Hacettepe Journal of Mathematics and Statistics
Volume 35 (2) (2006), 227 – 234

# OPTIMAL RESTRICTED THREE-STAGE DESIGNS

Sevil Bacanli*

Received 15 : 01 : 2006 : Accepted 08 : 12 : 2006

**Abstract**

In this study optimal restricted three stage designs are examined and compared with optimal restricted two stage, fixed sample and sequential designs. Then the results are discussed.

**Keywords:** Optimal restricted three stage design, Optimal restricted two stage design, Sequential design, Fixed sample design, Efficiency.

*2000 AMS Classification:* 62 L 05, 62 L 10, 62 L 15.

## 1. Introduction

In general data are analyzed after groups of observations are entered into a group sequential study. Group sequential designs are generally more practical and they provide much of the saving possible from sequential designs.

In most randomized clinical trials with sequential patient entry, a fixed sample size design is unjustified on ethical grounds and sequential designs are often impractical. Therefore group sequential designs are widely used in clinical trials. Group sequential designs are reviewed in detail by Jennison&Turnbull [8].

A two-stage design is the simplest form of group sequential design. Owen [9] described two-stage tests for one-sided hypothesis about a normal mean with known variance. Hald [7] derived optimal designs for this same problem using minimax and Bayes weighted average optimality criteria. Calton&McPherson [1] considered hypothesis tests for normal and binomial responses and presented optimal two-stage designs, which did not allow acceptance of the null hypothesis at the first stage. Dewith [5] extended the work of Calton&McPherson [1] for binomial responses by developing optimal designs that allowed acceptance or rejection at the first stage none of these designs used the fixed sample critical value at the final stage. Case et. al. [2] developed the optimal restricted two-stage design ($OR_2$) that have the restriction of using the fixed sample critical value at the final stage.

*Department of Statistics, Hacettepe University, Beytepe, 06532, Ankara, Turkey.
E-mail: sevil@hacettepe.edu.tr

Case et. al. [3] have suggested the optimal restricted three-stage design ($OR_3$). This design, an extension of the $OR_2$ design but the sample sizes are the same at each stage.

This study is organized as follows: In section 2, the $OR_2$ design is described. The $OR_3$ design and the efficiency of the $OR_3$ design relative to other designs are examined in section 3 and section 4, respectively.

## 2. Optimal restricted two-stage designs

In this section, we examined $OR_2$ design for response variable has an normal distribution with mean ($\theta$) and known variance ($\sigma^2$) . For testing $H_0 : \theta = \theta_0$ against $H_1 : \theta > \theta_0$, the $OR_2$ design is defined as follows;

Stage I: Accrue $n_1$ observations and calculate the test statistic,

$$Z_1 = \frac{\hat{\theta} - \theta_0}{\sigma_{\hat{\theta}}}, \tag{1}$$

where $\hat{\theta}$ is calculated from data on the first $n_1$ observations. If $Z_1 < C_1$; Accept $H_0$, if $Z_1 > C_2$; Reject $H_0$, otherwise; continue to the second stage.

Stage II: Accrue an additional $n_2$ observations. Let $n = n_1 + n_2$ and calculate,

$$Z = \frac{\hat{\theta} - \theta_0}{\sigma_{\hat{\theta}}}, \tag{2}$$

where $\hat{\theta}$ is calculated from data on all $n$ observations. If $Z < C_3$; Accept $H_0$, otherwise reject $H_0$.

Here, $Z_1$ and $Z$ have a standard normal distribution and their joint distribution is bivariate normal with zero means, unit variance, and correlation $(n_1/n)^{1/2}$.

The maximum sample size for the two-stage design is $n$ and is realized whenever a second stage is necessary. The expected sample size (ESS) of the two-stage design is given by Equation (3) below:

$$\mathrm{ESS}_2(\theta) = n\big[1 - (1-p)P_s(\theta)\big], \tag{3}$$

where $P_s(\theta)$ denote the probability that the trial will be stopped at the first stage, and $p$ is the ratio of the number of observations at the first stage to the number of total observations at the second stage, that is $p = n_1/n$. The value $\theta$ can be computed for $\theta_0$ and $\theta_1$.

There are five unknown parameters in the two-stage design, namely: $n_1$, $n_2$, $C_1$, $C_2$ and $C_3$. The critical value at the second stage, $C_3$, will be set equal to that of the fixed sample test

$$C_3 = \phi^{-1}(1-\alpha), \tag{4}$$

where $\phi(x)$ denotes the standard normal distribution function. The other four parameters of interest are chosen to satisfy the two equations:

$$\alpha = 1 - \phi(C_2) + B(C_1, C_2; C_3, \infty; p), \tag{5}$$

$$1 - \beta = 1 - \phi(C_2 - u\sqrt{p}) + B(C_1 - u\sqrt{p}, C_2 - u\sqrt{p}; C_3 - u, \infty; p), \tag{6}$$

where,

$$B(a, b, c, d, p) = \frac{1}{2\pi\sqrt{1-p}} \int_a^b \int_c^d \exp\big[-(1/2)(1-p)(y^2 - 2\sqrt{pyz} + z^2)\big]\, dy\, dz,$$

and $u = \sqrt{n}(\theta_1 - \theta_0)/\sigma$.

Now, the probability of rejecting $H_0$ at the first stage plus the probability of continuing the trial and rejecting $H_0$ at the second stage is equal to $\alpha$, when assuming $H_0$ is true. The desired power of the trial $1-\beta$ is the same probability under the alternative hypothesis. Equations (5) and (6) are solved iteratively by numerical integration of the bivariate normal distribution using a double precision function [2, 3].

The optimal parameter values which are necessary for the $OR_2$ design, are obtained using the program written by Case et. al. [2, 10].

With five parameters and only three constraints given by equations (4), (5) and (6), minimax or Bayes optimality criteria are used to determine the parameter values [2]. In this study, we have examined the Bayes criteria.

**Bayes Criterion:** Minimize a weighted average of the ESS under $H_0$ and $H_1$, that is:

$$\text{Minimize } \mathrm{ESS}_w(\theta) = (1-w)\mathrm{ESS}(\theta_0) + w\mathrm{ESS}(\theta_1) \tag{7}$$

Using a weight of $w = 0$ for this criterion gives the most efficient designs if the null hypothesis is true while a weight of $w = 1$ gives the most efficient designs if the specified alternative is true [2, 3].

The optimal design parameters $(C_1, C_2, C_3, n_1, n_2)$, the probabilities $P_s(\theta)$, and the maximum and expected sample sizes have been calculated for several values of $\alpha$ and $1-\beta$. Sometimes the choice of $p$ is determined by factors unrelated to an optimal design. For some studies it might be practical to choose equal samples $p = 0.50$, at each stage.

The optimal design parameters, $P_s(\theta)$, $n$ and $\mathrm{ESS}(\theta)$ obtained using the Bayes criteria in $p = 0.50$ are given in Table 1 for $\alpha = 0.01, 0.05$, $1-\beta = 0.80, 0.90$. In the tables, $n_f$ denotes the fixed sample size.

**Table 1. Optimal restricted two-stage one-sided designs for bayes criterion with $\alpha = 0.01, 0.05$; $1-\beta = 0.80, 0.90$ $(p = 0.50)$.**

| w | $\alpha$ | $1-\beta$ | $p$ | $C_1$ | $C_2$ | $C_3$ | $n_f^a$ | $n^a$ | $\mathrm{ESS}(\theta_0)^a$ | $\mathrm{ESS}(\theta_1)^a$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0.01 | 0.80 | 0.50 | 1.052 | 2.833 | 2.326 | 10.036 | 10.849 | 6.212 | 8.641 |
| | | 0.90 | 0.50 | 1.014 | 2.856 | 2.326 | 13.017 | 14.085 | 8.123 | 10.778 |
| | 0.05 | 0.80 | 0.50 | 0.638 | 2.150 | 1.645 | 6.183 | 6.907 | 4.303 | 5.194 |
| | | 0.90 | 0.50 | 0.595 | 2.178 | 1.645 | 8.564 | 9.558 | 6.029 | 6.886 |
| 1 | 0.01 | 0.80 | 0.50 | 1.310 | 2.690 | 2.326 | 10.036 | 11.612 | 6.343 | 8.561 |
| | | 0.90 | 0.50 | 1.253 | 2.720 | 2.326 | 13.017 | 15.009 | 8.266 | 10.687 |
| | 0.05 | 0.80 | 0.50 | 0.768 | 2.066 | 1.645 | 6.183 | 7.203 | 4.328 | 5.175 |
| | | 0.90 | 0.50 | 0.700 | 2.109 | 1.645 | 8.564 | 9.874 | 6.046 | 6.864 |

[a] Multiply each value by $(\sigma/\delta)^2$

## 3. Optimal restricted three-stage designs

In this section the $OR_3$ design will be examined. General construction of the design is as in the $OR_2$ design given in section 2. However there are six unknown parameters and the stage number is three in this design. Also, the sample sizes must be equal for each stage of the design [3].

The $OR_3$ design for normal mean testing is given as follows:

Stage I: Accrue $n_1$ observations and calculate test statistic,

$$Z_1 = \frac{\hat{\theta} - \theta_0}{\sigma_{\hat{\theta}}}, \tag{8}$$

where $\hat{\theta}$ is calculated from data on the first $n_1$ observation. If $Z_1 < C_1$; Accept $H_0$, if $Z_1 > C_2$; Reject $H_0$, otherwise; continue to the second stage.

Stage 2: Accrue an additional $n_2$ observations. Let $n = n_1 + n_2$ and calculate,

$$Z_2 = \frac{\hat{\theta} - \theta_0}{\sigma_{\hat{\theta}}}, \tag{9}$$

where $\hat{\theta}$ is calculated from data on $n$ observations. If $Z_2 < C_3$; Accept $H_0$, If $Z_2 > C_4$; Reject $H_0$, otherwise; continue to the third stage.

Stage 3: Accrue an additional $n_3$ observations. Let $n = n_1 + n_2 + n_3$ and calculate,

$$Z_3 = \frac{\hat{\theta} - \theta_0}{\sigma_{\hat{\theta}}}, \tag{10}$$

where $\hat{\theta}$ is calculated from data on all $n$ observations. If $Z_3 < C_5$; Accept $H_0$, otherwise, reject $H_0$.

There are eight unknown parameters in the $OR_3$ design, namely $n_1$, $n_2$, $n_3$, $C_1$, $C_2$, $C_3$, $C_4$ and $C_5$. The critical value at the final stage $C_5$, is equal to that of the fixed sample test. However this design is used in the case of equal sample sizes at each stage, so reducing the number of unknown parameters to six.

The joint distribution of $Z_1$, $Z_2$ and $Z_3$ is trivariate normal with zero mean vector and correlation matrix ($\Sigma$) given by

$$\Sigma = \begin{bmatrix} 1 & \rho_{12} & \rho_{13} \\ & 1 & \rho_{23} \\ \text{sym} & & 1 \end{bmatrix},$$

where $\rho_{12} = \big[n_1/(n_1+n_2)\big]^{1/2}$, $\rho_{13} = \big[n_1/(n_1+n_2+n_3)\big]^{1/2}$ and $\rho_{23} = \big[n_1+n_2/(n_1+n_2+n_3)\big]^{1/2}$.

However, as the sample size is equal for each stage, the correlation matrix will be as follows,

$$\Sigma = \begin{bmatrix} 1 & \sqrt{1/2} & \sqrt{1/3} \\ & 1 & \sqrt{2/3} \\ \text{sym} & & 1 \end{bmatrix}$$

The maximum sample size for the three stage design is $n = n_1+n_2+n_3$, and is calculated whenever all the stages are necessary. The expected sample size of the three-stage design is given by equation (11) below:

$$\text{ESS}_3(\theta) = n_1 + (1 - P_1(\theta))n_2 + (1 - P_2(\theta))n_3, \tag{11}$$

where $P_i(\theta)$ denotes the probability that the trial will be stopped at the i$th$ stage.

The six unknown parameters for a three-stage test are chosen to satisfy the two equations:

$$\alpha = 1 - \phi(C_2) + B(C_1, C_2; C_4, \infty; \rho_{12}) + T(C_1, C_2; C_3, C_4; C_5, \infty; \Sigma), \tag{12}$$

$$\begin{aligned} 1 - \beta = {} & 1 - \phi(C_2 - u\rho_{13}) + B(C_1 - u\rho_{13}, C_2 - u\rho_{13}; C_4 - u\rho_{23}, \infty; \rho_{12}) \\ & + T(C_1 - u\rho_{13}, C_2 - u\rho_{13}; C_3 - u\rho_{23}, C_4 - u\rho_{23}; C_5 - u\rho_{12}, \infty; \Sigma), \end{aligned} \tag{13}$$

where $B(a, b; c, d; \rho)$ and $u$ were as given in section 2, and

$$T(a, b; c, d; e, f, \Sigma) = \frac{1}{\sqrt{2\pi\Sigma}} \int_a^b \int_c^d \int_e^f \exp\left[-(1/2)(X^{'}\Sigma^{-1}X)\right] dx,$$

Equation 12, which is the probability of rejecting $H_0$ at the first stage plus the probability of continuing the trial and rejecting $H_0$ at the second stage plus the probability of continuing the trial and rejecting $H_0$ at the third stage is equal to $\alpha$ under the $H_0$ hypothesis. Equation 13 is the same probability under the $H_1$ hypothesis [2, 3].

Equations 12 and 13 are solved iteratively by numerical integration of the multivariate normal distribution using the subroutines of Donnely [6] and Schervish [11].

With six parameters and only two constraints, the parameter values are chosen to minimize ESS($\theta$) for $H_0$ or $H_1$ (Bayes criteria). Therefore the algorithm used to obtain the parameter values for the $OR_3$ design is almost identical in the $OR_2$ design [3].

**Table 2. Optimal design parameters for the $OR_3$ one-sided designs for $\alpha = 0.01, 0.05$; $1 - \beta = 0.80, 0.90$.**

| w | $\alpha$ | $1-\beta$ | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | $n_f^a$ | $n^a$ | ESS($\theta_0$)$^a$ | ESS($\theta_1$)$^a$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0.01 | 0.80 | 0.738 | 3.819 | 1.318 | 2.598 | 2.326 | 10.036 | 11.642 | 5.018 | 8.430 |
| | | 0.90 | 0.649 | 3.747 | 1.335 | 2.632 | 2.326 | 13.017 | 15.100 | 6.639 | 10.544 |
| | 0.05 | 0.80 | 0.342 | 2.539 | 0.877 | 1.945 | 1.645 | 6.183 | 7.543 | 3.710 | 4.946 |
| | | 0.90 | 0.234 | 2.470 | 0.879 | 2.015 | 1.645 | 8.564 | 10.362 | 5.310 | 6.423 |
| 1 | 0.01 | 0.80 | 0.816 | 2.796 | 1.724 | 2.661 | 2.326 | 10.036 | 12.646 | 5.219 | 8.029 |
| | | 0.90 | 0.535 | 2.719 | 1.907 | 2.696 | 2.326 | 13.017 | 16.662 | 7.290 | 9.763 |
| | 0.05 | 0.80 | 0.312 | 2.150 | 1.184 | 2.023 | 1.645 | 6.183 | 7.976 | 3.833 | 4.823 |
| | | 0.90 | 0.012 | 2.095 | 1.313 | 2.067 | 1.645 | 13.017 | 11.048 | 5.738 | 6.252 |

[a] Multiply each value by $(\sigma/\delta)^2$

The design parameters ($C_1$, $C_2$, $C_3$, $C_4$ and $C_5$), and the maximum and expected sample sizes obtained using the Bayes criteria are given in Table 2 for $\alpha = 0.01, 0.05$, $1 - \beta = 0.80, 0.90$.

### An Example

Suppose that an investigator is interested in conducting a clinical trial with the $OR_3$ design for comparing a test drug (T) with a placebo (P). Based on information obtained from a pilot study, data from the test drug and the placebo seem to have a common variance, i.e., $\sigma^2 = \sigma_1^2 = \sigma_2^2 = 4$ with $\mu_T = \mu_P = 1$, [4].

Suppose we wish to design this trial, using a 5% significance level for a one-sided test of the hypothesis with 90% power to distinguish between the test drug and the placebo. We assume that the measurements are normally distributed.

The required fixed sample size is

$$n_f = \frac{(8.564)(2)(4)}{1^2} \simeq 69.$$

The maximum sample sizes needed for the $OR_3$ design optimized under $H_0$, and optimized under $H_1$ are given by

$$n_{0_{\max}} = (10.362)8 = 82.89 \simeq 83 \text{ and } n_{1_{\max}} = (11.048)8 = 88.38 \simeq 88.$$

Hence, it is necessary to have

$$n_0 = 83/3 \simeq 27 \text{ and } n_1 = 88/3 \simeq 29$$

patients per group for each analysis.

## 4. Comparison with other designs and results

In this section, the $OR_3$ design will be compared with the fixed sample, sequential and $OR_2$ designs.

The efficiency of the $OR_3$ design relative to the fixed sample design is presented in Table 3 given $\alpha = 0.01, 0.05$ and $1-\beta = 0.80, 0.90$. Here, the efficiencies are computed as

$$R_1 = \frac{\text{ESS}(\theta_1)}{n_f} * 100 \text{ and } R_0 = \frac{\text{ESS}(\theta_0)}{n_f} * 100.$$

Therefore, the savings can be defined as

$$S_i = \frac{n_f - \text{ESS}(\theta_i)}{n_f}, \ i = 0, 1.$$

**Table 3. Efficiency of the $OR_3$ Design compared to the Fixed Sample Size Design.**

| | | w=0 | | w=1 | |
|---|---|---|---|---|---|
| $\alpha$ | $1-\beta$ | $R_0$ | $R_1$ | $R_0$ | $R_1$ |
| 0.01 | 0.80 | 50.0 | 84.0 | 52.0 | 80.0 |
| | 0.90 | 51.0 | 81.0 | 56.0 | 75.0 |
| 0.05 | 0.80 | 60.0 | 80.0 | 62.0 | 78.0 |
| | 0.90 | 62.0 | 75.0 | 67.0 | 73.0 |

It is seen that the $OR_3$ design provides better savings than the fixed sample design for both situations ($w = 0$ and $w = 1$). However, when $H_1$ is true, the $OR_3$ design gives much smaller savings.

The expected sample size under the $H_0$ and $H_1$ hypothesis for the sequential design of Wald are given approximately by,

$$\text{ESS}_{sprt}(\theta_0)\Delta^2 = -2\big[\alpha ln\big(\frac{1-\beta}{\alpha}\big) + (1-\alpha)\ln\big(\frac{\beta}{1-\alpha}\big)\big],$$
$$\text{ESS}_{sprt}(\theta_1)\Delta^2 = 2\big[\beta ln\big(\frac{\beta}{1-\alpha}\big) + (1-\beta)\ln\big(\frac{1-\beta}{\alpha}\big)\big],$$

where $\Delta = \dfrac{\theta_1 - \theta_0}{\sigma}$, [12, 10].

A comparison of these expected sample sizes and the three-stage expected sample sizes is shown in Table 4. Here, relative efficiency is defined as

$$S = \frac{n_f - \text{ESS}_3(\theta_i)}{n_f - \text{ESS}_{\text{SPRT}}}(\theta_i) * 100, \ i = 0, 1$$

**Table 4. Efficiency of the $OR_3$ Design compared to the Sequential Design.**

| | | w=0 | | w=1 | |
|---|---|---|---|---|---|
| $\alpha$ | $1-\beta$ | $S_0$ | $S_1$ | $S_0$ | $S_1$ |
| 0.01 | 0.80 | 71.8 | 46.1 | 69.2 | 56.0 |
| | 0.90 | 73.8 | 45.0 | 67.0 | 59.6 |
| 0.05 | 0.80 | 70.3 | 52.8 | 67.8 | 58.3 |
| | 0.90 | 71.7 | 55.3 | 62.6 | 61.2 |

From Table 4 it is clear that the $OR_3$ design provides better savings than the sequential design for both situations ($w = 0$ and $w = 1$). While the $OR_2$ design provides a %50 saving compared with the sequential design, the $OR_3$ design provides as much as 70% of the possible savings under $H_0$ [10].

Finally, Table 5 gives the efficiency of the $OR_3$ design relative to the $OR_2$ design for several $\alpha$ and $1-\beta$ values. The $OR_2$ design with equal sample sizes at each stage is used for this comparison because this restriction is used in obtaining the three-stage results.

**Table 5. Efficiency of the $OR_3$ Design compared to the $OR_2$ Design.**

| | | w=0 | | w=1 | |
|---|---|---|---|---|---|
| $\alpha$ | $1-\beta$ | $R_0$ | $R_1$ | $R_0$ | $R_1$ |
| 0.01 | 0.80 | 80.8 | 97.6 | 82.3 | 93.8 |
| | 0.90 | 81.7 | 97.8 | 88.2 | 91.4 |
| 0.05 | 0.80 | 86.2 | 95.2 | 88.6 | 93.2 |
| | 0.90 | 88.1 | 93.3 | 95.0 | 91.1 |

Here, efficiency is defined as

$$R = \frac{\mathrm{ESS}_3(\theta_i)}{\mathrm{ESS}_2(\theta_i)} * 100, \ i = 0, 1.$$

It can be seen that little is gained by the addition of a third stage for $w = 0$ and $w = 1$ when $H_1$ is true. The greatest benefits usually occur when $H_0$ is true.

Consequently, if we compare the $OR_3$ design with other designs, we can say the $OR_3$ design is preferable in terms of sample size and performance.

## References


[1] Calton, T. and McPherson, K. *Two stage plans compared with fixed-sample size and Wald SPRT plans*, J. Am. Stat. Assoc. **71**, 80–86, 1976.

[2] Case, L. D., Morgan, T. M. and Davis, C. E. *Optimal restricted two stage designs*, Cont. Clin. Trials **8**, 146–156, 1987.

[3] Case, L. D., Morgan, T. M. and Davis, C. E. *Three stage designs for monitoring clinical trials*, Comm. in Stat. Theory and Methods **23** (7), 1875–1893, 1994.

[4] Chow, S. C., Shao, J. and Wang, H. *Sample Size Calculations in Clinical Research* (Marcel Deccer, Inc., New York, 2003).

[5] DeWith, C. *Two stage plans for the testing of binomial parameters*, Cont. Clin. Trials **4**, 215–226, 1983.

[6] Donnely, T. G. *Algorithm 462-Bivariate normal distribution [515]*, Communications of the association of computing Machines **16**, 638, 1973.
[7] Hald, A. *Optimum double sampling tests of given strength. The normal distribution*, J. Am. Stat. Assoc. **70**, 451–456, 1975.
[8] Jennison, C. and Turnbull, B. W. *Group Sequential Methods with Applications to Clinical Trials* (Chapman&Hall, 2000).
[9] Owen, D. B. *A double sample test procedure*, Ann. Math. Stat **24**, 449–457, 1953.
[10] Peker, K. Í. and Bacanli, S. *Optimal restricted two-stage design*, Anadolu University Journal of Science and Technology **1**, 95–103, 2000.
[11] Schervish, M. J. *Corrections: Algorithm AS-195: multivariate normal probabilities with error bound*, Applied Statistics **34**, 103–104, 1985.
[12] Wald, A. *Sequential Analysis* (Dover Pub. Inc., New York, 1947).