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Optimal Allocation of Sample Sizes to Multicenter Clinical Trials

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Abstract

In this article, we discussed an approach for optimal sample size allocation in designing multicenter clinical trials. The method we studied was adopted from a stratified sampling survey design. The sample size allocated to centers is a function of center's treatment cost, the standard deviation of the endpoint and the availability of patients. We illustrated our approach using two hypothetical scenarios derived from our experiences in designing and conducting multicenter clinical trials. Simulation results were also presented.

Keywords

Cost Constraints; Multicenter Clinical Trials; Optimal Allocation; Sample Size; Weighting

1. Introduction

Clinical trials are vital to drug discovery and interventional therapeutics in treating patients and improving the health of general public. Traditional controlled double blind randomized clinical trials conducted by a single clinical site may encounter a lack of convincing evidence due to a limited number of available patients who meet the inclusion criteria and are willing to participate in the trial. Therefore, increasingly popular, clinical trials are becoming joint efforts of multiple clinical centers under the sponsorship of pharmaceutical companies or governmental agencies with the intent to more effectively test hypotheses although some controversies still exist [1]. In designing clinical trials, sample size issues for proposed multicenter clinical trials require careful statistical justifications [2]. There has been extensive literature on sample size determination according to various principles [3, 4]. After the total sample size is obtained for multicenter clinical trials, a simple approach is to allocate the total required samples equally among the clinical centers. However, because of various uncertainties and constraints, it is very likely that recruiting centers will have different numbers of patients at the end of the clinical trial. Another common approach is to allocate the patients through bidding among clinical centers. There have been very few applications of optimal allocation principles for allocating patients to clinical centers when designing multicenter clinical trials even though there are many articles on this issue for survey sampling [5, 6].

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In our study, we utilized an optimal sample allocation scheme for stratifying recruitment in multicenter clinical trial settings by treating clinical centers as strata in surveys. The optimization was based on minimizing the variance of the estimate taking into account the total available patients, the variability of the measurements by site, and the cost of treating patients at each center. We showed how the procedure might be applied to allocating sample sizes via two hypothetical multicenter clinical trials. We also performed simulation studies to compare and evaluate the approaches resulting from the optimal allocation and the equal allocation.

The remaining of this article is organizing in the following manner. In Section 2, we review and derive the optimal allocation scheme for multicenter clinical trials. Two illustrative examples and simulation results are presented in Section 3. In Section 4, we discuss the total sample size under the constraints of total cost or given variance. Discussions are given in Section 5 and concluding remarks are provided in Section 6.

2. Optimal Allocation

Optimization principles have been used in mathematics and statistics as well as in many other fields. Much of statistical inference and estimation are based on maximizing the likelihood function [7]. In designing clinical trials, after the total sample size is determined for the proposed multicenter clinical trials, a simple scheme was to divide the number of the required subjects equally into clinical centers. Equal allocation of patients is neither optimal nor achievable for most multicenter clinical trials [1]. In this section, we adopt the widely used approach of allocating sample sizes in stratified survey design [5, 6] to multicenter clinical trials.

The design of experiments and sampling surveys seem like two very different disciplines of applied statistics. However, there are many common features in these two fields [8]. Naturally, clinical trials are special cases in the domain of design of experiments. Although there have been many methods developed for sample size determination for various types of clinical trials and allocation of subjects to treatments, there are a lack of studies on methods for allocating subjects to clinical centers for multicenter clinical trials after the total sample size has been determined. On the other hand, statisticians working in sampling survey have worked extensively on strategies for allocating samples to strata [8]. If we treat clinical centers in multicenter clinical trials as strata in survey sampling, we can apply various optimal allocation schemes when planning recruitments for multicenter clinical trials.

In our study, we treated each clinical center in a multicenter trial similarly to a stratum as in designing a survey. Let n be the total number of sample size needed for a multicenter clinical trial. We would like to allocate n patients into the L clinical centers with n_h patients in center h , where $\sum_{h=1}^L n_h = n$. Suppose the cost of obtaining data from each patient in center h is c_h . Then, under the constraint of the total cost $C = \sum_{h=1}^L c_h n_h$, the optimal allocation of patients to center h is

$$n_h = \left(\frac{N_h \sigma_h / \sqrt{c_h}}{\sum_{h=1}^L N_h \sigma_h / \sqrt{c_h}} \right) n \quad (1)$$

where N_h is the total potential patients that center h may have and σ_h is the standard deviation of the primary endpoint in center h . Expression (1) was derived under stratification

survey setting. This allocation would minimize the variance of the estimate of the mean of the primary outcome given the constraint of the cost $C = \sum_{h=1}^L c_h n_h$.

To derive expression (1), we note that [6],

$$\text{var}(\bar{y}) = \sum_{h=1}^L \frac{N_h^2 \sigma_h^2}{n_h N^2} - \sum_{h=1}^L \frac{N_h \sigma_h^2}{N^2} \quad (2)$$

Where $N = \sum_{h=1}^L N_h$, $\bar{y} = \sum_{h=1}^L N_h \bar{y}_h / N$, $\bar{y}_h = \sum_{i=1}^{n_h} y_{hi} / n_h$ and y_{hi} is the primary endpoint of patient i in clinical center h . We want to minimize variance $\text{var}(\bar{y})$ given the cost constraint $C = \sum_{h=1}^L c_h n_h$, which is equivalent to minimizing

$$\left(\sum_{h=1}^L \frac{N_h^2 \sigma_h^2}{n_h N^2} \right) \left(\sum_{h=1}^L n_h c_h \right). \quad (3)$$

Let $a_h = \frac{N_h \sigma_h}{\sqrt{n_h} N}$, $b_h = \sqrt{n_h c_h}$, then, by Cauchy-Schwarz inequality,

$$\left(\sum_{h=1}^L a_h^2 \right) \left(\sum_{h=1}^L b_h^2 \right) \geq \left(\sum_{h=1}^L a_h b_h \right)^2. \quad (4)$$

The equality holds if and only if a_h / b_h is a constant. Therefore, $n_h = \left(\frac{N_h \sigma_h / \sqrt{c_h}}{N} \right)$. Hence

$$\frac{n_h}{n} = \left(\frac{N_h \sigma_h / \sqrt{c_h}}{N} \right) / \sum_{h=1}^L \left(\frac{N_h \sigma_h / \sqrt{c_h}}{N} \right) = \frac{N_h \sigma_h / \sqrt{c_h}}{\sum_{h=1}^L N_h \sigma_h / \sqrt{c_h}}, \quad (5)$$

So that

$$n_h = \left(\frac{N_h \sigma_h / \sqrt{c_h}}{\sum_{h=1}^L N_h \sigma_h / \sqrt{c_h}} \right) n. \quad (6)$$

When the primary endpoint is a binary response, let P_h be the proportion of positive outcome from clinical center h , then $\sigma_h = \sqrt{P_h (1 - P_h)}$.

If we assume each clinical center has the same potential of eligible patients for recruitment

($N_1 = N_2 = \dots = N_L$), then $n_h = \left(\frac{\sigma_h / \sqrt{c_h}}{\sum_{h=1}^L \sigma_h / \sqrt{c_h}} \right) n$. Further, if the standard deviation of the primary endpoint is also the same for each center, we have a simplified optimal allocation formula

$$n_h = \left(\frac{1 / \sqrt{c_h}}{\sum_{h=1}^L 1 / \sqrt{c_h}} \right) n.$$

3. Illustrative Examples and Simulations

In this section, we illustrate the method discussed above through two hypothetical multicenter clinical trials, Study One and Study Two. Suppose, after careful preparation of sample size calculations, the investigators needed sample sizes of 174 and 360 for Study One and Study Two, respectively. Assume both multicenter clinical trials will be carried out by 6 clinical centers. An important consideration when designing multicenter clinical trials is to the allocation of sample sizes to each center. Following an equal allocation of sample sizes, each clinical center would expect to recruit 29 and 60 patients for Study One and Study Two, respectively. As mentioned previously, another commonly used scheme is to divide the patients through bidding among the clinical centers. Although the 6 clinical centers follow the same protocol for each study, the cost of obtaining data from patients is different. Suppose after lengthy negotiations, the funding agency and the clinical centers negotiated a cost of \$6,436, \$5,811, \$6,512, \$6,322, \$5,681 and \$6,123 per patient for the clinical centers for Study One and \$18,631, \$10,123, \$16,716, \$17,426, \$16,681 and \$21,467 for the centers in Study Two.

According to expression (6) and assuming each center has the same potential number for recruiting and equal variance on the measurement of primary endpoint, we obtained 28, 30, 28, 29, 30, 29 for Study One and 56, 76, 59, 58, 59, 52 for Study Two, respectively. Note that there is little variation of the sample size for Study One due to the relatively even cost. We observed more variation of sample size for Study Two due to higher heterogeneity of cost among clinical centers.

In deriving the optimal allocations of sample sizes described above, we assumed equal sizes of available patients across the clinical centers and equal standard deviations of the measurement of the primary endpoint. This assumption may not be true in reality. As it is stated in expression (6), the optimal allocation of the samples size of each clinical center is proportional to the total sample size n . The proportion is a function of available patients, the standard deviation of the measurement and the cost per patient. To further take into account the variability of the number of possible available patients and the standard deviations, we simulated 5,000 realizations of the proportions using independent Poisson random variable with mean 300 as N_h and independent uniform(1,2) for the standard deviation σ_h . The histograms are plotted in Figure 1 and Figure 2 for Study One and Study Two, respectively. All histograms are shown in the same scale except for center 2 in Figure 2 which used a different scale to accommodate all the simulated proportions. Figures 1 and 2 indicate that the proportions of patients for Study One are more evenly distributed than that of Study Two since Study One has less variability in its cost for an individual patient across the centers. The estimated standard deviation of the simulated averages of the proportions by centers was 0.0047 and 0.0225 for Study One and Study Two, respectively. The estimated standard deviation of Study Two was about 5 times that of Study One.

From our simulations, we usually observed slightly different sample allocations as compared to the situations under equal N_h and equal σ_h assumptions. However, when the number of realizations increases, if the mean value of the simulated proportions is used for the allocation, the discrepancies as compared to the equal cases become smaller. We have tried

many experiments with 5,000 simulations and have found that the allocations of the sample sizes were almost the same as that under the assumptions of equal available patients and equal standard deviations. The simulation results showed that the assumptions of equal available patients and equal standard deviations might be reasonable for optimally allocating patients into clinical centers if the underlying distributions of the available patients and standard deviations are similar in each of the centers. The mean proportions from the simulations are compared with the proportions under equal N_h and equal σ_h in Table 1.

The optimal allocation scheme is based on minimizing the variance of the estimate under the constraints of the total cost and given total sample size. To further investigate the differences of variances of the estimates between the designs of optimal and equal allocations, we performed more simulations. For Study One, we continued to assume that the total sample size was 174. The available patients for each clinical center followed a Poisson distribution with mean 300 and the standard deviation of the outcome in each center followed a uniform distribution in (10,20). The cost per patient for each clinical center followed normal distribution with a mean of \$6,436, \$5,811, \$6,512, \$6,322, \$5,681 and \$6,123, respectively, and a common standard deviation of \$500. We assumed the cost constraint for each realization in the simulation was equal to that of the optimal allocation. We applied this constraint to allocate 29 patients to the first 5 centers and let the sixth clinical center have the allowable number of patients under the cost constraint (The sixth clinical center may not have exactly 29 patients). We simulated 5000 realizations of the variances under the optimal and equal allocation, respectively. The pairwise t test on the realizations of the variances showed no statistically significant differences between the simulated variances (p-value = 0.0575). To summarize the outcome, we plotted the empirical cumulative distribution functions under both optimal and equal allocation for Study One in Figure 3. Under our settings, the statistically insignificant results were mainly due to the relatively equal cost per patient across the clinical centers. For Study Two, we assumed more heterogeneous cost per patient for the 6 clinical centers. In our simulations for Study Two, we let the cost per patient for the 6 clinical centers follow independent normal distribution with mean \$18,631, \$10,123, \$16,716, \$17,426, \$16,681 and \$21,467, respectively, and a common standard deviation \$1000. We assumed all other conditions were the same as in Study One. The pairwise t test on the realizations of the variances showed strong statistically significant differences between the simulated variances (p-value < 0.0001). The empirical cumulative distribution functions are plotted in Figure 4. Figure 4 indicates that there was a great improvement for the variance under optimal allocation for Study Two. For Study One, the variance under the optimal allocation was about 4% smaller than that of the equal allocation on average. However, for Study Two, variance under optimal allocation was about 50% smaller than that of the equal allocation on average. These results showed that the significance of the improvement of the optimal allocation depends on the actual study settings. In general, under our settings, the more heterogeneous of the cost per patient is, the more improvement the optimal allocation provides. The summary results are provided in Table 2.

4. Sample Sizes under Constraints of Cost and Variance

In Sections 2 and 3, we assumed that the total sample size n of the clinical trial was known. The sample size determination for a clinical trial is usually based on the control of type I and type II error rates and its possible detectable treatment effect without considering the cost. However, if there is a constraint of total cost C , we can also recalculate the possible total sample size n through optimal allocation by substitute n_h of expression (6) into

$$C = \sum_{h=1}^L c_h n_h \text{ and get:}$$

$$n = \frac{C \sum_{h=1}^L (N_h \sigma_h / \sqrt{c_h})}{\sum_{h=1}^L (N_h \sigma_h / \sqrt{c_h})}. \quad (7)$$

Similarly, if one wants to achieve the variance V of the estimate, we can substitute n_h of expression (6) into

$$V = \sum_{h=1}^L \frac{N_h^2 \sigma_h^2}{n_h N^2} - \sum_{h=1}^L \frac{N_h \sigma_h^2}{N^2},$$

and solving for n :

$$n = \frac{\left(\sum_{h=1}^L N_h \sigma_h \right) \left(\sum_{h=1}^L N_h \sigma_h / \sqrt{c_h} \right)}{V + \left(\sum_{h=1}^L N_h \sigma_h^2 \right) / N^2}. \quad (8)$$

For example, suppose we have one million dollars to spend on Study One. Then, each center has the potential number for recruiting and equal variance on the measurement of the primary endpoints. Following expression (7), we would only be able to recruit 163 patients for the study one and each center would have 27, 28, 26, 27, 28 and 27, respectively. For Study Two, if we have six million dollars to spend, the total sample size for the study would be 365 and each center would have 57, 77, 60, 59, 60, 53, respectively, for the optimal allocation. Following expression (8), one can calculate the optimal total sample size when the variance of the primary endpoint is fixed.

5. Discussions

In this article we applied the popular optimal sample allocation used in designing stratification survey sampling to obtaining optimal sample allocation for designing multicenter clinical trials. Our technique was assessed through simulations and illustrated with two hypothetical multicenter clinical trials. Although the expected number of patients was equally allocated in the original protocols under our monitoring, our computations indicated the optimal allocation could be differed significantly from the equal allocation if cost of treatment were very different given other conditions fixed. For example, the variance of the estimate in Study Two under equal allocation would be 50% larger than that under the optimal allocation. In fact, the funding agency would work hard to produce a relatively even cost per patient for the clinical centers for the actual studies. This effort would lead to a quite even optimal allocation that is not too different from the equal allocation (Study One). It is also noteworthy that we assumed that each clinical center had the same potential number of patients for recruitment and the same variability on the measurement of the primary endpoints. These assumptions may not be true in reality.

Optimal allocation leads to minimizing the variance of the estimate of the overall treatment effect. Hence, it would maximize the power of detecting the treatment effect if other conditions are fixed. Our results are consistent with the statistical analysis of multicenter studies discussed in [9].

There have been extensive studies on optimal allocation in survey designs. However, these issues are usually ignored in designing multicenter clinical trials. Survey sampling and the design of experiments have different perspectives although the statistical foundations for these two fields are mostly the same [8]. In designing multicenter clinical trials, there is a general tendency to pursue equal sample size although equality is seldom met in real clinical trials [1]. We should recognize that equal allocation may be less desirable as compared to optimal allocations with unequal samples in multicenter clinical trials.

We noticed that the ratio λ of harmonic mean to the arithmetic mean of the sample sizes in clinical centers was defined as the coefficient of imbalance [10]. The ratio λ is given as

$$\lambda = \left(L / \sum_{h=1}^L \frac{1}{n_h} \right) \left(\sum_{h=1}^L n_h / L \right).$$

The harmonic mean is always smaller than or equal to the arithmetic mean. Therefore λ is less or equal to 1. In [10], it was assumed that unequal sample size for the clinical centers would result in less powerful design for unweighted analysis. However, if the outcomes from the centers are properly weighted in estimating the overall treatment effect, the unequal (optimal) allocation is more powerful than the design with equal allocation due to the minimization of the variance of the estimate.

In our simulation studies, although we included the variability of the available patients and the standard deviations, we still used the common mean of 300 for the Poisson random variable as the available patients and the common range for the uniform random variable as the standard deviations. We would certainly obtain different allocations if these parameters were not the same, which might be more realistic under the true setting. However, expression (6) remains the same and can be easily applied based on various costs of treatments, different availabilities of the patients for recruitment and changing variations of the endpoint measurements.

6. Concluding Remarks

The principles used in this article are simple and extensively studied in the design of surveys. However, they are not being widely applied in the design of multicenter clinical trials. Traditionally, in survey sampling, researchers are focusing on providing more accurate estimates for underlying parameters under the given constraints. In clinical trials, researchers are more interested in testing hypotheses. Therefore, cost plays an important role in designing sampling surveys and the Type I and Type II error rates are the central considerations in designing clinical trials. In practice, most clinical trials are designed under cost constraints. However, the cost constraints are not actively and expressively dealt with in the literature of clinical trial designs. Our study promotes the application of the optimization principles in designing multicenter clinical trials.

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References

- [1]. Senn S. Some controversies in planning and analyzing multi-centre trials. *Statistics in Medicine*. 1998; 17:1753–1765. [PubMed: 9749445]
- [2]. Vierron E, Giraudeau B. Sample size calculation for multicenter randomized trial: Taking the center effect into account. *Contemporary Clinical Trials*. 2007; 28:451–458. [PubMed: 17188941]
- [3]. Kim KM, DeMets DL. Sample-size determination for group sequential clinical trials with immediate response. *Statistics in Medicine*. 1992; 11:1391–1399. [PubMed: 1518999]
- [4]. Moye LA. Sizing clinical trials with variable endpoint event rates. *Statistics in Medicine*. 1997; 20:2267–2282. [PubMed: 9351164]
- [5]. Cochran, WG. *Sampling Techniques*. 3rd. Wiley; New York: 1977.
- [6]. Levy, PS.; Lemeshow, S. *Sampling of Populations: Methods and Applications*. 3rd. Wiley; New York: 1999.
- [7]. Casella, G.; Berger, RL. *Statistical Inference*. 2nd. Duxbury; Pacific Grove: 2002.
- [8]. Fienberg SE, Tanur JM. Experimental and sampling structure: Parallels, diverging and meeting. *International Statistical Review*. 1987; 55:75–96.
- [9]. Lin Z. An issue of statistical analysis in controlled multi-center studies: How shall we weight the centers. *Statistics in Medicine*. 1999; 18:365–373. [PubMed: 10070679]
- [10]. Revuna F. Unequal center size, sample size, and power in multicenter clinical trials. *Drug Information Journal*. 2004; 38:387–394.

Figure 1.

The histograms of the proportions simulated for Study One with 5,000 realizations of the available patients (N_h) in the centers following Poisson distribution of mean=300 and standard deviation (σ_h) following a uniform distribution of range [1, 2]. The estimated standard deviation of the simulated proportion averages across the centers was 0.0047.

Figure 2.

The histograms of the proportions simulated for Study Two with 5,000 realizations of the available patients (N_h) in the centers following Poisson distribution of mean=300 and standard deviation (σ_h) following a uniform distribution of range [1, 2]. The estimated standard deviation of the simulated proportion averages across the centers was 0.0225.

Figure 3. The empirical cumulative distribution functions of the simulated variances for Study One with 5,000 realizations. The dotted line is based on the optimal allocation and the solid line is based on the equal allocation.

Figure 4.

The empirical cumulative distribution functions of the simulated variances for Study Two with 5,000 realizations. The dotted line is based on the optimal allocation and the solid line is based on the equal allocation.

Table 1

The mean proportions from the simulations and the proportions under equal N_h and equal σ_h for the optimal allocation.

	Center 1	Center 2	Center 3	Center 4	Center 5	Center 6
Equal Allocation	0.1667	0.1667	0.1667	0.1667	0.1667	0.1667
Study One						
Equal N_h, σ_h	0.1609	0.1724	0.1609	0.1667	0.1724	0.1667
Simulated	0.1620	0.1714	0.1624	0.1646	0.1734	0.1663
Study Two						
Equal N_h, σ_h	0.1556	0.2111	0.1639	0.1611	0.1639	0.1444
Simulated	0.1559	0.2101	0.1635	0.1614	0.1645	0.1446

Table 2

The averages of the simulated variances for the equal allocation and the optimal allocation.

	Equal Allocation	Optimal Allocation	Percentage of Change	P-value (Pairwise T)
Study One	1.2219	1.1744	−3.89	0.0575
Study Two	1.0274	0.5069	−50.66	<0.0001