

How Many Subjects? – A Bayesian Approach to the Design of a Clinical Trial

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Abstract

An inferential Bayesian framework for sample size determination for a clinical trial is presented. It is assumed that the data are from a normal distribution for which the variance is known. We shall apply a Bayesian argument to show how we may use the prior information on the two treatment effects to decide how many patients are needed in each of these two groups.

Keywords: *Clinical trials; Sample size determination; Inferential Bayesian approach; Number of patients in each of the two treatment groups.*

1 Introduction

The problem of sample size determination is a well known problem both in quality control, and in clinical trials. In the frequentist approach sample sizes are usually determined either from power and size control rules or from an absolute error criterion (see, for example Adcock (1997)). The Bayesian approach to the sample size question is divided into two sets of procedures; fully Bayesian or decision theoretic, and inferential Bayesian. In the decision theoretic approach the sample size is determined by balanceing expected costs and benefits, using a Bayesian prior distribution for the unknown parameters. The inferential approach deals with the problem by applying precision conditions on the parameters of the posterior distribution.

The first paper on the fully Bayesian approach was by Grundy *et al.*

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(1956); the methodology was set out in detail by Raiffa and Schlaifer (1961), and has been described by Lindley (1997). A major problem in following this approach is that the ultimate decision on whether or not to use the new treatment is taken by a large number of patients and their advisers, and does not depend on the outcome of the trial in any clear-cut way. To find a utility function which would make the Raiffa and Schlaifer paradigm of a single rational decision maker convincing is not easy, and its use is not common.

Stallard (1998) applies a fully Bayesian approach to the question of the size of a clinical trial in phase II. Pezeshk and Gittins (1999) and Gittins and Pezeshk (2000a) and (2000b) return to the decision theoretic analysis of Raiffa and Schlaifer, with the modification that instead of a utility maximising terminal decision a plausible model is assumed for the way patients and their medical advisers respond to the evidence from a trial. Inferential Bayesian methods without utility functions are reviewed by Adcock (1997).

As pointed out by Pham-Gia and Turkkan (1992), in contrast to the classical approach, in the Bayesian context sample size question are less frequently discussed. There are some reasons for this. First, it is sometimes argued that a Bayesian statistician is interested more in a sequential procedure, using the posterior distribution at one step as the prior for the following step, until a conclusion is reached. So it seems that there is no need for a fixed sample size. In real life it is not always possible to use a sequential approach, and therefore it is important to find a suitable sample size prior to sampling. Secondly, precision conditions are not as widely used as in classical statistics, mainly because of computational problems. For example, the computation of exact credible intervals (or posterior confidence intervals) using the highest posterior density (HPD) region may require the use of special tables such as those constructed by Isaacs *et al.* (1974) or special software. The associated question of the sample size required so that these intervals are shorter than a given quantity then becomes a complicated iterative process.

A number of researchers have considered inferential Bayesian approaches to the sample size determination problem. For the mean of a normal distribution, Adcock (1988) developed closed formulae for both the known and unknown variance cases by averaging the

coverage of fixed length posterior credible sets over the predictive distribution of the data. Joseph and Belisle (1997) used similar techniques to derive closed form formulae for the case of average lengths of fixed coverage posterior credible sets, as well as worst case criteria.

Bayesian sample size determination for estimating the success probability in binomial sampling has received considerable attention (see, for example, Adcock (1992), (1995), Pham-Gia and Turkkan (1992), Joseph *et al.* (1995)).

The case of the difference between two binomial parameters has been considered by Joseph *et al.* (1997).

In this paper we apply the inferential Bayesian approach to the size of a clinical trial for which there is a control group. The data are assumed to come from a normal distribution, $N(\theta, \sigma^2)$, with unknown parameter, θ (this might be the average therapeutic effect of a new treatment), and known variance σ^2 . A normal prior distribution is assumed for θ .

2 Numbers of Patients in Each of the Two Treatments

We shall apply a Bayesian argument to show how we may use the prior information on the two treatment effects to decide how many patients are needed in each of the two treatment groups.

Suppose that θ_p and θ_t are, respectively, the unknown responses for patients using placebo (or existing treatment) and for those using the new treatment (or another treatment). To formulate our prior knowledge on the two treatment effects let us assume $\theta_p \sim N(\mu_p, \tau_p^2)$, i.e. θ_p has a normal prior with parameter μ_p and τ_p^2 , similarly let us assume $\theta_t \sim N(\mu_t, \tau_t^2)$.

The parameter of interest is the difference between the two treatment effects, $\delta = \theta_t - \theta_p$. The question is how we may determine the number of patients in each of these two groups.

The prior density for δ is

$$N(\mu_t - \mu_p, \tau_t^2 + \tau_p^2).$$

Let X_1, X_2, \dots, X_{n_t} and Y_1, Y_2, \dots, Y_{n_p} be, respectively, the outcomes for patients using the new treatment and for those using placebo, and let $X_i \sim N(\theta_t, \sigma^2)$ and $Y_j \sim N(\theta_p, \sigma^2)$. If \bar{x}_t and \bar{y}_p are the sample means then the posterior distribution of δ is

$$N\left(\frac{\mu_t \tau_t^{-2} + \bar{x}_t n_t \sigma^{-2}}{\tau_t^{-2} + n_t \sigma^{-2}} - \frac{\mu_p \tau_p^{-2} + \bar{y}_p n_p \sigma^{-2}}{\tau_p^{-2} + n_p \sigma^{-2}}, (\tau_t^{-2} + n_t \sigma^{-2})^{-1} + (\tau_p^{-2} + n_p \sigma^{-2})^{-1}\right). \quad (1)$$

One possible answer to the above question is to find n_t and n_p so as to minimize the posterior variance of the parameter of interest, δ . Formally the problem is to find n_t and n_p so as to minimize

$$f(n_t, n_p) = (\tau_t^{-2} + n_t \sigma^{-2})^{-1} + (\tau_p^{-2} + n_p \sigma^{-2})^{-1},$$

subject to the condition

$$g(n_t, n_p) = n_t + n_p - n = 0. \quad (2)$$

We may use the Lagrange multiplier technique to find the stationary points of $f(n_t, n_p)$. This leads to the following system of equations

$$\begin{cases} \frac{\partial f}{\partial n_t} + \lambda \frac{\partial g}{\partial n_t} = 0 \\ \frac{\partial f}{\partial n_p} + \lambda \frac{\partial g}{\partial n_p} = 0 \\ n_t + n_p - n = 0, \end{cases}$$

or equivalently

$$\begin{cases} -(\tau_t^{-2} + n_t \sigma^{-2})^{-2} \sigma^{-2} + \lambda = 0 \\ -(\tau_p^{-2} + n_p \sigma^{-2})^{-2} \sigma^{-2} + \lambda = 0 \\ n_t + n_p - n = 0 \end{cases} \quad (3)$$

Solving for the numbers of patients in the treatment group, n_t , and

in the control (placebo) group, n_p , using the first two equations in (3), and then substituting into the third one gives

$$\lambda^{-1/2} = \frac{n + (\tau_t^{-2} + \tau_p^{-2})\sigma^2}{2\sigma}$$

So:

$$n_t = (\tau_p^{-2} - \tau_t^{-2})\frac{\sigma^2}{2} + \frac{n}{2} \quad n_p = (\tau_t^{-2} - \tau_p^{-2})\frac{\sigma^2}{2} + \frac{n}{2} \quad (4)$$

or finally

$$n_t = \max\left\{0, (\tau_p^{-2} - \tau_t^{-2})\frac{\sigma^2}{2} + \frac{n}{2}\right\},$$

$$n_p = \max\left\{0, (\tau_t^{-2} - \tau_p^{-2})\frac{\sigma^2}{2} + \frac{n}{2}\right\}.$$

Thus n_t and n_p should be chosen so as to make the posterior variances for θ_t and θ_p as nearly equal as possible.

3 Discussion

If the prior information on the placebo and the new treatment are the same (ie $\tau_p^2 = \tau_t^2$) then $n_t = n_p = n/2$. This means a sample of size $n/2$ should be taken from each of the two groups.

If the prior information on the placebo is more than for the new treatment (i.e. $\tau_p^2 < \tau_t^2$) then (4) implies $n_p < n/2 < n_t$. This means that we have to make the treated group larger than the control group. If the prior information on the placebo is less than for the new treatment (ie $\tau_p^2 > \tau_t^2$) then (4) implies $n_t < n/2 < n_p$. So we need to make the control group larger than the treated group.

For instance, suppose that we would like to decide how to divide 100 patients into two groups in a clinical trial. Suppose that our prior knowledge on the new treatment implies a normal prior with the mean 2 and the variance 1 and the prior distribution for the placebo or

control treatment is assumed to be a normal distribution with the mean zero and the variance 4. Let us assume that $\sigma^2 = 48$ and the data are n_p placebo observations drawn from $N(\mu_p, \tau_p^2)$ and n_t new treatment observations drawn from $N(\mu_t, \tau_t^2)$.

Using (4) we see that for minimizing the posterior variance of the difference between μ_t and μ_p it suffices to assign 32 patients to the treatment group and 68 patients to the control group.

It might be worth trying to investigate the same question for the unknown variance case, and for binomially distributed data. It would be of interest to establish for all these three cases the conditions on

the parameter values under which $\frac{n_p}{n_t} \approx 1$.

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