave examples of testing H_0 against K_0 for binomial populations. The test statistic is

$$\chi^2 = \sum_{k=1}^K n_k (R_k^* - R)^2 / R(1 - R).$$

Large sample approximate test of significance level α of H_0 against K_0 is defined as "reject H_0 when $\chi^2 \geq \bar{\chi}^2(\alpha; K)$, where $\bar{\chi}^2(\alpha; K)$ is the upper α point of χ^2 statistic of Bartholomew (1959a). The distribution function of this statistic is given by Bartholomew(1959a,b) and Barlow et al. (1972). When K is 3 or 4, the approximate null distribution function can be exactly calculated.

3.2 Jonckheere type test

Jonckheere (1954) and Terpstra (1954) proposed a distribution free test of homogeneity against the ordered alternative K_0 for continuous observations. We will slightly modify his statistic as follows; $J_M = \sum_{i=1}^K U_{ij} / n_i n_j$, where U_{ij} is a centralized Mann-Whitney statistic. Then for quantal responses, we obtain a test statistic for testing H_0 against K_0 as $J_M = \sum_{k=1}^K (2k - 1 - K)R_k$. Thus the statistic for testing H_0 against K_0 is a test statistic for testing $\delta = 0$ against $\delta > 0$, where

$$\delta = \sum_{k=1}^K (2k - 1 - K)p_k.$$

The test statistic is identical to the Cochran-Armitage test, which is discussed below, with equi-spaced score $\theta(D_k) = 2k - 1 - K, k = 1, \dots, K$.

3.3 Max Z test

Kuriki, Hirotsu and Hayter (1989) proposed a test of a hypothesis of normal means $\mu_1, \dots, \mu_K$ that for some $k, \mu_1 = \dots = \mu_k < \mu_{k+1} = \dots = \mu_K$. Hirotsu, Kuriki and Hayter (1992) proposed applying the same idea to the rank order test. The test is referred to as the max t-test, because the test statistic is based on the maximum of $K-1$ t-statistics. The same test statistic is considered by Ruberg (1989) using step contrasts. Their idea is immediately applied to our situation for testing H_0 against K_1 by considering a situation where the common variance is known. The resultant test statistic is $Z_{\max} = \text{Max}(Z_1, \dots, Z_{K-1})$, where

$$Z_k = \frac{(R_{[k+1,K]} - R_{[1,k]})}{\sqrt{R(1-R)\left(\frac{1}{n_{[k+1,K]}} + \frac{1}{n_{[1,k]}}\right)}}, \quad k = 1, \dots, K-1.$$

Critical points of $Z_{\max}$ for the cases $n_1 = \dots = n_K$ are obtained assuming asymptotic normality of $R_1 = \dots = R_K$ and are given by Kuriki, Hirotsu and Hayter (1989). When the sample sizes are not equal, exact asymptotic distribution should be calculated based on the formula given by Kuriki, Hirotsu and Hayter (1989) and Hirotsu, Kuriki and Hayter (1992). Ruberg (1989) gives conservative critical points. Let $Z_{\max}(\alpha)$ be upper α point of $Z_{\max}$ statistic calculated from Kuriki, Hirotsu and Hayter (1989) and Hirotsu, Kuriki and Hayter (1992). Then the large sample approximate test is defined as “reject H_0 when $Z_{\max} \geq Z_{\max}(\alpha)$ ”.

3.4 Williams type test

Williams (1971) proposed a stepwise test for determining the lowest dose level at which there is evidence for a difference from the control. A modification of his test for treating quantal response is the test of H_0 against K_2 and is defined by the statistic $\bar{Z}$, where

$$\bar{Z} = \frac{(R_K - R_1)}{\sqrt{R(1-R)\left(\frac{1}{n_1} + \frac{1}{n_K}\right)}}$$

Then the large sample approximate test is defined by “reject H_0 when $\bar{Z} \geq \bar{Z}(\alpha)$ ”, where $\bar{Z}(\alpha)$ is the upper α point of Williams test statistic with infinite degrees of freedom, which is given in Williams (1971, 1972).

3.5 A modified Williams type test

A modification of Williams test was suggested by Williams (1971) and was examined by Marcus (1976). The test statistic can be modified for normal means with known variance. Thus we consider the following test statistic:

$$\bar{Z}_M = \frac{(R_K - R_1)}{\sqrt{R(1-R)\left(\frac{1}{n_1} + \frac{1}{n_K}\right)}}$$

Then the large sample approximate test is defined by “reject H_0 when $\bar{Z}_M \geq \bar{Z}_M(\alpha)$ ”, where $\bar{Z}_M(\alpha)$ is the upper α point of modified Williams test statistic with infinite degrees of freedom, which is given in the table in Marcus (1976) for the case that all sample sizes are equal.

3.6 Cochran-Armitage test

Armitage (1955) and Cochran (1955) proposed a test of H_0 against K_3 for binomial populations. Let $\mathbf{x} = (x_1, \dots, x_K)$ be a given constant vector associated with dose levels like $x_k = \theta(D_k)$, $k = 1, \dots, K$, where $\theta(\cdot)$ is a monotone increasing function and satisfy that $x_1 \leq \dots \leq x_K$ and $x_1 < x_K$. We refer to $\mathbf{x}$ as a score vector for the Cochran-Armitage test. Then the test statistic is given by

$$Z = \frac{\sum_{k=1}^K r_k \bar{x}_k - r \bar{x}}{\sqrt{\frac{r(n-r)}{n^2} \sum_{k=1}^K n_k (\bar{x}_k - \bar{x})^2}}$$

where $\bar{x} = \sum_{k=1}^K n_k \bar{x}_k / n$. This statistic has asymptotically standard normal distribution under H_0 .

Therefore H_0 is rejected when Z is equal to or greater than $Z(\alpha)$.

Cox (1958) shows that an equivalent test statistic is derived from a conditional argument for testing $\beta=0$ against $\beta>0$ when p_k is given by a logistic model $p_k = 1/[1 + \exp(-\alpha - \beta \theta(D_k))]$, $k = 1, \dots, K$. Taron and Gart (1980) show that the test is a $C(\alpha)$ test for the model $p_k = H(\alpha + \beta \theta(D_k))$, $k = 1, \dots, K$, where H is any monotone, and twice differentiable function.

3.7 Dunnett type multiple comparison test

A natural test of H_0 against K_4 is a Dunnett type multiple comparison. The test statistic is

$$Z_D = \text{Max}\{Z_2, \dots, Z_K\}$$

where

$$Z_k = \frac{(R_k - R_1)}{\sqrt{R(1-R)\left(\frac{1}{n_1} + \frac{1}{n_k}\right)}}, \quad k = 2, \dots, K$$

The test is defined as "reject H_0 when $Z_D \geq Z_D(\alpha; K)$ ", where $Z_D(\alpha; K)$ is the upper α point of Dunnett test with infinite degrees of freedom. The critical point is given at the line for infinite degrees of freedom given in the tables of Dunnett (1955), and Dunnett (1964). When the heterogeneity of sample sizes is large, Bonferroni type test can be used: "If $Z_D \geq Z_{K-1}(\frac{\alpha}{K-1})$ then reject H_0 ",

where $Z_{K-1}(\frac{\alpha}{K-1})$ is the upper $\frac{\alpha}{K-1}$ point of the standard normal distribution. Although the hypothesis K_4 does not imply monotonicity of the dose-response curve, the Dunnett test is often used for testing dose response problems. Therefore, it is valuable to examine this test. Of course, it is possible to detect departure from the null hypothesis H_0 by using the Dunnett test when there really exists an appreciable dose-response relationship, and in some situations the Dunnett test may be powerful. However, caution is necessary in interpretation of the test results.

3.8 Note on conditional test

So far we defined an approximate unconditional test for every test discussed above. When sample sizes are small it is possible to adopt an exact test which is conditional on the observed total number of responses. For any test statistic $T(r)$ the probability is

$$\Pr[T(r)|n, r, H_0] = \frac{r!(n-r)! \prod_{k=1}^K n_k!}{n! \prod_{k=1}^K \{r_k!(n_k - r_k)!\}}$$

Therefore when

$$\Pr[T(R) \geq T(r)|n, r, H_0] = \sum_{r \in \mathcal{R}_{r, n}} \Pr[T(r)|n, r, H_0]$$

is greater than α reject the null hypothesis. In what follows we discuss only the large sample approximate tests.

4. Properties of test statistics and their exact unconditional distributions

In this section, we study some properties of test statistics and their exact unconditional distributions. The observed numbers of responses $r_1, \dots, r_K$ jointly have product binomial distribution

$$P(\mathbf{r} | \mathbf{n}, \mathbf{p}) = \prod_{k=1}^K n_k C_{r_k} p_k (1 - p_k)^{n_k - r_k}.$$

Thus for the given $\mathbf{n}$ and $\mathbf{p}$ we can exactly calculate the distribution of any statistic $T(\mathbf{R})$ defined in section 3 by the formula

$$\begin{aligned} F_T(t | \mathbf{n}, \mathbf{p}) &= \Pr(T(\mathbf{R}) \leq t) \\ &= \sum_{\mathbf{r} \in R(t)} P(\mathbf{r} | \mathbf{n}, \mathbf{p}), \end{aligned}$$

where $R(t)$ is a set of $\mathbf{r}$ which satisfies $T(\mathbf{r}) \leq t$. We refer to the distribution $F_T(t | \mathbf{n}, \mathbf{p})$ as exact unconditional distribution of a statistic $T(\mathbf{R})$ for given $\mathbf{n}$ and $\mathbf{p}$.

Now we introduce some terminology and notation. For given $\mathbf{p}$, $\mathbf{n}$ and $\mathbf{r}$, we write $\mathbf{p}^R = (p_K, \dots, p_1)$, $\mathbf{n}^R = (n_K, \dots, n_1)$ and $\mathbf{r}^R = (r_K, \dots, r_1)$, respectively, and refer to them as reverse of $\mathbf{p}$, $\mathbf{n}$ and $\mathbf{r}$, respectively. For given $\mathbf{a} = (a_1, \dots, a_K)$ where $0 \leq a_k \leq 1$, $k = 1, \dots, K$, there corresponds a K -tuple $\mathbf{b} = (b_1, \dots, b_K)$ where $b_k = 1 - a_{K+1-k}$, $k = 1, \dots, K$. We refer to $\mathbf{b}$ as the conjugate of $\mathbf{a}$ and denote it by $\mathbf{a}^c$. For the observed frequency vector $\mathbf{r}$, we define the conjugate of $\mathbf{r}$, denoted by $\mathbf{r}^c$, as $\mathbf{r}^c = \mathbf{n}^R - \mathbf{r}^R$. Let $\mathbf{x} = (x_1, \dots, x_K)$ be any score vector for the Cochran-Armitage test, and let $\mathbf{x}^c(\xi) = (\xi - x_K, \dots, \xi - x_1)$, where ξ is any given constant. Let $\mathbf{R}$ and $\mathbf{R}^*$ be the vectors of raw and max-min estimates of $\mathbf{p}$ as defined in section 2. We easily have the following propositions.

Proposition 1: The test statistics of the chi-square test, Jonckheere type test and the max-Z test have the property that $T(\mathbf{R}) = T(\mathbf{R}^c)$.

Proposition 2: Let $T(\mathbf{R} | \mathbf{x})$ and $T(\mathbf{R}^c(\xi) | \mathbf{x}^c)$ be Cochran-Armitage test statistics whose scores are $\mathbf{x}$ and $\mathbf{x}^c(\xi)$, respectively, then $T(\mathbf{R} | \mathbf{x}) = T(\mathbf{R}^c(\xi) | \mathbf{x}^c)$ holds. For an equi-spaced score $\mathbf{x}$, $T(\mathbf{R} | \mathbf{x}) = T(\mathbf{R}^c | \mathbf{x}^c)$ holds.

Proposition 3: The chi-bar square statistic and modified Williams statistic have the property that $T(\mathbf{R}^*) = T(\mathbf{R}^{*c})$.

Proofs of these propositions are trivial, so omitted. Note that the Williams type test statistic does not satisfy these properties. For example, suppose $\mathbf{n} = (10, 10, 10, 10)$ and $\mathbf{r} = (3, 1, 7, 9)$, then $\mathbf{R} = (0.3, 0.1, 0.7, 0.9)$ and $\mathbf{R}^* = (0.2, 0.2, 0.7, 0.9)$, thus $\bar{z} = (0.9 - 0.1) / \{0.5^2(1/10 + 1/10)\}^{1/2}$ for $\mathbf{R}$. Whereas $\mathbf{R}^c = (0.1, 0.3, 0.9, 0.7)$ and $\mathbf{R}^{*c} = (0.1, 0.3, 0.8, 0.8)$ which give $\bar{z} = (0.8 - 0.1) / \{0.5^2(1/10 + 1/10)\}^{1/2}$. Contrary to the Williams type test statistic, the modified Williams type test statistic gives the same $\bar{z}_w$ values.

Suppose that K^* is one of the hypotheses K_0, K_1, K_2, K_3 and K_4 , and $\mathbf{p}$ satisfies K^* , then the conjugate of $\mathbf{p}$ also satisfies K^* . Let $(\mathbf{n}, \mathbf{p})$ stand for an experiment where n_k subjects are administered dose D_k with response probability p_k , $k = 1, \dots, K$. What we want to show is a sufficient condition that two experiments $(\mathbf{n}, \mathbf{p})$ and $(\mathbf{m}, \mathbf{q})$ give the same distribution of a given test statistic for testing H_0 against K^* . The main result is stated in the Theorem 1 and Theorem 2. For showing Theorem 1, first we show Proposition 4.

Proposition 4: The following equality holds:

$$P(\mathbf{r} | \mathbf{n}, \mathbf{p}) = P(\mathbf{r}^c | \mathbf{n}^R, \mathbf{p}^c).$$

Proof Let $\mathbf{q} = (q_1, \dots, q_K) = \mathbf{p}^c$, $\mathbf{s} = (s_1, \dots, s_K) = \mathbf{r}^c$, then we have

$$\begin{aligned}
 P(\mathbf{r}^c | \mathbf{n}^R, \mathbf{p}^c) &= \prod_{k=1}^K n_{K+1-k} C_{s_k} q_k^{s_k} (1 - q_k)^{n_{K+1-k} - s_k} \\
 &= \prod_{k=1}^K n_{K+1-k} C_{n_{K+1-k} - r_{K+1-k}} (1 - p_{K+1-k})^{n_{K+1-k} - r_{K+1-k}} p_{K+1-k}^{r_{K+1-k}} \\
 &= \prod_{h=1}^K n_h C_{r_h} p_h^{r_h} (1 - p_h)^{n_h - r_h} \\
 &= P(\mathbf{r} | \mathbf{n}, \mathbf{p}).
 \end{aligned}$$

Thus the proposition was shown.

Theorem 1: Let $T=T(\mathbf{R})$ be a statistic of $\mathbf{R}$ satisfying $T(\mathbf{R})=T(\mathbf{R}^c)$. Then the exact unconditional distribution of T under the experiment $(\mathbf{n}, \mathbf{p})$ is identical to that under the experiment $(\mathbf{n}^R, \mathbf{p}^c)$, that is, $F_T(t | \mathbf{n}, \mathbf{p}) = F_T(t | \mathbf{n}^R, \mathbf{p}^c)$.

Proof: Let $\mathbf{r}$ be any sample from $(\mathbf{n}, \mathbf{p})$. Then the sample $\mathbf{r}^c$ from the experiment $(\mathbf{n}^R, \mathbf{p}^c)$ has the same probability as $\mathbf{r}$. Furthermore $\mathbf{R}$ and $\mathbf{R}^c$ are derived from $\mathbf{r}$ and $\mathbf{r}^c$, respectively and give the same statistic $T(\mathbf{R})=T(\mathbf{R}^c)$.

Let $R_{T(t)}$ be the set of $\mathbf{r}$ giving $T(\mathbf{R}) \leq t$. Then

$$\begin{aligned}
 P(T(\mathbf{R}) \leq t | (\mathbf{n}, \mathbf{p})) &= \sum_{\mathbf{r} \in R_{T(t)}} P(\mathbf{r} | \mathbf{n}, \mathbf{p}) \\
 &= \sum_{\mathbf{r}^c \in R_{T(t)}} P(\mathbf{r}^c | \mathbf{n}^R, \mathbf{p}^c) \\
 &= P(T(\mathbf{R}^c) \leq t | (\mathbf{n}^R, \mathbf{p}^c)).
 \end{aligned}$$

Thus the assertion is proved.

Similar statement holds for a statistic defined by $\mathbf{R}^*$.

Proposition 5: Let $\mathbf{s} = (s_1, \dots, s_K)$ be the conjugate of $\mathbf{r}$. Then the max-min estimate of $\mathbf{q}$ under K_0 based on $\mathbf{s}$ is given by $\mathbf{R}^{*c}$.

Proof: Denote Q_k^* as the max-min estimate of q_k based on $\mathbf{r}^c$. Then we have

$$\begin{aligned}
 Q_k^* &= \text{Max}_{1 \leq u \leq k} \text{Min}_{k \leq v \leq K} \left(1 - \frac{r_{[K+1-v, K+1-u]}}{n_{[K+1-v, K+1-u]}} \right) \\
 &= \text{Max}_{1 \leq u \leq k} \left(1 - \text{Max}_{k \leq v \leq K} \frac{r_{[K+1-v, K+1-u]}}{n_{[K+1-v, K+1-u]}} \right) \\
 &= 1 - \text{Min}_{1 \leq u \leq k} \text{Max}_{k \leq v \leq K} \frac{r_{[K+1-v, K+1-u]}}{n_{[K+1-v, K+1-u]}} \\
 &= 1 - \text{Min}_{K+1-k \leq u \leq K} \text{Max}_{1 \leq v \leq K+1-k} \frac{r_{[u, v]}}{n_{[u, v]}} \\
 &= 1 - \text{Max}_{1 \leq u \leq K+1-k} \text{Min}_{K+1-k \leq v \leq K} \frac{r_{[u, v]}}{n_{[u, v]}} \\
 &= 1 - \mathbf{R}
 \end{aligned}$$

Thus the proposition is shown.

Theorem 2: Let $T=T(\mathbf{R}^*)$ be a statistic of $\mathbf{R}^*$ satisfying $T(\mathbf{R}^*)=T(\mathbf{R}^{*c})$. Then the exact unconditional distribution function of T under the experiment $(\mathbf{n}, \mathbf{p})$ is identical to that under the experiment $(\mathbf{n}^R, \mathbf{p}^c)$,

that is, $F_T(t|\mathbf{n}, \mathbf{p}) = F_T(t|\mathbf{n}^R, \mathbf{p}^c)$ holds.

Proof Let $\mathbf{r}$ be any sample from $(\mathbf{n}, \mathbf{p})$. Then $\mathbf{r}^c$ is the sample from $(\mathbf{n}^R, \mathbf{p}^c)$ which gives the same probability element as that of $\mathbf{r}$. Since $\mathbf{R}^*$ and $\mathbf{R}^{*c}$ give the same value of statistic T for the set of samples $\mathbf{R}^{*T(t)} = \{\mathbf{r}; T(\mathbf{R}^*) \leq t\}$, next equality holds;

$$\begin{aligned} P(T(\mathbf{R}^*) \leq t | (\mathbf{n}, \mathbf{p})) &= \sum_{\mathbf{r} \in \mathbf{R}^{*T(t)}} P(\mathbf{r} | (\mathbf{n}, \mathbf{p})) \\ &= \sum_{\mathbf{r} \in \mathbf{R}^{*T(t)}} P(\mathbf{r}^c | (\mathbf{n}^R, \mathbf{p}^c)) \\ &= P(T(\mathbf{R}^{*c}) \leq t | (\mathbf{n}^R, \mathbf{p}^c)). \end{aligned}$$

Thus the assertion of the theorem 2 was proved.

From the above theorems and proposition 1,2 and 3, it follows that each of the test statistics of the chi-square test, chi-bar square test, Jonckheere type test, Cochran-Armitage test with equi-spaced score, Max-Z test and modified Williams type test have the same distribution for $(\mathbf{n}, \mathbf{p})$ and $(\mathbf{n}^R, \mathbf{p}^c)$. Thus the chi-bar square test, for example, has the same power for the alternative $\mathbf{p}=(0.2, 0.3, 0.7)$ with samples $\mathbf{n}=(15, 17, 13)$ as for the alternative $\mathbf{p}=(0.3, 0.7, 0.8)$ with samples $\mathbf{n}=(13, 17, 15)$.

5. Example

Let us apply these tests to actual dose-response studies. Table 1 shows rates of patients who showed sufficient reduction of heart rates when administered 2.5mg, 5.0mg or 10mg of diltiazem under operation. Maximum likelihood estimates of R_1 , R_2 and R_4 under K_0 are 0.3200, 5703 and 0.5703, respectively, and $R=0.4722$. We have

$$\begin{aligned} \chi^2 &= 8.702 > \bar{\chi}^2(0.01;3)=6.822, \\ Z_{\max} &= 2.950 > Z_{\max}(0.01;3)=2.588, \\ \bar{Z} &= 2.572 > \bar{Z}(0.01;3)=2.366, \\ \bar{Z}_M &= 2.572 > \bar{Z}_M(0.01;3)=2.400, \\ Z &= 2.938 > Z_D(0.01;3), \\ Z &= 2.146 > Z(0.025) = 1.960. \end{aligned}$$

Thus every test except for the Cochran-Armitage test indicates that the dose-response is significant at one percent level of significance of one-sided test. The Cochran-Armitage test is significant at five percent level of significance. $Z_{\max}$ is given by Z_1 and Z_D is given by Z_2 . Every test indicates that 5.0mg is more effective than 2.5mg. The chi-square test statistic for testing equality of response rates of 5.0mg and 10mg is 0.533. This indicates that the results that 10mg gave lower response rate than 5mg is highly possible by chance. Thus it can be concluded that 5mg is more effective than 2.5mg and is equivalent to 10mg, that is, 5mg is a plateau dose.

Table 1. Effect of diltiazem on heart rate reduction

Dose	number of subjects			response rate (%)
	effective	not effective	total	
2.5 mg	16	34	34	32.0
5.0 mg	35	23	23	60.3
10.0 mg	30	26	26	53.6

6. Type I error rates of the large sample approximate tests

We derived large sample approximate tests of H_0 against ordered alternatives. However, due to

their discrete nature of response variables, and since they are asymptotically valid, the sample sizes may affect their validity. That is, when the sample sizes are small or moderate, the actual type I error rates possibly differ from the nominal significance level. It is worthwhile to examine agreement of the actual type I error rates and the nominal significance levels. For this purpose we calculate type I error rates by exact enumeration of the unconditional probability function $F_T(t|\mathbf{n}, \mathbf{p})$ at the nominal level 0.05, and 0.01. That is, the exact type I error rate is calculated by $1 - F_T(t(\alpha)|\mathbf{n}, \mathbf{p})$, where $t(\alpha)$ is the upper α point described in section 3. Since the number of dose levels in a dose-response study is mostly three or four, we show the

Table 2. Type I error rate of the unconditional tests for trend in case of 3 populations and equal sample sizes of n_0 .

n_0	p	α	χ^2	$\bar{\chi}^2$	Z	$Z_{\max}$	Z_D	$\bar{Z}$	$\bar{Z}_M$
20	.20	5.0	4.98	5.04	4.91	4.80	5.10	5.09	5.19
		1.0	.85--	.98	.91-	.89--	.87--	.95	.87--
	.30	5.0	5.22	5.09	5.43+	4.99	5.39+	5.10	5.07
		1.0	.89--	1.03	1.00	.90--	.99	.99	.96
	.40	5.0	5.00	5.18	4.58-	4.98	5.47+	4.77	4.98
		1.0	.90-	1.00	.87--	1.04	1.06+	.92-	.95
	.50	5.0	4.96	5.14	4.13--	5.01	4.39--	4.96	4.99
		1.0	.88--	.94-	.84--	1.08+	.83--	.97	.98
	.20	5.0	4.90	5.00	5.18	4.96	5.23	4.99	5.09
		1.0	4.90-	.98	.98	.88--	1.02	.92-	.98
30	.30	5.0	5.17	4.97	5.22	4.95	5.23	4.91	4.86
		1.0	.98	.99	1.00	.94-	1.02	1.00	1.02
	.40	5.0	5.06	5.12	4.51-	5.20	4.58-	5.00	5.36+
		1.0	.96	1.01	1.17++	1.01	1.13++	1.00	.94-
	.50	5.0	4.80	4.98	4.63-	5.57++	4.71-	5.19	5.72++
		1.0	.97	.98	1.08+	.91-	1.28++	.82--	.88--
	.20	5.0	4.93	5.07	5.07	4.99	5.15	5.02	4.92
		1.0	.96	.95-	.99	.99	1.01	.95-	.98
	.30	5.0	5.01	5.10	5.12	5.11	5.16	5.06	4.94
		1.0	.97	.97	1.01	.99	1.00	.99	1.00
50	.40	5.0	5.22	5.09	4.82	4.98	4.81	4.87	5.22
		1.0	1.01	.99	.95	1.03	1.01	1.02	1.10+
	.50	5.0	4.80	5.41+	4.44--	5.12	5.14	5.02	5.55++
		1.0	.96	1.02	1.05	.91-	1.14++	1.14++	1.22++

p stands for the common response rate.

results of $K=3$ and 4 in Table 2 and Table 3, respectively. We show only the cases where K samples have the same size, $n_0=20, 30$ and 50. The response probabilities of null hypotheses examined are 0.2, 0.3, 0.4 and 0.5. The results are the same for 0.6, 0.7, 0.8 as for 0.4, 0.3 and 0.2, respectively. This fact results from Theorem 1 and Theorem 2

Since the exact distribution of any statistic is discrete, it is usually impossible for any test to exactly attain the nominal level. So we accept the relative error less than five percent of the given nominal level. In Table 2 and 3, the super scripts + and ++ indicate that the actual level exceeds the nominal level by more than 5 percent and 10 percent of the nominal level, respectively. The symbols - and -- indicate that the actual level is less than the nominal level more than 5 percent and 10 percent of the nominal level, respectively. The results of every test are summarized as follows.

(1) Chi-square test : The test is acceptable when n_0 is equal to or greater than 20.

(2) Chi-bar square test : The type I error rate is more stable than the other tests studied. Even when n_0 is equal to twenty, it keeps type I error rate at almost the nominal level.

Table 3. Type I error rate of the unconditional tests for trend in case of 4 populations and equal sample sizes of n_0 .

n_0	p	α	χ^2	$\bar{\chi}^2$	Z	$Z_{\max}$	Z_D	$\bar{Z}$	$\bar{Z}_M$
20	.20	5.0	4.77	5.15	5.25	4.93	5.56++	5.06	5.06
		1.0	.87--	.96	.93-	.92-	.99	.87--	.96
	.30	5.0	5.05	5.18	5.18	5.00	5.37+	5.07	4.93
		1.0	.91-	1.00	.97	.96	1.03	.96	.94-
	.40	5.0	4.99	4.96	5.07	5.20	4.72-	4.85	5.09
		1.0	.91-	.97	1.00	1.04	.86--	.90--	.94-
30	.50	5.0	4.87	4.96	4.99	5.25	4.92	5.13	5.25+
		1.0	.94-	.95-	.96	1.12++	.89--	.96	1.00
	.20	5.0	4.93	4.92	5.04	5.20	5.46+	4.91	4.97
		1.0	.89--	.97	.96	.88--	1.02	.97	.93-
	.30	5.0	5.05	4.99	5.07	5.00	5.14	4.82	4.95
		1.0	.94-	.98	.99	.97	1.06+	.97	.98
50	.40	5.0	4.96	5.02	5.12	4.89	6.06++	5.13	5.30+
		1.0	.97	.99	.99	.97	.89--	.97	.89-
	.50	5.0	5.06	4.96	4.88	4.84	6.50++	5.37+	4.41-
		1.0	.97	.96	.99	.98	.86--	.82-	.92-
	.20	5.0	4.90	5.01	5.16	4.86	5.39+	4.96	4.95
		1.0	.95-	.97	.99	.99	1.02	.94-	.95-
50	.30	5.0	4.96	5.08	5.05	5.12	5.19	5.01	4.91
		1.0	.97	.99	1.00	1.00	1.02	.99	.95-
	.40	5.0	5.02	5.07	5.07	5.03	4.87	5.00	5.13
		1.0	.96	.99	1.00	1.00	.94-	1.04	1.02
	.50	5.0	5.12	4.98	5.13	4.88	4.53-	5.22	4.42--
		1.0	.97	1.04	1.04	1.09+	.92-	1.17++	.83--

p stands for the common response rate.

(3) Cochran-Armitage test : When K is four, it well keeps the nominal levels even when n_0 is equal to twenty. However, when K is three, it is not so stable as chi-bar square test and is slightly conservative. This is because the test statistic for 3 samples case is actually a test of difference of proportions between the first and the third samples due to the equi-spaced scores. Thus except for the error variance there is no contribution of the second sample, which results in slow convergence to the asymptotic distribution. In case of four samples, all samples contribute to the test statistic, thus convergence is faster compared to the three sample case.

(4) Max-Z test : The results show that the Max-Z test is not so stable as chi-bar square test but more stable than Cochran-Armitage test.

(5) Dunnett type test : The type I error rate seems fairly unstable even the size of each sample is fifty. One reason for the slow convergence to the asymptotic distribution may be that the test is essentially a two-sample test except for the estimates of variance. Therefore there are no contributions of other samples than the relevant pair of samples. This fact results in the greater discreteness of probability distribution.

(6) Williams type test : When n_0 is equal to or greater than thirty the actual type I error rate is close to the nominal level. The second sample contributes to the test statistic to some extent, but the slow approximation to the asymptotic distribution is due to the isolate use of the first sample.

(7) Modified Williams type test : The type I error rate of the modified Williams test is not so stable as that of the chi-bar square test. It is difficult to know why the type I error rate is so high for some cases even when sample sizes are 50.

It is often said that for small samples, an exact test conditional on the given marginal totals should be used in order to avoid dependence of the type I error rate on the null response probabilities. However, since the actual type I error rate is between 95% and 105% of the nominal level for most response probabilities, the large sample approximate tests seem applicable for samples of which sizes are as large

as twenty.

7. Power comparisons

In this section, we examine powers of the tests considered in section 3. Since the number of doses tested in clinical dose-response trials are usually three or four, we examined various non-decreasing dose-response patterns with dose levels of three or four. The power is given by $P(T(R) \geq t(\alpha))$ for given p and n , which is obtained by exactly enumerating the product binomial probabilities as is in section 6. Among huge number of cases examined, only typical results are given in Fig.1, Fig.2 and Table 4. The significance level is five percent. In Table 4, to identify powerful tests, the highest value among the six tests is underlined and values which do not differ from the highest values by more than one percent are highlighted by asterisks.

It is possible to identify which test is most powerful for some of the alternatives. For example for K_3 , the Cochran-Armitage test should be most powerful. For K_1 , the max-Z test should be most powerful. For K_4 where $p_1 < p_2 = \dots = p_k$, the Dunnett type test seems to be very powerful, because all $K-1$ samples equally contribute to rejecting the null hypothesis. However, there are many situations where pattern of p is between these typical patterns. For such a pattern it is very difficult to predict which test is the most powerful. For quantitatively describing how the tests perform for a typical pattern of p , numerical comparisons by exact calculation of powers is inevitable.

First, let us summarize findings about cases of three dose-levels. Fig. 1 and Fig.2 show power curves as functions of p_2 when p_2 changes from p_1 to p_3 . Figure 1 and Figure 2 show the case that $p_1=0.20$, $p_3=0.40$, $n=(60,60,60)$ and the case $p_1=0.20$, $p_3=0.50$, $n=(30,30,30)$, respectively.

(1) For the alternative K_3 , the Cochran-Armitage test is expected to give the highest power. However, the modified Williams type test and Williams type test often give a power as high as that of the Cochran-Armitage test. These three tests seem to be equally powerful against K_3 .

(2) For the case of K_1 , that is, $p_1=p_2 < p_3$ or $p_1 < p_2=p_3$, the chi-bar square test is always better than the Cochran-Armitage test. The Max-Z test and the modified Williams type test seem as powerful as the chi-bar square test as expected. It should be noted that for any p satisfying K_1 , p^c also satisfies K_1 , and each of the Max-Z test, modified Williams type test and chi-bar square test individually gives the same power for p and p^c .

(3) The Williams type test and Dunnett type test are as powerful as chi-bar square test when $p_1 < p_2 = p_3$, but they are considerably inferior to others when $p_1 = p_2 < p_3$.

(4) The Williams type test is the most powerful when p_2 is between $(p_1+p_3)/2$ and p_3 . Almost the same feature is observed for several charts obtained by changing p_2 from p_1 to p_3 . It can be said that when p_2 is greater than $(p_1+p_3)/2$ William test is recommended.

(5) The chi-bar square, modified Williams type and Max-Z tests are similar to each other. Chi-bar square test and modified Williams type test keep relatively higher power for any particular hypothesis.

Next we consider the case of four doses. The results are given in Table 4. The properties of the tests are more remarkable.

(1) For K_3 the Cochran-Armitage test is most powerful as expected. The Williams type test and Modified-Williams type test are ranked second. Chi-bar square is slightly less powerful than these tests.

(2) When $p_1=p_2=p_3 < p_4$, chi-bar square test, Max-Z test and modified Williams type test give almost the same power, but other tests are considerably inferior to the above three tests.

(3) When $p_1 < p_2 = p_3 = p_4$ the Dunnett type test and the Williams type test are most powerful, and chi-bar square test, Max-Z test and the modified Williams type test are somewhat inferior to the above two tests. The Cochran-Armitage test is considerably inferior to others.

(4) When $p_1 < p_2 \leq p_3 \leq p_4$, the Williams type test is most powerful.

(5) When $p_1 = p_2 < p_3 = p_4$, the Max-Z test is expected to be most powerful. The chi-bar square test and the Cochran-Armitage test give as high power as the Max-Z test. The modified Williams type test is somewhat inferior to the above three tests.

(6) When $p_1 = p_2 < p_3 < p_4$, the chi-bar square and Max-Z tests seem generally powerful, modified Williams

Figure 1. Power curves of several tests with P_2 changing from P_1 to P_a .
($n_1 = n_2 = n_3 = 60$)

Figure 2. Power curves of several tests with P_2 changing from P_1 to P_a .
($n_1 = n_2 = n_3 = 30$)

type test is also powerful. The power of the Cochran-Armitage test changes depending on departure from linearity.

It may be concluded that 1) for K_1 , the chi-bar square test and Max-Z test are generally suitable, and 2) for K_2 , the chi-bar square, the Cochran-Armitage, the Max-Z and the modified Williams type tests are comparable.

8. Determination of test procedure and sample sizes for a dose-response study

8.1 General procedure

Approximate formulae for calculating sample size are available for the chi-square test and the Cochran-Armitage test. But for other tests no formulae are available. Thus we calculate exact unconditional power of the given test for several n 's by the method described in the previous sections, and search for the appropriate n . When $n = n_0(n_1, \dots, n_K)$, we can get the required sample size in the following manner. First, select several n_0 , say n_{0i} , $i=1, \dots, I$, and compute powers $P(n_{0i})$, $i=1, \dots, I$, thus we get pairs $(n_{0i}, P(n_{0i}))$, $i=1, \dots, I$. Next, fit a polynomial to the power plot $(n_{0i}, P(n_{0i}))$, $i=1, \dots, I$ and then get the solution to the equation that the polynomial value is equal to the required power. The first approximate n_0 , say n_A is obtained as the minimum integer which is not less than the solution to the above equation. The sample size vector $n_A(n_1, \dots, n_K)$ is an estimate of the sample sizes. Unfortunately the power function is not necessarily monotonic with respect to n_0 , so it is better to calculate the powers for consecutive n_0 around n_A to get a more precise value.

Table 4. Powers of tests in case of four dose-groups at 5% level of significance and equal sample sizes.

n_0	p_1	p_2	p_3	p_4	χ^2	$\bar{\chi}^2$	Z	$Z_{\max}$	Z_D	$\bar{Z}$	$\bar{Z}_M$
20	0.1	0.2	0.3	0.4	47.38	73.05	<u>77.43</u>	69.58	66.75	75.34	73.79
	0.2	0.3	0.4	0.5	39.25	64.27	<u>69.21</u>	62.18	54.39	64.32	64.88
	0.3	0.4	0.5	0.6	35.93	60.60	<u>65.23</u>	58.81	51.27	61.78	62.52
	0.2	0.2	0.2	0.5	56.58	<u>73.58</u>	65.68	72.63*	54.80	66.53	73.19*
	0.2	0.2	0.2	0.6	81.61	<u>91.59</u>	84.85	91.39*	77.25	85.35	91.36*
	0.2	0.2	0.5	0.5	66.31	82.91*	82.69*	<u>83.13</u>	65.20	70.88	76.72
	0.3	0.3	0.6	0.6	61.23	78.91*	<u>79.02</u>	78.22*	61.16	68.11	73.05
	0.2	0.5	0.5	0.5	49.76	68.86	58.05	69.61	72.03*	<u>72.81</u>	69.52
30	0.1	0.2	0.3	0.4	67.59	87.07	<u>90.16</u>	85.52	82.83	88.56	87.59
	0.2	0.3	0.4	0.5	56.83	79.83	<u>83.66</u>	77.41	73.67	80.26	81.01
	0.1	0.1	0.1	0.4	86.24	93.85*	89.42	<u>94.71</u>	83.97	89.85	94.21*
	0.2	0.2	0.2	0.5	75.36	87.41*	79.92	87.13*	71.08	80.49	<u>87.44</u>
	0.1	0.1	0.4	0.4	92.83	97.77*	97.24*	<u>97.87</u>	91.42	93.21	95.85
	0.2	0.2	0.5	0.5	85.01	94.18*	93.55*	<u>94.25</u>	83.55	85.96	90.82
	0.1	0.2	0.2	0.4	66.21	84.36	85.49	82.20	80.41	<u>87.38</u>	86.98*
	0.1	0.2	0.4	0.4	80.34	92.98*	<u>93.70</u>	92.52	89.90	92.17	91.67
	0.1	0.4	0.4	0.4	79.89	91.93	79.38	91.81	<u>93.18</u>	93.17	91.76
	0.2	0.5	0.5	0.5	70.43	85.36	74.11	84.84	<u>89.80</u>	87.59	85.47
	0.1	0.1	0.2	0.4	80.07	<u>92.34</u>	82.82	92.08*	82.07	88.65	91.98*
	0.1	0.1	0.3	0.4	84.47	94.70*	<u>95.40</u>	94.51*	89.68	89.81	92.82
	0.1	0.3	0.3	0.4	64.19	83.91	82.14	82.20	83.87	<u>87.97</u>	85.82
	0.1	0.3	0.4	0.4	74.71	90.37	87.82	89.68	89.89	<u>91.83</u>	90.33
	0.2	0.6	0.6	0.6	93.37	97.85*	91.96	97.90*	<u>98.78</u>	98.30*	97.55
	0.3	0.3	0.4	0.7	71.51	87.39*	85.42	87.18*	70.86	81.09	<u>87.92</u>
	0.3	0.3	0.6	0.7	78.49	91.82*	<u>92.66</u>	91.00	76.71	84.68	89.67

8.2 An example of sample size determination in a dose-response study

When we calculate the required number of subjects for a dose-response study, we first estimate the

response rate of each dose group and then select a testing procedure based on an expected response pattern and the primary hypothesis. The estimation of response rates is usually based on assumptions or earlier study results. Thus the assumed response rates for the planned study are not restricted to just one tuple of response rates. It is better to consider several plausible tuples of response rates. Furthermore, the power of the test depends on the response pattern. Therefore, it is advisable to calculate sample size for each test discussed in previous sections for several cases of response pattern, and choose the most efficient and also robust test.

Let us consider an example, see Minaguchi et al.(1996). Suppose we plan a dose-response study where four doses of a drug are compared based on a quantal response. The doses are equi-spaced on a logarithmic scale, so $D_1=D$, $D_2=2D$, $D_3=4D$ and $D_4=8D$. The response rates of the lowest dose group and the maximum dose group were estimated to be $p_1=0.20$ and $p_4 = 0.45$ based on previous experiments. D_3 is assumed to give almost the maximum effect, so that p_3 is assumed to be 0.40 or 0.45. D_2 is assumed to be less effective than D_3 . Based on these considerations, the power of each test was calculated for samples of size $n_1 = n_2 = n_4 = n_3 = 25, 30, 35, 40$ and 45 and for seven combinations of p_2 and p_4 ;

case 1 : (0.20,0.20,0.20,0.45), case 2 : (0.20,0.20,0.40,0.45), case 3 : (0.20,0.20,0.45,0.45),
 case 4 : (0.20,0.25,0.40,0.45), case 5 : (0.20,0.25,0.45,0.45), case 6 : (0.20,0.30,0.40,0.45),
 case 7 : (0.20,0.40,0.40,0.45).

The chi-bar square test and Cochran-Armitage test were comparable for case 2, 3 and 5. The chi-bar square test was preferred to the Cochran-Armitage test for case 1 and 7, and vice-versa for case 4 and 6. From these results it was recommended to use the chi-bar square test and to enroll 40 subjects to each dose group. Because the chi-bar square test give the minimum value among seven tests of the maximum sample size among four combinations.

8.3 Sample sizes for several cases

It is very valuable to know the sample size for typical cases. From the results of power comparisons, it may be a good strategy to use the chi-bar square test or Williams test depending on response rates of intermediate dose levels. Table 5 gives sample sizes of required to assure 80% or 90% of powers for these two test of one-sided 5% level significance for experiments of three doses and $p_4 - p_1 = 0.20$ and $p_4 - p_1 = 0.30$. The sample sizes were calculated by the method described in section 7.3.

Table 5a. Sample sizes of chi-bar square and Williams type tests in case of three dose with 5% level of significance and 80% of power.

p_1	p_2	p_3	$\bar{\chi}^2$	$\bar{Z}$	p_1	p_2	p_3	$\bar{\chi}^2$	$\bar{Z}$	p_1	p_2	p_3	$\bar{\chi}^2$	$\bar{Z}$
10	10	30	40	46	10	20	30	51	48	10	30	30	43	42
20	20	40	55	64	20	30	40	69	64	20	40	40	57	55
30	30	50	64	77	30	40	50	79	76	30	50	50	65	62
40	40	60	67	79	40	50	60	83	78	40	60	60	67	64
50	50	70	65	78	50	60	70	79	77	50	70	70	64	62
60	60	80	57	70	60	70	80	69	66	60	80	80	55	53
70	70	90	43	55	70	80	90	51	49	70	90	90	40	38
10	10	40	20	23	10	25	40	26	24	10	40	40	22	21
20	20	50	26	31	20	35	50	33	31	20	50	50	27	27
30	30	60	29	33	30	45	60	37	36	30	60	60	29	28
40	40	70	29	37	40	55	70	37	36	40	70	70	29	28
50	50	80	27	32	50	65	80	33	32	50	80	80	26	25
60	60	90	22	27	60	75	90	26	25	60	90	90	20	20

Table 5b. Sample sizes of chi-bar square and Williams type tests in case of three dose with 5% level of significance and 90% of power.

p ₁	p ₂	p ₃	$\bar{\chi}^2$	$\bar{z}$	p ₁	p ₂	p ₃	$\bar{\chi}^2$	$\bar{z}$	p ₁	p ₂	p ₃	$\bar{\chi}^2$	$\bar{z}$
10	10	30	54	63	10	20	30	70	66	10	30	30	58	56
20	20	40	74	89	20	30	40	95	90	20	40	40	77	74
30	30	50	87	103	30	40	50	110	105	30	50	50	88	87
40	40	60	91	109	40	50	60	114	108	40	60	60	91	89
50	50	70	88	108	50	60	70	110	106	50	70	70	87	84
60	60	80	77	97	60	70	80	95	90	60	80	80	74	73
70	70	90	58	73	70	80	90	70	68	70	90	90	54	53
10	10	40	28	31	10	25	40	35	33	10	40	40	29	28
20	20	50	35	42	20	35	50	45	42	20	50	50	36	36
30	30	60	39	48	30	45	60	50	48	30	60	60	39	38
40	40	70	39	49	40	55	70	50	48	40	70	70	39	38
50	50	80	36	43	50	65	80	45	43	50	80	80	35	35
60	60	90	29	37	60	75	90	35	35	60	90	90	28	26

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