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**Progress in Biological Sciences**
Vol. 6, Number 1, Winter / Spring 2016/1-9

# A mixed Bayesian/ Frequentist approach in sample size determination problem for clinical trials

**Maryam Bideli[1], John Gittins[2], Hamid Pezeshk[1,3]***

[1] *School of Mathematics, Statistics and Computer Science, University of Tehran.*

[2] *Department of Statistics, University of Oxford, UK*

[3] *School of Biological Sciences, Institute for Research in Fundamental Sciences, (IPM), Tehran, Iran*

Received: September 29, 2015; Accepted: January 1, 2016

## ABSTRACT

In this paper we introduce a stochastic optimization method based on a mixed Bayesian/ frequentist approach to a sample size determination problem in a clinical trial. The data are assumed to come from a normal distribution for which both the mean and the variance are unknown. In contrast to the usual Bayesian decision theoretic methodology, which assumes a single decision maker, our method recognizes the existence of three decision makers, namely: the company conducting the trial, which decides on its size; the regulator, whose approval is necessary for the drug to be licensed for sale; and the public at large, who determine ultimate usage. Moreover, w model the subsequent usage by plausible assumptions for actual behaviour. A Markov Chain Monte Carlo is applied to find the maximum expected utility of conducting the trial.

**Keywords:** Sample Size Determination; Mixed Bayesian/ Frequentist Approach; Normal Distribution; Regulatory Authority; The Markov Chain Monte Carlo (MCMC) Method

## Introduction

Sample size determination problem is an important task in the planning of trials. The problem may be formulated formally in statistical terms. The most frequently used methods are based on the required size, and power of the trial for a specified treatment effect (1, 2, 3). Several authors have recognized the value of using prior distributions rather than point estimates in sample size calculations. In one case, the author gives a comprehensive review of different techniques for sample size determination using both frequentist and Bayesian approaches (4).

The Bayesian approach can be divided into two major types; the inferential Bayesian and the fully Bayesian or decision theoretic approach. Also a simplified version of the problem of sample size determination for a clinical trial for which the solution was expressed in algebraic terms (5). In addition the fully Bayesian model has been extended to more realistic cases (6-11). In this paper we apply a stochastic optimization approach to find the optimum size of a clinical trial. The work extends the former

* **Corresponding author:** pezeshk@khayam.ut.ac.ir

research (7) by considering a regulatory authority in the model. Alternative formulations of the regulator's requirements are considered, expressed either in frequentist or in Bayesian terms. Optimisation is carried out using the Markov Chain Monte Carlo method.

In next section we state the sample size problem and introduce the notation. The objective function, which is the expected net benefit of conducting the trial, is also introduced in next section. In "Results and Discussion" the regulatory authority as the third decision maker is introduced. We present two algorithms for the sample size determination problem for both the cases with a frequentist authority and with a Bayesian authority.

## Material and Methods

Suppose that for i=1, 2, ..., n, the $X_i$ 's are the clinical outcomes on some appropriate scale for users (patients) using the new treatment and the $Y_i$ 's are those for users (patients) using another treatment. Assume that $X_i \sim N(\mu+\delta, \sigma^2)$ and $Y_i \sim N(\mu, \sigma^2)$. Consider $\bar{Z}_n = \bar{X}_n - \bar{Y}_n$. Therefore $\bar{Z}_n \sim N(\delta, \frac{2\sigma^2}{n})$. The joint likelihood function for $S_x^2, S_y^2$ and $\bar{Z}_n$ is proportional to:

$$(\sigma^2)^{(-(2n-1)/2)} \exp\left(-\frac{1}{2\sigma^2}(s_x^2 + s_y^2 + \frac{n}{2}(\bar{z}_n - \delta)^2)\right)$$

For every user who goes on to use the new treatment as a result of the trial there is a benefit. The objective (or expected net benefit) function r(n), for a trial with n users, is the total expected benefit from the resulting change in the number of users of the new treatment minus the cost of the trial. The benefit per user may correspond to a public health benefit depending on δ or might be a commercial benefit more appropriate for the company conducting the trial. The question is, how many observations may maximize the total expected benefit?

Let the cost of carrying out a trial with n observations be cn if n>0, and 0 if n=0.

Following (13), let us assume that the prior density functions for δ and $\sigma^2$ are of the form shown below,for $\sigma^2$ the prior distribution is

$$\pi(\sigma^2) = \left(\frac{a}{2}\right)^{\frac{g}{2}} \frac{1}{\Gamma(g/2)} (\sigma^2)^{-\frac{g+2}{2}} \exp\left(-\frac{a}{2\sigma^2}\right) \qquad (1)$$

This is a kind of inverse chi-squared distribution, because the distribution of $a/\sigma^2$ is chi-squared with g degrees of freedom. Also

$$\pi\left(\delta|\sigma^2\right) = \frac{1}{\sigma\omega^{1/2}\sqrt{2\pi}}$$
$$\exp\left(-(1/2)\frac{(\delta-\mu)^2}{\sigma^2\omega}\right) \sim N\left(\mu, \sigma^2\omega\right) \qquad (2)$$

The mean and variance of the prior distribution for δ are μ and ωa/(g-2)= τ², respectively. The marginal posterior density function of δ can be obtained by integrating the joint posterior density over σ². Applying Bayes' theorem the posterior densities turn out to be a non central t-distribution

$$\pi^n(\delta|z) = (\omega' a')^{-(1/2)}$$
$$\frac{1}{B(1/2, g'/2)}\{1+(\delta-\mu)^2/\omega' a'\}^{-(g+1)/2} \qquad (3)$$

and

$$\pi^n(\sigma^2|z) = \frac{\left(\frac{a'}{2}\right)^{g'/2}}{\Gamma\left(\frac{g'}{2}\right)}\left(\sigma^2\right)^{-\frac{g'+2}{2}}$$
$$\exp\left(-\frac{a'}{2\sigma^2}\right) \sim \Gamma\left(\frac{g'}{2}, \frac{a'}{2}\right), \qquad (4)$$

where

$$\omega' = \frac{2\omega}{2+n\omega}, \qquad \mu' = \frac{2\mu + n\omega\overline{z_n}}{2+n\omega}$$

$$g' = g + 2n - 1, \qquad a' = a + s^2 + \frac{n\left(\overline{z_n} - \mu\right)^2}{2+n\omega}$$

Therefore $(\delta - \mu')/(\omega' a')^{-1/2}$ has a Student t-distribution with $g'$ degrees of freedom. So the posterior mean and variance of δ (provided $g' > 2$) are

$$\mu'(\overline{z_n}) = \frac{2\mu + n\omega\overline{z_n}}{2+n\omega}, \qquad \tau^2\left(\overline{z_n}, s^2\right) = \frac{\omega' a'}{g'-2}$$

Let us suppose that m the number of subsequent users, depends on the mean $\mu'$ and the standard deviation $\tau'$ of the posterior distribution for δ as shown by Fig. 1.

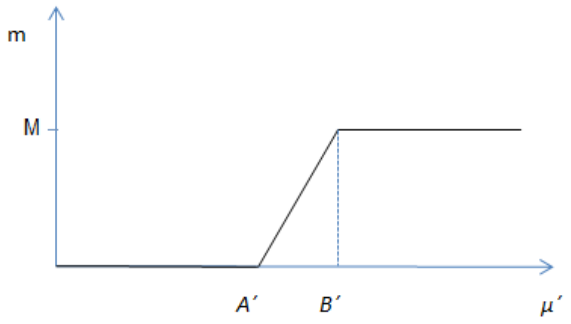


**Figure 1.** $A' = A + 1.5\tau'\left(\bar{z}, s^2\right)$, $B' = B + 1.5\tau'\left(\bar{z}, s^2\right)$

The parameter $M$ is the expected total number of users, given a substantial improvement in performance. $A$ and $B$ are two parameters which must be estimated. Their values depend on the difference between the expected cost of the new treatment and that of the current service.

This function corresponds to assuming that each individual has a personal threshold difference between A and B, and is prepared to switch to the new treatment provided that the apparent difference between the two treatments exceeds this threshold by at least 1.5 standard deviations of the posterior distribution for the difference.

Using some algebra, we see that

$$f\left(\overline{z_n}, s^2\right) = \frac{\Gamma\left(\frac{g+n}{2}\right)}{\Gamma\left(\frac{g}{2}\right)\Gamma\left(\frac{1}{2}\right)}\left(\frac{a^{\frac{g}{2}}}{\Gamma\left(\frac{n-1}{2}\right)}\right)\left(\frac{n}{2+n\omega}\right)^{\frac{1}{2}}$$

$$* \left(s^2\right)^{\frac{n-1}{2}-1}\left(a + s^2 + \frac{n\left(\overline{z_n} - \mu\right)^2}{2+n\omega}\right)^{-\frac{g+n}{2}} \qquad (5)$$

The number of subsequent users of the new treatment can be written in algebra form as:

$$m = \begin{cases} 0 & \mu' < A' \\ \dfrac{M}{B' - A'}(\mu' - A') & A' < \mu' < B' \\ M & B' < \mu' \end{cases}$$

Appropriate values for A and B were found by some authors (8), while other authors apply a logistics type function to represent the number of subsequent users of the new treatment (9).

We shall now proceed to write down the objective function for two types of benefit function. We shall call these the public health and the commercial benefit function, respectively. Numerical examples follow.

*The public health benefit function*

The benefit per user of taking the new treatment is assumed to be $b_1\delta$ in which $b_1$ is a constant. The objective (i. e. expected net benefit) function, which is proposed, consisting of total benefit from the resulting change in the number of users taking the new treatment minus the cost, can be written as

$$r(n) = \iint_{A' \le \mu' \le B'} \frac{Mb - 1}{B - A} \left\{\mu' - A - 1.5\sqrt{\frac{\omega' a'}{g' - 2}}\right\} \mu' f\left(\overline{z_n}, s^2\right) d\overline{z_n}\, ds^2$$

$$+ Mb_1 \iint_{\mu' \ge B'} \mu' f\left(\overline{z_n}, s^2\right) d\overline{z_n}\, ds^2 - cn, \qquad (7)$$

Note that $a'$ depends on $\overline{z_n}$ and $s^2$. Solving for $\overline{z_n}$ in the first equation produces a quadratic equation with two real roots, the larger of which may be shown to be $H_1$. $H_2$ may be found in similar fashion. We have used the MCMC method to find the maximum of *r(n)* and consequently the optimum sample size in expression (8).

*The commercial benefit function*

If we assume that for each user taking the new treatment there is a benefit $b_2$ independent of δ, then

(8)

$$r(n) = \int_{\bar{z}} \int_{s^2} b_2 m f\left(\bar{z}, s^2\right) ds^2 d\bar{z} - cn = b_2 E[m] - cn,$$

By proceeding as in section (2.1) it can be shown that the objective function is

$$r(n) = \iint_{A' \le \mu' \le B'} \frac{Mb_2}{B - A} \left\{\mu' - A - 1.5\sqrt{\frac{\omega' a'}{g' - 2}}\right\} f\left(\bar{z}_n, s^2\right) d\bar{z}_n ds^2$$

$$+ Mb_2 \iint_{\mu' \ge B'} f\left(\bar{z}_n, s^2\right) d\bar{z}_n ds^2 - cn. \qquad (9)$$

See (3) for more details.

In this paper, we use the symbols $H_1$ and $H_2$ for the bounds of the integrals in the objective function appeared in both the commercial and public health cases.

The MCMC method was used to find the maximum of the above objective function for the case with a logistic utility function representing the number of subsequent users of the new treatment (6). Here we use the MCMC method for maximizing the expected net benefit function for the case where there exists a regulatory authority. We generate two large samples from $s^2$and $\bar{z}$ to approximate $E[m\mu']$.

*The regulatory authority as the third decision maker*

As discussed above we include two decision makers in our model, the company conducting the trial and the users or their medical advisors who decide on whether to use it. In this section we take the regulatory authority as the third decision maker into account. Both the frequentist and Bayesian regulatory authority will be considered.

*Licensing the new treatment; a frequentist regulator*

In this case, we assume that the regulator performs a test δ=0 against δ>0, the critical region for rejecting the null assumption in favor of the alternative is of the form

$$\overline{z_n} > z_\alpha \sqrt{\frac{2\sigma^2}{n}}$$

We show this condition by $H_r$. There are three cases to be considered.

Case 1) :

$$z_\alpha \sqrt{2\sigma^2}/n \leq H_1 < H_2$$

In this case the regulator's decision does not have an effect on the number of subsequent users of the new treatment.

The objective function for this case is similar to the case with no regulator (Fig. 2-2).

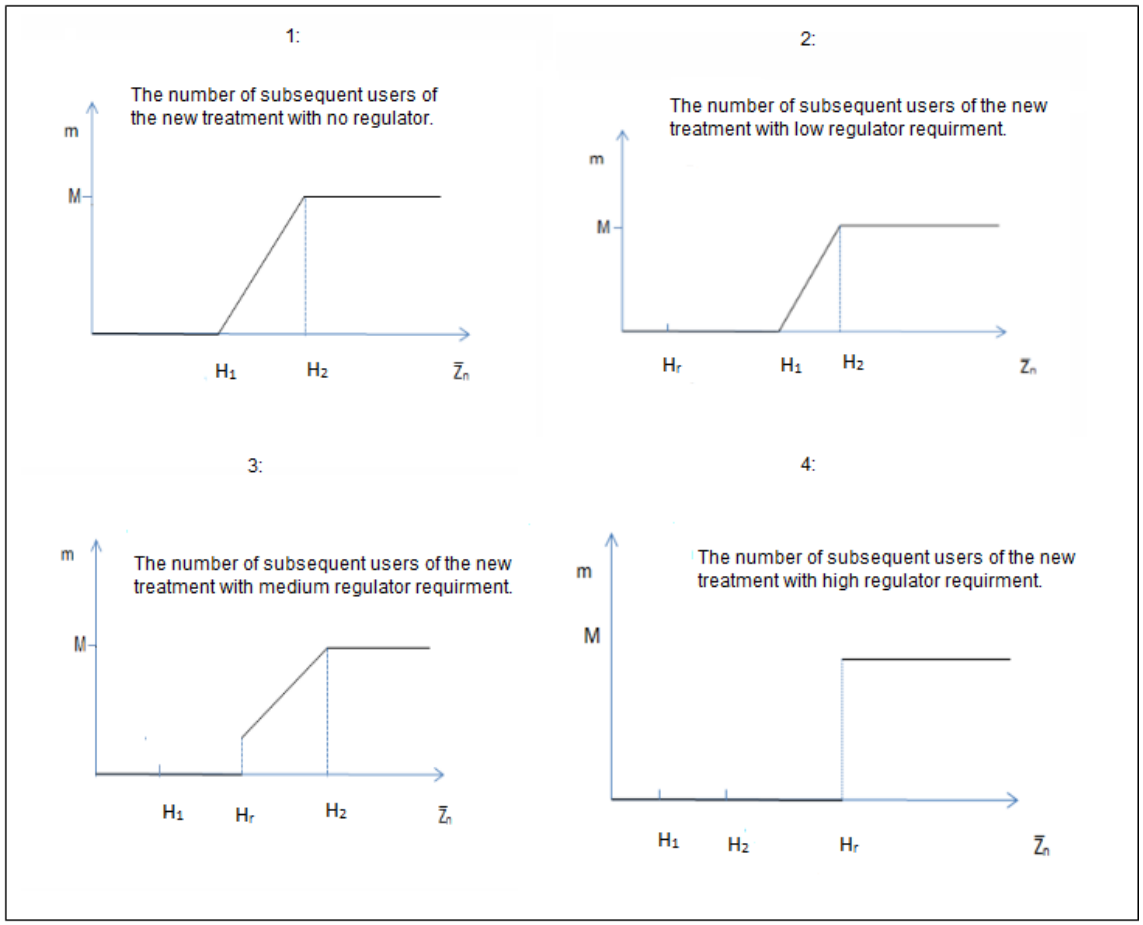


**Figure 2. The number of subsequent users when a regulator authority appears. It should be noted that $H_r$ (denoting the regulator condition) can be written from a frequentist or a Bayesian perspective.**

Case 2) :

$$H_1 \le z_\alpha \sqrt{2\sigma^2}/n < H_2$$

In this case it is assumed that the minimum amount of improvement in performance required by the regulator to grant a license is bigger than the one assumed by the company conducting the trial (see Figure 2-3).

Case 3) :

$$H_1 < H_2 < z_\alpha \sqrt{2\sigma^2}/n$$

As shown by Fig. 2-4, if the condition holds, all users will switch to the new treatment.

**Table 1. The optimal sample size for various parameter values**

| Public Health Function | | | | | | |
|---|---|---|---|---|---|---|
| | | | Without Regulator | | With Frequentist Regulator | |
| $\mu$ | c | α | r(n) | n | r(n) | n |
| 0 | 6000 | 0.05 | 0 | 0 | 0 | 0 |
| 1 | 6000 | 0.05 | 509750.3 | 69 | 509750.3 | 69 |
| 2 | 6000 | 0.05 | 4549842 | 137 | 4081590 | 122 |
| 3 | 6000 | 0.05 | 11801206 | 122 | 6609274 | 192 |
| 4 | 6000 | 0.05 | 18934348 | 48 | 8575274 | 192 |
| 2 | 2000 | 0.1 | 4542842 | 137 | 4183597 | 122 |
| 2 | 6000 | 0.05 | 5238123 | 196 | 4764177 | 196 |

*Licensing the new treatment; a Bayesian regulator*

Let us suppose that the regulator uses a prior density for δ which is $N(\mu_r, \tau_r^2)$. The subscript *r* will indicate the corresponding parameters for the regulator's prior distribution. Also suppose that the new treatment will be approved if and only if $\mu_r' < L + 1.5\tau_r'$ in which *L* is the minimum amount of improvement required by the regulatory authority. This inequality may be written as $\overline{z_n} < H_r$. Using this notation once again there are three cases to be considered; 1) $H_r \le H_1 \le H_2$ , 2) $H_1 \le H_r \le H_2$ and 3) $H_1 \le H_2 \le H_r$.

Now we are in a position to introduce our two algorithms based on MCMC methods to find the optimum sample size. We rewrite this condition in terms of $\overline{z_n}$ and show it by $H_r$. As in the case of frequentist regulator, obviously there are three cases to be considered.

*Two algorithms for sample size determination*

In this section we present the required algorithms to find the optimum sample size by maximizing the expected net benefit resulting from the trial.

1. Set *n=2*.

2. Generate samples $\sigma_{(j)}^2$ for *j=1, 2, ..., N* from equation (1).

3. Generate a sequence of $\delta_{(j)}$ for *j=1, 2, ..., N* from $N(\mu, \sigma^2\omega)$ using the values of $\sigma_{(j)}^2$ obtained from the previous step.

4. Using the fact that $s_{(n)}^2/\sigma^2$ has a chi-squared distribution with *2n-2* degrees of freedom

generate *n* vectors of dimension *N*, $(s_{(n,1)}^2, s_{(n,2)}^2, \dots, s_{(n,N)}^2)$.

5. Generate values of $(\overline{z_{(n,1)}}, \overline{z_{(n,2)}}, \dots, \overline{z_{(n,N)}})$ of the $\overline{z_{(n)}}$ by sampling from $N(\delta, \frac{2\sigma^2}{n})$ with values $(\delta_{(1)}, \delta_{(2)}, \dots, \delta_{(N)})$ for $\delta$ and $(\sigma_{(1)}^2, \sigma_{(2)}^2, \dots, \sigma_{(N)}^2)$ for $\sigma^2$.

6.

6-1. Calculate value of $h_n = z_\alpha\sqrt{(2\sigma^2/n)}$, if the condition holds then calculation is continued, otherwise it will stop.

6-2. In the case of a Bayesian regulator, repeat steps 2 to 5.

7.

7-1. If at any stage $h_n < \overline{z_{(n)}}$ , then $\mu'$ and $a'$ will both be calculated using $\overline{z_{(n)}}$. Otherwise,

they are set to zero.

7-2. If $\mu' \geq L' = L + 1.5\tau'_r$, then continue the computation.

8. Calculate values of $l_{(n,j)}, j = 1, 2, \ldots, N$, in order to calculate the total benefit for the public health and the commercial benefit functions using the following formulas, respectively:

$$l_{(n,j)} = m\left(\overline{z_{(n,j)}}, s^2_{(n,1)}\right)\mu'\left(\overline{z_{(n,j)}}\right)$$

$$l_{(n,j)} = m\left(\overline{z_{(n,j)}}, s^2_{(n,1)}\right)$$

The expected net benefit is calculated as follows:

$$r(n) \simeq b\frac{\sum_{j=1}^{N} l_{(n,j)}}{N} - cn$$

9. Set *n=n+1* and repeat steps 2-8.

10. Obtain the optimal sample size with maximizing the expected net benefit *r (n).*

It should be noted here that another parameter of interestis $R(n) = \frac{r(n)}{Mb}$ which is a sort of scaled benefit.

## Results and discussion

In this section we present the results of performing MCMC to find the optimal sample size for some trials. Several programs have been written in R to maximize the expected net benefit functions. Different parameter values have been examined to discuss the sensitivity of the results to the parameter values.

The sensitivity analysis is considered for both the cases with the frequentist regulator and the Bayesian regulatory authority.

*The Public Health Utility Function*

Here we assume that the regulator uses a frequentist approach for assessing the difference between the performances of two treatments. The results are shown in Table 1 and Fig3.

If the variance increases then the sample size increases. The optimal sample size decreases with the increase in the cost of trial. The optimal sample size is also affected by the significance level.

In other case we assume that the regulator uses a Bayesian approach. The minimum amount of improvement in the condition or *L*, is an important factor in determining the required sample. According to Table 3, we see that when *L* is increased then the optimal sample size is decreased. However, sample size decreases with the increase in cost.

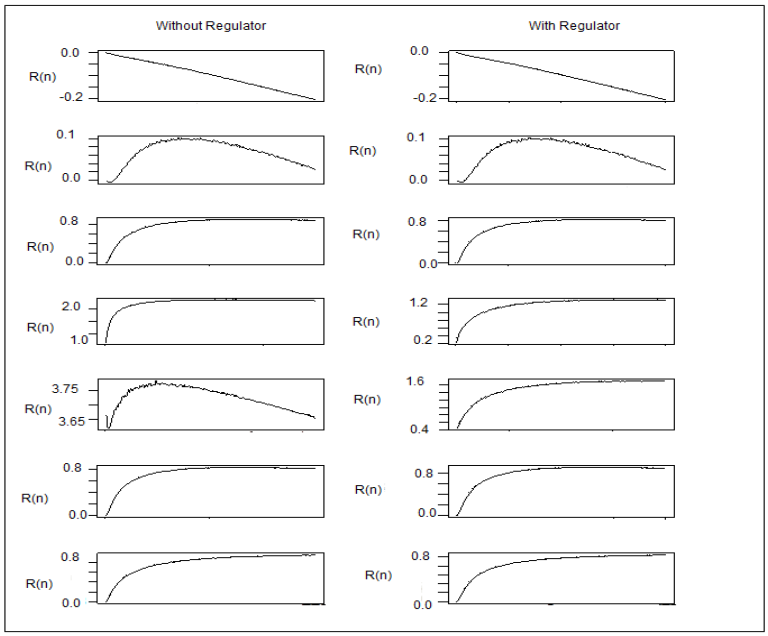


**Figure 3. The impact of changes in the cost, prior variance and the significance level of statistical test on the sample size and the net benefit function for public health utility function (curves from top to bottom correspond to the rows of the Table 1).**

**Table 2. The optimal sample size for various parameter values**

| Commercial Benefit Function | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Without Regulator | | | With Frequentist Regulator | | |
| $\mu$ | c | $\alpha$ | r(n) | R(n) | n | r(n) | R(n) | n |
| 0 | 6000 | 0.05 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 6000 | 0.05 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 6000 | 0.05 | 1153243 | 0.2306485 | 63 | 960943.5 | 0.1921887 | 63 |
| 3 | 6000 | 0.05 | 3107154 | 0.6214308 | 60 | 1241600 | **0.24832** | 63 |
| 4 | 6000 | 0.05 | 4516602 | 0.9033205 | 1 | 1241600 | 0.24832 | 63 |
| 2 | 6000 | 0.1 | 1153243 | 0.2306485 | 63 | 1014950 | **0.20299** | 63 |
| 2 | 2000 | 0.05 | 1548795 | 0.309759 | 156 | 1327323 | 0.2654647 | 137 |

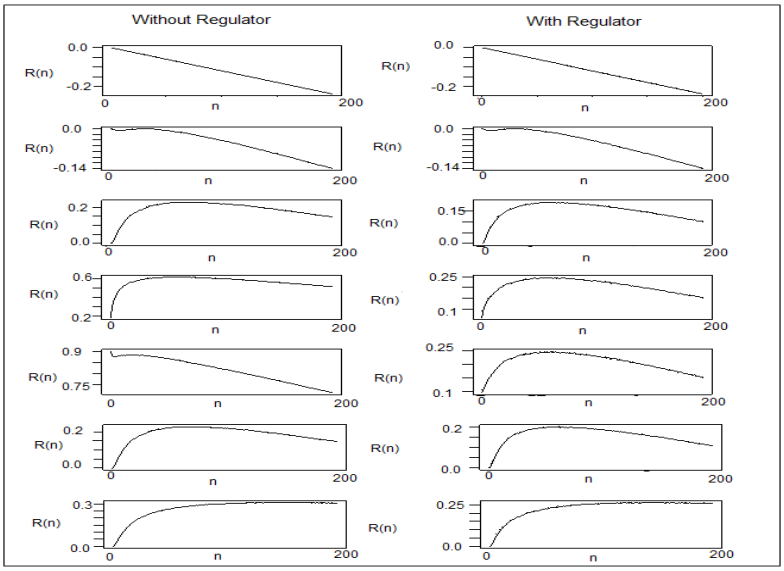


**Figure 4. The impact of changes in the cost, prior variance and the significance level of statistical test on the sample size and the net benefit function for commercial utility function (curves from top to bottom correspond to the rows of the Table 2 ).**

**Table 3. The optimal sample size for various parameter values**

| Public Health Function | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Without Regulator | | | With Bayesian Regulator | | |
| $\mu$ | c | a | r(n) | R(n) | n | r(n) | R(n) | n |
| 0 | 6000 | 120 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 6000 | 120 | 510611.5 | 0.1021223 | 86 | 0 | 0 | 0 |
| 2 | 6000 | 120 | 4549312 | 0.9098625 | 122 | 0 | 0 | 0 |
| 3 | 6000 | 120 | 11815380 | 2.363076 | 122 | 101421 | 0.02028421 | 25 |
| 4 | 6000 | 120 | 18906566 | 3.781313 | 60 | 222205.8 | 0.04444116 | 22 |
| 2 | 2000 | 120 | 5238113 | 1.047623 | 199 | 42296.5 | 0.008459299 | 34 |
| 2 | 6000 | 20 | 3674404 | 0.7348808 | 107 | 0 | 0 | 0 |

*The commercial utility function*

In this section the problem of sample size determination for the case with a commercial utility function is considered. When a frequentist regulator exists the optimal sample size is affected by the cost of the trial and the size of the statistical test.

With a Bayesian regulator, if we increase the prior variances of both the regulator and company, the optimal sample size is increased. Clearly any increase in cost will result in a decrease in sample size and consequently in the expected net benefit function.

It should be noted here that for all the cases discussed in Tables 1, 2, 3 and 4, the following parameter values are assumed. The variations of objective function for various parameter values are shown in Figs. 3, 4, 5, and 6.

$$b = 2.5 \times 10^4, g = 32, \omega_r = 1, g_r = 5, \mu_r = 0, A = 1.5,$$

$$B = 2.5, \omega = 0.25, Mb = 5 \times 10^6$$

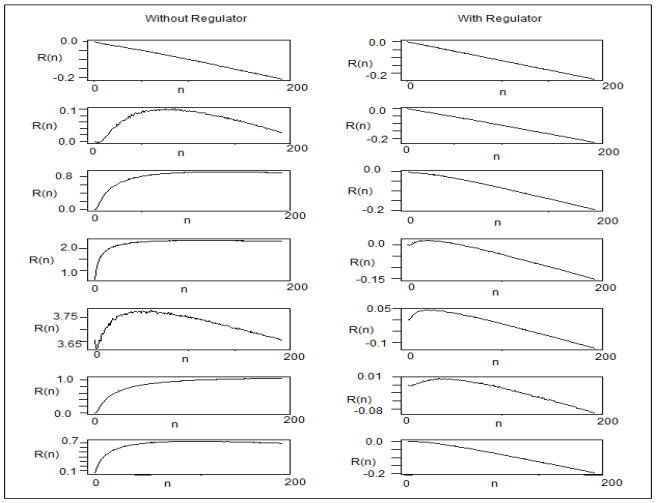


**Figure 5. The impact of changes in the cost, prior variance and the significance level of statistical test on the sample size and the net benefit function for public health utility function (curves from top to bottom correspond to the rows of the Table 3).**

**Table 4. The optimal sample size for various parameter values**

| Commercial Benefit Function | | | | | | |
|---|---|---|---|---|---|---|
| | | | Without Regulator | | With Bayesian Regulator | |
| $\mu$ | c | a | r(n) | n | r(n) | n |
| 0 | 6000 | 120 | 0 | 0 | 0 | 0 |
| 1 | 6000 | 120 | 1153243 | 63 | 0 | 0 |
| 2 | 6000 | 120 | 1146125 | 76 | 0 | 0 |
| 3 | 6000 | 120 | 3114055 | 60 | 81327.27 | 25 |
| 4 | 6000 | 120 | 4508831 | 1 | 193018.8 | 27 |
| 2 | 2000 | 120 | 1549733 | 166 | 37133.15 | 34 |
| 2 | 6000 | 20 | 1321036 | 60 | 0 | 0 |

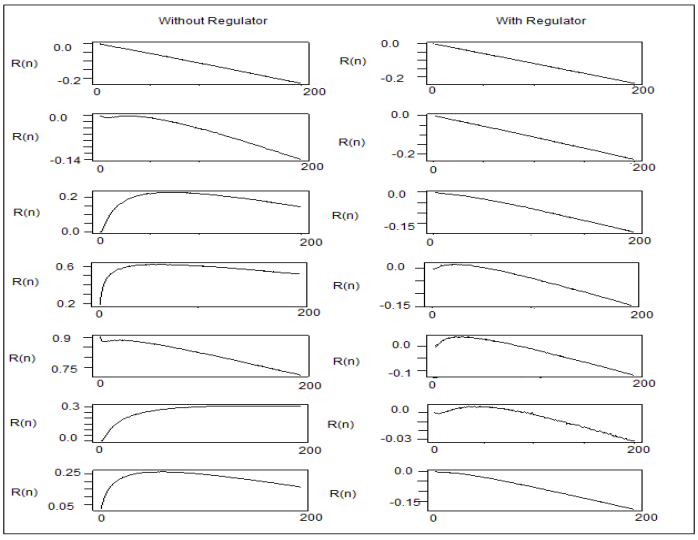


**Figure 6. The impact of changes in the cost, prior variance and the significance level of statistical test on the sample size and the net benefit function for commercial utility function (curves from top to bottom correspond to the rows of the Table 4).**

## Conclusions

The problem of sample size determination under specific conditions have been discussed by several authors (6, 10, 14). In this paper, their approach is extended to more general and realistic conditions. Data are assumed to come from a normal distribution with unknown mean and unknown variance. We also assume there is a regulator where his decision on whether to grant a license to the new treatment will affect the size of the trial and consequently on the benefit resulting from the trial. Both the frequentist and Bayesian regulatory authorities are considered. Using the Markov chain Monte Carlo methods, several computer programs are written in R to calculate the optimal sample sizes, for two utility functions named, the public health and commercial. The cods are available from authors.

## Acknowledgements

The authors would like to thank two anonymous referees for helpful comments. Maryam Bideli and Hamid Pezeshk are grateful to College of Science, University of Tehran. The financial support of School of Biology at Institute for Studies in Fundamental Sciences is gratefully acknowledged.

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