Imbalanced randomization in clinical trials

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Randomization is a common technique used in clinical trials to eliminate potential bias and confounders in a patient population. Equal allocation to treatment groups is the standard due to its optimal efficiency in many cases. However, in certain scenarios, unequal allocation can improve efficiency. In superiority trials with more than two groups, the optimal randomization is not always a balanced randomization. In noninferiority (NI) trials, additive margin with equal variance is the only instance with balanced randomization. Optimal randomization for NI trials can be far from 1:1 and can greatly improve efficiency, a fact which is commonly overlooked. A tool for sample size calculation for NI trials with additive or multiplicative margin with normal, binomial, or Poisson distribution is available at http://www.statlab.wisc.edu/shiny/SSNI/.

KEYWORDS
efficiency, noninferiority trial, randomization

1 INTRODUCTION

Randomization remains a gold standard method in clinical trial methodology to eliminate potential bias and confounders. Randomization eliminates a systematic difference between subjects in treatment groups inducing approximate balance with respect to covariates, both observed and unobserved. Equal allocation to treatment groups is commonly used due to its high efficiency in many cases. Increasing the efficiency of estimators improves the likelihood of correctly rejecting the null hypothesis when the alternative is true. Power is inversely proportional to the variance of the estimators, thus minimizing the total variance will maximize the power. The goal is to maximize their common power.

The ethics of imbalanced randomization is highly debated. Pocock asserts that there is a little loss in power with a moderate imbalanced randomization scheme.1 Edwards et al argue that even though, imbalanced randomization might increase recruitment in a trial, the patients’ expected benefit of a treatment might increase due to the notion of an increased chance of getting their preferred treatment.2 On the other hand, there is a growing trend in trials with imbalanced treatment allocation.3 Imbalanced randomization is suggested to have an ethical advantage over balanced design due to the facts that more subjects are assigned to the new treatment than the control treatment and the new treatment is likely to be superior.4 Avins argue that if the chance of success is higher with a new intervention, randomizing a greater proportion of subjects to the new intervention is highly desirable.5 Imbalanced randomization in a clinical trial might seem to be a favorable design due to several constraints such as limitation of available resources, desire to increase chances of attaining required sample size, and preference for testing the side effects of a new treatment/drug.

In certain trials, limitation of resources tends to hinder the success of a trial. Thus, investigators could reduce the patient allocation in the scarce group to overcome this issue. For instance, in the Cardiovascular Patient Outcomes

Abbreviations: ARE, asymptotic relative efficiency; CI, confidence interval; CPORT, Cardiovascular Patient Outcomes Research Team; NI, noninferiority.
Research Team (CPORT) trial randomization was 3:1 in favor of without on-site vs with on-site cardiac surgery (see Section 4 for more details) in order to provide sufficient training to surgeons in the study sites, which tended to be small. But imbalanced randomization in this study also has implications for efficiency as shown in Figure 1. On the other hand, the cost can also contribute to the imbalance in a trial. Imbalanced allocation of patients might be beneficial to reduce the overall cost of a trial. Compared to inefficient trial, in an efficient trial, fewer patients are required to be recruited in a trial to attain the appropriate statistical power.

Patients tend to be frustrated with equal allocation trials of a deadly disease due to the low chances of getting the new treatment. Thus, imbalanced trials tend to attract more patients due to a higher tendency of getting a new treatment. However, imbalance could reduce the statistical power and increase the sample size required. Even though early phase trials are designed to study the efficacy of dosage of new treatment, these trials are conducted in a small sample and they fail to capture the complete effect of a treatment. Thus, imbalanced trials favoring an experimental treatment might be helpful to further analyze its side effects.

After briefly looking at the optimal randomization ratio for multiple doses against control in superiority trials, we provide a quick introduction to noninferiority (NI) trials. Then, we move on to the optimal allocation in a NI trials with equal and unequal variance and additive and multiplicative NI margins. We also derive the optimal randomization ratio for the number of events required for survival data in a NI trial before moving on to use the CPORT study of percutaneous revascularization as an example.

2 “ALL-DOSES-AGAINST-CONTROL” IN SUPERIORITY TRIALS

Dunnett’s article on comparing several treatments to a control illustrates the low efficiency of assigning all treatments equally for comparing multiple treatments to a control, but not to each other. However, the article did not provide a closed-form solution. This is derived here.

2.1 Equal variance

Consider a superiority trial in which multiple experimental treatments, for example, different doses of the same test drug, are compared to a control. The observed endpoint is continuous and follows normal distribution with total sample size \( N \) and mean outcomes \( \mu_i \), where \( i \) indexes group, and constant variance \( \sigma^2 \). There are a total of \( k \) groups, where Group 1 is the control dose and the other \( k-1 \) groups are the experimental doses, and we want to compare the experimental groups to the control but not to each other. The \( k-1 \) null hypotheses are as follows, with alternatives of greater/less than depending on the study design. In hypotheses below, the higher means denote better outcomes.

\[
H_{0,1} : \mu_2 \leq \mu_1 \quad H_{A,1} : \mu_2 > \mu_1, \\
H_{0,2} : \mu_3 \leq \mu_1 \quad H_{A,2} : \mu_3 > \mu_1, \\
\vdots \\
H_{0,k-1} : \mu_k \leq \mu_1 \quad H_{A,k-1} : \mu_k > \mu_1.
\]

Denote the sample size allocated in the control group \( cN \), so that every other group is allocated \( N(1-c)/(k-1) \). In order to compute the optimal \( c \), we minimize the total variance below with respect to \( c \) (0 < \( c \) < 1). This is the same results obtained but not derived by Wong and Zhu and Fackle-Fornius and Nyquist.\(^8\)\(^9\) Let \( \bar{X}_1 \) be the sample mean of the control group and \( \bar{X}_i \) be the sample mean for the treatment groups (2 ≤ \( i \) ≤ \( k \)).

\[
\sum_{i=2}^{k} \text{Var}(\bar{X}_i - \bar{X}_1) \propto \frac{k-1}{1-c} + \frac{1}{c}
\]

\[
\frac{\partial}{\partial c} \sum_{i=2}^{k} \text{Var}(\bar{X}_i - \bar{X}_1) \propto \frac{-1}{c^2} + \frac{k-1}{(1-c)^2} = 0.
\]

\[
c = \begin{cases} 
\frac{1}{2}, & \text{if } k = 2 \\
\frac{-1+\sqrt{k-1}}{k-2}, & \text{if } k > 2.
\end{cases}
\]
The asymptotic relative efficiency (ARE) of the optimal allocation (A1) relative to equal allocation (A2) is

\[ \text{ARE}(A1, A2) = \frac{2k(k-1)}{(\sqrt{k-1} + k-1)^2} > 1, \text{ for } k > 2. \]

2.2 Unequal variance

If each of the dosage groups has a different variance, this becomes a harder optimization problem. Denote the variance of group \( i \) by \( \sigma_i^2 \). The sample size allocated to each group is \( c_iN \) for group \( i \) where \( 1 \leq i \leq k \) (\( 0 < c_i < 1, \sum_{i=1}^{k} c_i = 1 \)). Similar results were attained by Wong and Zhu.\(^9\) Let \( \bar{X}_1 \) be the sample mean of the control group and \( \bar{X}_i \) be the sample mean for the treatment groups \( (2 \leq i \leq k) \). The objective function is

\[
\sum_{i=2}^{k} \text{Var}(\bar{X}_i - \bar{X}_1) \propto \frac{(k-1)\sigma_1^2}{c_1} + \frac{\sigma_2^2}{c_2} + \ldots + \frac{\sigma_k^2}{c_k}.
\]

The optimal solution for the \( c_1, \ldots, c_{k-1} \) is

\[
c_1 = \frac{\sigma_1 \sqrt{k-1}}{\sigma_1 \sqrt{k-1} + \sum_{i=2}^{k} \sigma_i}, \quad c_h = \frac{\sigma_h}{\sigma_1 \sqrt{k-1} + \sum_{i=2}^{k} \sigma_i} \quad \text{for } h \geq 2.
\]

This reverts to the results of the Section 2.1 when \( \sigma_i = \sigma \).

The ARE of the optimal allocation (A1) relative to equal allocation (A2) is

\[
\text{ARE}(A1, A2) = \frac{k(k-1)\sigma_1^2 + k \sum_{i=2}^{k} \sigma_i^2}{\sigma_1 \sqrt{k-1} (\sigma_1 \sqrt{k-1} + \sum_{i=2}^{k} \sigma_i) + \sum_{i=2}^{k} \sigma_i (\sigma_1 \sqrt{k-1} + \sum_{i=2}^{k} \sigma_i)}
\]

\[
= \frac{k(k-1)\sigma_1^2 + k \sum_{i=2}^{k} \sigma_i^2}{(\sigma_1 \sqrt{k-1} + \sum_{i=2}^{k} \sigma_i)^2} > 1 \quad \text{for } k > 2.
\]

3 Efficiency vs Randomization Ratio in NI Trials with Two Treatments

3.1 NI trials

NI trials are clinical trials designed to establish that a new treatment is not that much worse than a standard control.\(^10\) A new treatment can be favorable even if it is slightly worse than the current treatment. Unlike equivalence trials, NI trials do allow the possibility of the new treatment being better than the standard treatment.\(^11\) The new treatment is believed to offer ancillary benefit in terms of side effects, safety or other factors.

A margin is introduced to allow a small loss in effect by the new treatment compared to the control treatment. This margin serves as a maximum acceptable threshold and is determined in advance.\(^12,13\) Factors such as historical data and physician's experience play a vital role in the decision of setting a margin for a NI trial. The selection of margin scale used (difference in means of two groups, ratios of means, and so on) is less commonly stated but is important for computing sample sizes and interpretation of results.\(^14\)

Denote \( \Delta > 0 \) for an additive and \( \Delta > 1 \) for a multiplicative margin. The corresponding NI trial hypotheses for an additive margin to test the difference in means are

\[
H_0 : \mu_C - \mu_T \geq \Delta \quad H_A : \mu_C - \mu_T < \Delta
\]
where $\mu_C$ is the mean of the control group and $\mu_T$ is the mean of the experimental group. On the other hand, the corresponding NI trial hypotheses for a multiplicative margin to test the differences in means are

$$H_0 : \frac{\mu_C}{\mu_T} \geq \Delta$$
$$H_A : \frac{\mu_C}{\mu_T} < \Delta$$

where $\mu_C$ is the mean of the control group and $\mu_T$ is the mean of the experimental group. Higher means are considered favorable.

### 3.2 Imbalance in NI trials: equal variance

The optimal allocation for different scenarios is computed below. The variance for both the treatment and control groups is denoted by $\sigma^2$.

#### 3.2.1 Optimal allocation for additive $\Delta$

$$H_0 : \mu_C - \mu_T \geq \Delta \quad H_A : \mu_C - \mu_T < \Delta.$$  

Let $\bar{X}_C$ be the sample mean of the control group and $\bar{X}_T$ be the sample mean for the treatment group. In this case, the optimal randomization ratio is 1:1 since $\text{Var}(\bar{X}_C) = \text{Var}(\bar{X}_T)$.

#### 3.2.2 Optimal allocation for multiplicative $\Delta$

$$H_0 : \frac{\mu_C}{\mu_T} \geq \Delta \quad H_A : \frac{\mu_C}{\mu_T} < \Delta.$$  

The optimal sample size allocated in the control group is denoted $hN$ and the treatment group is allocated $(1-h)N$. Let $\bar{X}_C$ be the sample mean of the control group and $\bar{X}_T$ be the sample mean for the treatment group. In order to compute the optimal $h$ we minimize the variance below with respect to $h$, $(0 < h < 1)$.

\[
\text{Var}(\bar{X}_C - \Delta \bar{X}_T) \propto \frac{1}{h} + \Delta^2 \frac{1}{1-h}
\]

\[
\frac{\partial \text{Var}(\bar{X}_C - \Delta \bar{X}_T)}{\partial h} \propto -\frac{1}{h^2} + \Delta^2 \frac{1}{(1-h)^2} = 0
\]

\[h = \frac{1}{\Delta + 1}.
\]

The ARE of the optimal allocation ($A_1$) relative to equal allocation ($A_2$) is

$$\text{ARE}(A_1, A_2) = \frac{2(1 + \Delta^2)}{(\Delta + 1)^2} \geq 1.$$  

### 3.3 Imbalance in NI trials: unequal variance

The variances in the treatment groups are not equal, for example with binomial or Poisson outcomes. The variance is denoted by $\sigma_i^2 = V(\mu_i)$, where $V(\mu_i)$ is the variance of outcome subject to treatment $i$ and is a function of $\mu_i$. 
3.3.1 | Optimal allocation for additive \( \Delta \)

\[
H_0 : \mu_C - \mu_T \geq \Delta \quad H_A : \mu_C - \mu_T < \Delta.
\]

The optimal sample size allocated in the control group is denoted \( hN \) and the treatment group is allocated \((1 - h)N\). Let \( \overline{X}_C \) be the sample mean of the control group and \( \overline{X}_T \) be the sample mean for the treatment group. In order to compute the optimal \( h \), we minimize the variance below with respect to \( h \), \((0 < h < 1)\).

\[
\text{Var}(\overline{X}_C - \overline{X}_T - \Delta) \propto \frac{\sigma_C^2}{h} + \frac{\sigma_T^2}{1 - h}
\]

\[
\frac{\partial \text{Var}(\overline{X}_C - \overline{X}_T - \Delta)}{\partial h} \propto \frac{-\sigma_C^2}{h^2} + \frac{\sigma_T^2}{(1 - h)^2} = 0
\]

\[h = \frac{\sigma_C}{\sigma_C + \sigma_T}.
\]

The ARE of the optimal allocation (A1) relative to equal allocation (A2) is

\[
\text{ARE}(A_1, A_2) = \frac{2(\sigma_C^2 + \sigma_T^2)}{(\sigma_C + \sigma_T)^2} \geq 1.
\]

3.3.2 | Optimal allocation for multiplicative \( \Delta \)

\[
H_0 : \frac{\mu_C}{\mu_T} \geq \Delta \quad H_A : \frac{\mu_C}{\mu_T} < \Delta.
\]

The optimal sample size allocated in the control group is denoted \( hN \) and the treatment group is allocated \((1 - h)N\). Let \( \overline{X}_C \) be the sample mean of the control group and \( \overline{X}_T \) be the sample mean for the treatment group. In order to compute the optimal \( h \), we minimize the variance below with respect to \( h \), \((0 < h < 1)\).

\[
\text{Var}(\overline{X}_C - \Delta \overline{X}_T) \propto \frac{\sigma_C^2}{h} + \frac{\Delta^2 \sigma_T^2}{1 - h}
\]

\[
\frac{\partial \text{Var}(\overline{X}_C - \Delta \overline{X}_T)}{\partial h} \propto \frac{-\sigma_C^2}{h^2} + \frac{\Delta^2 \sigma_T^2}{(1 - h)^2} = 0
\]

\[h = \frac{\sigma_C}{\sigma_C + \Delta \sigma_T}.
\]

The ARE of the optimal allocation (A1) relative to equal allocation (A2) is

\[
\text{ARE}(A_1, A_2) = \frac{2(\sigma_C^2 + \Delta^2 \sigma_T^2)}{(\sigma_C + \Delta \sigma_T)^2} \geq 1.
\]

3.4 | The general case for generalized linear models

The derivation for binomial and Poisson null hypothesis are illustrated below. In the binomial case, consider \( \pi_C \) and \( \pi_T \) as the probability of success for control and treatment group. Meanwhile, in the Poisson group consider \( \lambda_C \) and \( \lambda_T \) as the mean of control and treatment group, respectively.

The optimal sample size allocated in the control group is denoted \( hN \) and the treatment group is allocated \((1 - h)N\). In order to compute the optimal \( h \), we minimize the variance below with respect to \( h \), \((0 < h < 1)\).
3.4.1 | Additive hypothesis

Binomial

\[ H_0 : \pi_C - \pi_T \geq \Delta \quad H_A : \pi_C - \pi_T < \Delta. \]
\[
 h = \frac{\sqrt{\pi_C(1 - \pi_C)}}{\sqrt{\pi_C(1 - \pi_C) + \Delta \sqrt{\pi_T(1 - \pi_T)}}}.
\]

The ARE of the optimal allocation (A1) relative to equal allocation (A2) is

\[
\text{ARE}(A_1, A_2) = \frac{2(\pi_C(1 - \pi_C) + \pi_T(1 - \pi_T))}{(\sqrt{\pi_C(1 - \pi_C) + \Delta \sqrt{\pi_T(1 - \pi_T)}})^2} \geq 1.
\]

Poisson

\[ H_0 : \lambda_C - \lambda_T \geq \Delta \quad H_A : \lambda_C - \lambda_T < \Delta. \]
\[
 h = \frac{\sqrt{\lambda_C}}{\sqrt{\lambda_C + \Delta \sqrt{\lambda_T}}}
\]

The ARE of the optimal allocation (A1) relative to equal allocation (A2) is

\[
\text{ARE}(A_1, A_2) = \frac{2(\lambda_C + \lambda_T)}{(\sqrt{\lambda_C + \Delta \sqrt{\lambda_T}})^2} \geq 1.
\]

3.4.2 | Multiplicative hypothesis

Binomial

\[ H_0 : \frac{\pi_C}{\pi_T} \geq \Delta \quad H_A : \frac{\pi_C}{\pi_T} < \Delta. \]
\[
 h = \frac{\sqrt{\pi_C(1 - \pi_C)}}{\sqrt{\pi_C(1 - \pi_C) + \Delta \sqrt{\pi_T(1 - \pi_T)}}}.
\]

The ARE of the optimal allocation (A1) relative to equal allocation (A2) is

\[
\text{ARE}(A_1, A_2) = \frac{2(\pi_C(1 - \pi_C) + \Delta^2 \pi_T(1 - \pi_T))}{(\sqrt{\pi_C(1 - \pi_C) + \Delta \sqrt{\pi_T(1 - \pi_T)}})^2} \geq 1.
\]

Poisson

\[ H_0 : \frac{\lambda_C}{\lambda_T} \geq \Delta \quad H_A : \frac{\lambda_C}{\lambda_T} < \Delta. \]
\[
 h = \frac{\sqrt{\lambda_C}}{\sqrt{\lambda_C + \Delta \sqrt{\lambda_T}}}
\]

The ARE of the optimal allocation (A1) relative to equal allocation (A2) is

\[
\text{ARE}(A_1, A_2) = \frac{2(\lambda_C + \Delta^2 \lambda_T)}{(\sqrt{\lambda_C + \Delta \sqrt{\lambda_T}})^2} \geq 1.
\]
3.5 Survival analysis

In clinical trials of outcomes which are time to events and therefore subject to censoring, sample size and efficiency depend on the number of events observed in each group. We now adapt the methods described above to the two sample log-rank test for time-to-event outcomes of NI trials. For purposes of experimental design we assume proportional hazards. The hazard function for the control treatment is denoted by \( \lambda_C(t) \) and the hazard function for the treatment group is denoted by \( \lambda_T(t) \). Under the proportional hazards assumption, \( \Delta = \frac{\lambda_T(t)}{\lambda_C(t)} \) denotes the hazard ratio and the NI margin is set to \( \Delta_0 > 1 \), with unfavorable events.

We obtained the derivation of the number of events required, \( D \), under the hypotheses and denote \( pN \) as the sample size allocated in the control group and \((1 - p)N\) the sample size allocated in the treatment group and \( \alpha \) and \( 1 - \beta \) corresponds to the respective type I error rate and power for the clinical study.

\[
H_0 : \Delta \geq \Delta_0 \quad H_A : \Delta < \Delta_0.
\]

We then compute the derivative of \( D \) with respect to \( p \) in order to find the allocation ratio which minimizes the number of events \( D \) and therefore optimizes efficiency. From Junge et al,\textsuperscript{15}

\[
D = \frac{\sqrt{\Delta_0 z_{1-\alpha} + (p + (1-p)\Delta_0)z_{1-\beta})}^2}{p(1-p)(\Delta_0 - 1)^2}
\]

By substituting \( a = \sqrt{\Delta_0 z_{1-\alpha}} \), \( b = \Delta_0 \), \( c = z_{1-\beta} \), and \( d = (\Delta_0 - 1)^2 \), we get

\[
D = \frac{\{a + (p + (1-p)b)c\}^2}{p(1-p)d}; \quad 0 < p < 1
\]

\[
\frac{\partial D}{\partial p} = \frac{2(a + bc - bcp + cp)(c - bc)(1 - p)d - (a + bc - bcp + pc)^2((1 - 2p)d)}{p^2(1-p)^2d^2}
\]

\[
= \frac{2(c(a + bc - bcp + cp)(1 - b)(1 - p)p - (a + bc - bcp + pc)^2(1 - 2p))}{p^2(1-p)^2}
\]

\[
= \frac{(a + bc - bcp + cp)(cp - a - bc + bcp + 2ap)}{p^2(1-p)^2}.
\]

Setting the numerator \( \frac{\partial D}{\partial p} = 0 \) to obtain the minimum and replacing \( a, b, \) and \( c \) respectively, we get

\[
p = \frac{\sqrt{\Delta_0 z_{1-\alpha} + \Delta_0 z_{1-\beta}}}{(\Delta_0 + 1)z_{1-\beta} + \sqrt{\Delta_0 z_{1-\alpha}}}
\]

Since \( 0 < p < 1 \), the optimal solution for \( p \) is \( \frac{\sqrt{\Delta_0 z_{1-\alpha} + \Delta_0 z_{1-\beta}}}{(\Delta_0 + 1)z_{1-\beta} + \sqrt{\Delta_0 z_{1-\alpha}}} \). The other solution of \( p \) provides a value of greater than 1 when \( \Delta_0 > 1 \). The only instance with balanced randomization is when \( \Delta_0 = 1 \), implying a superiority trial. Let \( S_C(t) \) and \( S_T(t) \) be the survivor functions of the survival distribution for the control and treatment groups. For NI trials, Chow et al provides a derivation for number of events required where the assumption of \( S_C(t) \approx S_T(t) \) is made.\textsuperscript{16} Under this assumption, the optimal solution is \( p = 0.5 \) always as shown in the derivation below.

\[
D = \frac{(z_{1-\alpha} + z_{1-\beta})^2}{p(1-p)(\log \Delta_0)^2}
\]

\[
\frac{\partial D}{\partial p} \propto -\frac{((1-p)(\log \Delta_0)^2 - p(\log \Delta_0)^2)}{(p(1-p)(\log \Delta_0)^2)^2}
\]
\[
\frac{(2p - 1)(\log \Delta_0)^2}{(p(1 - p)(\log \Delta_0)^2)^2}.
\]

Setting the numerator of \(\frac{\partial D}{\partial p} = 0\), we always get \(p = 0.5\). Thus their method yields optimality at 1:1 randomization whereas more realistic assumptions indicate otherwise.

4 | EXAMPLE: CPORT

The CPORT study provides a motivating example for the current work. In the CPORT study, physicians were interested in comparing the performance of percutaneous coronary intervention (PCI) at hospitals with vs without on-site cardiac surgery. PCI is often restricted to hospitals with on-site cardiac surgery which limits patients’ availability to receive the treatment. Based on previous studies, the control 6 weeks (all-cause) rate of mortality was estimated to be 0.8%. The CPORT research team was interested in showing a NI margin of \(\pi_T - \pi_C < 0.4\%\). \(\pi_C\) and \(\pi_T\) denote the proportion of mortality in hospitals with on-site cardiac surgery and hospitals without on-site cardiac surgery (\(\pi_C = 0.8\%\), \(\pi_T = 1.2\%\)).

CPORT was a multicenter randomized trial with 18,867 patients who were randomized at 3:1 in the treatment group to undergo PCI with 14,149 patients undergoing PCI at a hospital without on-site cardiac surgery and 4,718 patients undergoing PCI at hospitals with on-site cardiac surgery. The 6-week mortality rate observed was 0.9% at hospitals without on-site surgery and 1% vice versa. The 95% confidence interval for the difference in 6-week mortality rate was −0.31% to 0.23% with a \(P\)-value of 0.04 for NI. The results suggest that PCI performed at hospitals without on-site cardiac surgery was noninferior to PCI performed at hospitals with on-site cardiac surgery with respect to mortality at 6 weeks and major adverse cardiac events at 9 months.

However, the 3:1 randomization was not optimized statistically. The optimal randomization ratio is 1.22:1 which is illustrated in Figure 1 using relative efficiency curve. The computation of optimal allocation for different randomization ratio is illustrated in Figure 1 and Table 1.

5 | DISCUSSION

We have derived optimal allocation for superiority trials with multiple drugs vs control and computed the relative efficiency compared to a balanced allocation. The optimal allocation is unbalanced in a superiority trial with multiple drugs each compared to control. Even with superiority trials comparing two binomial endpoints, the optimal randomization is

![Figure 1](https://example.com/figure1.png)
not 1:1 because the power calculations use the variance of the difference in proportions under the alternative, although this difference is usually trivial.\(^\text{18}\) In NI trials, additive margin with equal variance is the only instance with balanced optimal randomization. With multiplicative margins, 1:1 randomization is less effective because we are estimating a weighted sum and even with additive margins in NI trials, variance differs under \(H_0\) for example with binary outcomes implying optimality with imbalanced randomization. In survival data, the balanced allocation is only optimal when the hazard ratio is equal to 1.

Although NI trials are discussed here because of their null hypotheses are not of equality, there are other examples, Chan et al\(^\text{19}\) discusses “super-superiority trials” of interventions such as antibiotics and vaccines, in which success is defined as showing substantial effect sizes and null may be a more modest but still positive effect.

As we demonstrated, it is sometimes optimal to implement an unequal allocation. In designing clinical trials, the ethical concerns intertwine with proper scientific judgment. Sometimes assigning more patients in a new treatment arm than the control arm has practical motivations. One scenario, common in investigational drug development, requires a minimum exposure of the test drug to allow enough data for drug safety or other evaluation before approval.\(^\text{20}\) For example, the ICH E1 recommends that at least 1500 patients exposed to investigational product, 300 patients with 6 months, and 100 patients with 12 months exposure.\(^\text{20}\) The FDA Type 2 diabetes guidance recommends at least 2500 subjects exposed to the investigational product with at least 1300 to 1500 of these subjects exposed for 1 year or more and at least 300 to 500 subjects exposed for 18 months or more.\(^\text{21}\)

Researchers have to be careful and wise in planning a trial to prevent failure in achieving the primary outcome. In unblinded trials, where patients are aware of treatment assignment, the dropout rates might be higher than blinded studies.\(^\text{22}\) Friedman et al asserted that the dropout rates tend to be higher in the control group where patients know the historical outcome of the treatment is undesirable (especially in cancer trials).\(^\text{23}\) However, they also believe that new interventions with unpleasant side effects could lead to higher dropouts in the treatment group(s).\(^\text{23}\) Dropout rates were nearly equal in the two arms of the CPORT study, which was highly imbalanced and clearly unblinded.\(^\text{17}\) Nevertheless, informative dropout is a concern in trials with any randomization ratio.

An application for a sample size calculator in a NI trial with randomization ratio and relative efficiency to balanced randomization is available at http://www.statlab.wisc.edu/shiny/SSNI/. The sample size calculator computes sample sizes for multiplicative or additive margin with normal, binomial, or Poisson distribution. The application also reveals other randomization ratios with their relative efficiency compared to the optimal allocation. Sample output is shown in Figure 2.

Figures 3 and 4 show the relative efficiency of optimal allocation relative to equal allocation in NI trial with multiplicative and additive hypothesis. Each line represents different NI trial parameters (either equal or unequal variance with large or small difference in variance). The blue and green line shows how differences with variance can affect the relative efficiency compared to a balanced allocation. For additive \(\Delta\), the line is shown for \(0 < \Delta \leq 0.5\) and for multiplicative \(\Delta\), the line is shown for \(1 < \Delta \leq 2\). Figure 5 shows the relative efficiency of number of events comparing the optimal allocation relative to equal allocation in NI trials with survival outcomes and different \(\delta_0\)s, the line is shown for \(1 < \Delta \leq 3\).
**FIGURE 2** The tool for sample size calculation for NI trial with additive or multiplicative margin with normal, binomial, or Poisson distribution [Colour figure can be viewed at wileyonlinelibrary.com]

**FIGURE 3** The asymptotic relative efficiency of optimal allocation relative to equal allocation in NI trial with multiplicative Δ and equal, unequal variance (small difference in variance), (σ_C = 20, σ_T = 30) and unequal variance (large difference in variance) (σ_C = 40, σ_T = 100), with different Δs [Colour figure can be viewed at wileyonlinelibrary.com]

**FIGURE 4** The asymptotic relative efficiency of optimal allocation relative to equal allocation in NI trial with additive Δ and equal, unequal variance (small difference in variance), (σ_C = 20, σ_T = 30) and unequal variance (large difference in variance) (σ_C = 40, σ_T = 100), with different Δs. [Colour figure can be viewed at wileyonlinelibrary.com]
FIGURE 5 The relative efficiency of number of events comparing the optimal allocation relative to equal allocation in NI trials with survival outcomes and different $\delta_0$s. The respective $\alpha$ and $\beta$s are highlighted in the legend. [Colour figure can be viewed at wileyonlinelibrary.com]

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CONFLICT OF INTEREST
Xiaodan Wei is an employee from Sanofi company and/or may hold company stock share.

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REFERENCES
1. Pocock SJ. Allocation of patients to treatment in clinical trials. *Biometrics*. 1979;35(1):183-197.
2. Edwards SJL, Braunholtz DA. Can unequal be more fair? a response to Andrew Avins. *J Med Ethics*. 2000;26(3):179-182.
3. Hey SP, Kimmelman J. The questionable use of unequal allocation in confirmatory trials. *Neurology*. 2014;82(1):77-79.
4. Pocock SJ. *Clinical Trials: A Practical Approach*. Hoboken, NJ: John Wiley & Sons; 2013.
5. Avins AL. Can unequal be more fair? Ethics, subject allocation, and randomised clinical trials. *J Med Ethics*. 1998;24(6):401-408.
6. Hey SP, Kimmelman J. Are outcome-adaptive allocation trials ethical? *Clin Trials*. 2015;12(2):102-106.
7. Dunnett CW. A multiple comparison procedure for comparing several treatments with a control. *J Am Stat Assoc*. 1955;50(272):1096-1121.
8. Fackle-Fornius E, Nyquist H. Optimal allocation to treatment groups under variance heterogeneity. *Stat Sin*. 2015;25:537-549.
9. Wong WK, Zhu W. Optimum treatment allocation rules under a variance heterogeneity model. *Stat Med*. 2008;27(22):4581-4595.
10. Cook TD, DeMets DL. *Introduction to Statistical Methods for Clinical Trials*. Boca Raton, FL: CRC Press; 2007.
11. Greene CJ, Morland LA, Durkalski VL, Frueh BC. Noninferiority and equivalence designs: issues and implications for mental health research. *J Trauma Stress*. 2008;21(5):433-439.
12. McDaniel LS, Yu M, Chappell R. Sample size under the additive hazards model. *Clin Trials*. 2016;13(2):188-198.
13. Blackwelder WC. “Proving the null hypothesis” in clinical trials. *Control Clin Trials*. 1982;3(4):345-353.
14. Chappell R. Non-inferiority trials. In: Ravina B, Cummings J, McDermott M, Poole RM, eds. *Clinical Trials in Neurology: Design, Conduct, Analysis*. Cambridge: Cambridge University Press; 2012:135-146.
15. Jung S, Kang SJ, McCall LM, Blumenstein B. Sample size computation for two-sample noninferiority log-rank test. *J Biopharm Stat*. 2005;15(6):969-979.
16. Chow SC, Shao J, Wang H, Lokhnygina Y. *Sample Size Calculations in Clinical Research*. Boca Raton, FL: Chapman & Hall/CRC; 2017.
17. Thomas A, Cynthia CL, Li L. Outcomes of PCI at hospitals with or without on-site cardiac surgery. *N Engl J Med*. 2013;366(19):1792-1802.
18. Rosenberger WF, Lachin JM. *Randomization in Clinical Trials: Theory and Practice*. Hoboken, NJ: John Wiley & Sons; 2015.
19. Chan ISF, Wang WWB, Heyse JF. *Vaccine Clinical Trials*. 2nd ed. New York, NY: Marcel Dekker, Inc; 2003:1005-1022.
20. Proprietary Medicinal Products (CPMP). CPMP/ICH/375/95 Committee. Note for guidance on Population Exposure: The Extent of Population Exposure to Assess Clinical Safety. 1995;
21. US Food and Drug Administration. *Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*. Rockville, Maryland: US Food and Drug Administration; 2008.

22. Page SJ, Persch AC. Recruitment, retention, and blinding in clinical trials. *Am J Occup Ther*. 2013;67(2):154-161.

23. Friedman LM, Furberg CD, DL DM, Reboussin DM, Granger CB. *Fundamentals of Clinical Trials*. New York, NY: Springer; 2015.

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