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이 학 석 사 학 위 논 문

Sample size calculation for cross-over designs

교차 설계의 표본크기 계산법

2018 년 2 월

서울대학교 대학원

통계학과

조 용 준

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지도교수 박 태 성

이 논문을 이학석사 학위논문으로 제출함

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Abstract

Sample size calculation for cross over designs

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In clinical research, it is important to compute an appropriate sample size. A sufficient sample size helps researchers convince the success of and intended trial. However, it costs a lot of money to recruit many subjects. So it is critical role to compute the optimal sample size n. A cross-over design(CD) is widely used for comparing effect of various treatment groups, because it has advantages of removing unexpected cause by subjects and reducing the number of subjects as subjects experience every treatment. From these advantages, we often use the

CD to identify biomarkers that have differences by groups. While there are some method to determine the sample size for two groups in CDs, there is no method for comparing more than two groups. In this study, we propose a new method to compute the sample size of CDs with multiple groups as well as to be able to apply CDs with two treatment groups.

Keywords: Sample size calculation, Cross-over design, Optimal sample size

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Chapter 1

Introduction

Determining sample size plays an important role in clinical research [1]. In clinical research, a sufficient number of subjects is needed to convince the validity and the success of an intened trial. The larger the number of subjects, the greater the precision and power for a given study design to identity whether statitically meaningful differences among group effects exists. However, due to a high cost and difficulties of recruiting subjects for clinical trials, it goes important to calculate an appropriate sample size n.

The cross-over design (CD) is the experiment design in which every subject experiences treatments more than two. On the other hand, in parallel design, each subject is randomly assigned only one group. A

CD has a different thing that each subject receives a sequence. Receiving a sequence, it has the advantages of removing any factor caused by between subjects and reducing the number of subjects. Observed resonse values are correlated, because each subject involves in many groups. T- test and linear regeression model assume independent observation. Although wash-out period is sufficiently considered, we cannot ignore correlation among observations from a CD, and we cannot use t-test and linear regression model. From this reason, linear mixed effect models (LMMs) are commonly used to analyze the data from the CDs.

In CDs, determining the sample size means how many subjects are allocated in each seqeunce. There are many types of CDs for the given number of groups. For the computational convenience, we only consider the balanced case where every sequence has the sample size and the CDs based on orthogonal Latin squared design. Table 1 is the orthogonal design for the two treatments; Table 2 is the orthogonal design for the four treatments.

TABLE 1 The example of orthogonal cross-over design with two treatments.

	Period 1	**Period 2**
Sequence 1	A	B
Sequence 2	B	A

TABLE 2 The example of orthogonal cross-over design with four treatments.

	Period 1	**Period 2**	**Period 3**	**Period 4**
Sequence 1	A	B	C	D
Sequence 2	B	A	D	C
Sequence 3	C	D	A	B
Sequence 4	D	C	B	A
Sequence 5	A	D	B	C
Sequence 6	B	C	A	D
Sequence 7	C	B	D	A
Sequence 8	D	A	C	B
Sequence 9	A	C	D	B
Sequence 10	B	D	C	A
Sequence 11	C	A	B	D
Sequence 12	D	B	A	C

Wang et al. [1] proposed a method for determining sample size for CDs with two treatments. Wang et al. derived the sample size based on t test statistics. This t test is to verify mean difference between two groups. For this reason, their method is difficult to be applied to CDs with multiple groups. In this paper, by deriving the power function from contrast test, we compute the sample size for CD where there are more than two treatments.

Chapter 2

Methodology

2.1 Model

Before we state a linear mixed effect model for CDs, a few assumptions for CDs are following. There are T treatments and M sequences with T periods. Let n be the sample size needed for each sequence. Let $\mathbf{y}_{ij}$, $i = 1, \dots, n$, $j = 1, \dots, M$, denote a $(T \times 1)$ response vector at the M^{th} sequence, X_{ij} be the model matrix for the fixed effects at the M^{th} sequence, and Z_{ij} be the model matrix for the random effects at the M^{th} sequence. For the orthogonal CDs, the following LMM is able to be used [2, 3],

$$\mathbf{y}_{ij} = X_{ij}\boldsymbol{\beta} + \boldsymbol{Z_{ij}}\mathbf{s_{ij}} + \boldsymbol{\epsilon}_{ij}, \qquad (1)$$

where

$$\boldsymbol{y_i} = \begin{bmatrix} \boldsymbol{y_{i1}} \\ \vdots \\ \boldsymbol{y_{iM}} \end{bmatrix}, \boldsymbol{X_i} = \begin{bmatrix} \boldsymbol{X_{i1}} \\ \vdots \\ \boldsymbol{X_{iM}} \end{bmatrix}, \boldsymbol{Z_i} = \begin{bmatrix} \boldsymbol{Z_{i1}} \\ \vdots \\ \boldsymbol{Z_{iM}} \end{bmatrix}.$$

Note that X_i can be defined by the design. Fixed effects are defined with overall mean, treatment effects, and period effects, and reflect the structural feature of CD. If we analyze the data from the CD with two treatment given in Table 1, then X_i is defined as follows:

$$\boldsymbol{X_i} = \begin{pmatrix} \mathbf{1} & \mathbf{1} & \mathbf{1} \\ \mathbf{1} & \mathbf{0} & \mathbf{0} \\ \mathbf{1} & \mathbf{0} & \mathbf{1} \\ \mathbf{1} & \mathbf{1} & \mathbf{0} \end{pmatrix}.$$

Let $\boldsymbol{\beta} = (\mu, \tau_1, \dots, \tau_{T-1}, \gamma_1, \dots, \gamma_{T-1})^t$ be a parameter vector for fixed effects, where τ_t represents the difference of treatment effect between t^{th} and the last treatment, and γ_t does the difference of the period effect between t^{th} and the last period. $\boldsymbol{s_i}$ denotes a random subject effect and is defined by $\boldsymbol{s_i} = (s_{i1}, \dots, s_{iM})$. Next, we assume the distribution for the random components such as $\boldsymbol{s_i}$ and $\boldsymbol{\epsilon_i}$. We assume that s_{ij} is identically independent distributed (iid) as normal distribution with 0 mean and σ^2_{inter} variance. ϵ_{ijk} is iid as normal distribution with 0 mean and σ^2_{intra} variance. Here, the subscripts "inter" and "intra" mean the variations between-subject and the

variations within-subject, respectively. Moreover, response values are independent. There is no correlation among subjects. In summary,

$$\boldsymbol{s}_i \sim MVN(\mathbf{0}_M, \sigma^2_{inter} I_M) := MVN(\mathbf{0}_M, G),$$

$$\boldsymbol{\epsilon}_i \sim MVN(\mathbf{0}_{M\times T}, \sigma^2_{inter} I_{M\times T}) := MVN(\mathbf{0}_{M\times T}, R),$$

where "MVN" represents multivariate normal distribution, and I_k is the $k \times k$ identity matrix. Thus, the variance of $\boldsymbol{y}_i$ can be obtained as

$$Var(\boldsymbol{y}_i) = Z_i G Z_i^t + R = V_i.$$

To help understanding how to shape data, the Figure 1 is following. The subjects in the first sequence are sequentially treated as treatment A and B by turn, and the subjects in the second sequence do as treatment B and A by turn. $\boldsymbol{y}_{11}$ is the response vector obtained from the first subject in the first sequence. $\boldsymbol{y}_{12}$ is the response vector obtained from the first subject in the second sequence. Combining these two vectors, we have $\boldsymbol{y}_1$. Similarly, $\boldsymbol{y}_2, \ldots, \boldsymbol{y}_n$ are obtained. As we mentioned, the design matrix for fixed effects is defined as like in this **Figure 1**. The design matrix for random effects is also called random subject effects or random intercept effects. Each one vector in the matrix corresponds to each subject. Lastly, as we treated in the model description, the parameter vectors are defined.

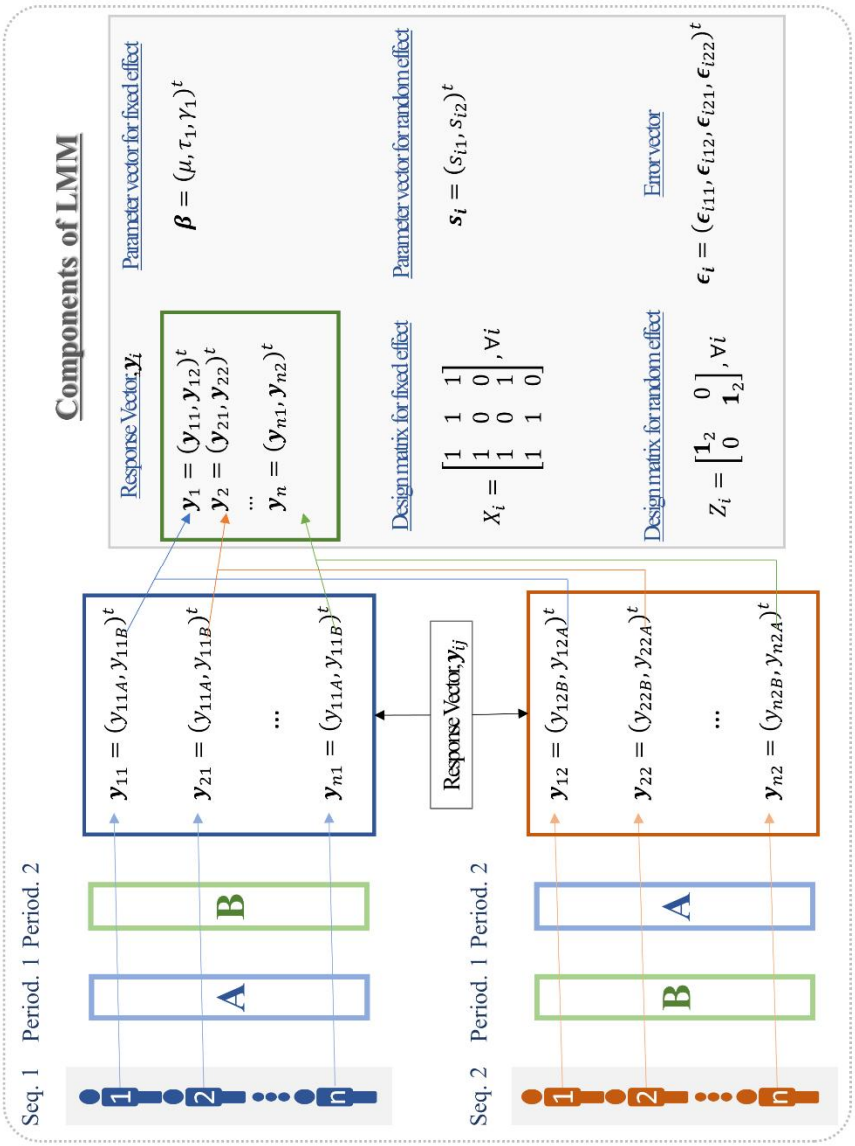

Figure 1. An example is for the orthogonal cross-over design with two treatments, and is for understanding how to get the model components.

2.2 Estimation

The parameters $\boldsymbol{\beta}$, σ^2_{inter}, σ^2_{intra} can be estimated by using restricted likelihood [4]. Restricted maximum likelihood estimation (REML) has two phase in which variance components, σ^2_{inter} and σ^2_{intra} are first estimated from the restricted likelihood, and then the fixed effect $\boldsymbol{\beta}$ are estimated via weighted least squared estimation using the variance matrix from the estimated σ^2_{inter} and σ^2_{intra}. These two phase are iterated until convergence.

The detail steps for estimating parameters of LMMs for CDs are following. The log-likelihood is given by

$$\boldsymbol{l = -\frac{1}{2} log\left(\sum_{i=1}^{n} \frac{2\pi}{|V_i|}\right) - \frac{1}{2}\sum_{i=1}^{n}(y_i - X_i\beta)^t V_i^{-1}(y_i - X_i\beta).} \qquad (2)$$

Differentiating l for a fixed V with respect to $\boldsymbol{\beta}$, we get

$$\frac{\partial l}{\partial \boldsymbol{\beta}} = \sum_{i=1}^{n}(X_i^t V_i^{-1} X_i)\boldsymbol{\beta} - \sum_{i=1}^{n}(X_i^t V_i^{-1} \boldsymbol{y}_i).$$

Solving the above equation with respect to 0, we have

$$\widetilde{\boldsymbol{\beta}} = (\sum_{i=1}^{n} X_i^t V_i^{-1} X_i)^{-1}(\sum_{i=1}^{n} X_i^t V_i^{-1} \boldsymbol{y}_i). \qquad (3)$$

Plugging-in $\widetilde{\boldsymbol{\beta}}$ into (2), we can obtain a profile log-likelihood,

$$l_p = -\frac{1}{2} log\left(\sum_{i=1}^{n} \frac{2\pi}{|V_i|}\right) - \frac{1}{2}\sum_{i=1}^{n}\left(\boldsymbol{y}_i - X_i\widetilde{\boldsymbol{\beta}}\right)^t V_i^{-1}\left(\boldsymbol{y}_i - X_i\widetilde{\boldsymbol{\beta}}\right). \qquad (4)$$

The restricted log-likelihood is the marginal log-likelihood for V, and is defined by

$$l_r = \log(\int L d\boldsymbol{\beta}). \tag{5}$$

The marginal likelihood for V can be derived by

$$\int (2\pi)^{-\frac{n}{2}} \prod_{i=1}^{n} |V_i|^{-\frac{1}{2}} \exp\left(\sum\nolimits_{i=1}^{n} (\boldsymbol{y}_i - X_i\boldsymbol{\beta})^t V_i^{-1} (\boldsymbol{y}_i - X_i\boldsymbol{\beta})\right) d\boldsymbol{\beta}.$$

Let $\mathrm{A_i} = X_i^t V_i^{-1} X_i$ and $\mathrm{B_i} = \mathrm{A_i^{-1}} \mathrm{X_i^t} V_i^{-1}$, then we can derive

$$(\boldsymbol{y}_i - X_i\boldsymbol{\beta})^t V_i^{-1} (\boldsymbol{y}_i - X_i\boldsymbol{\beta}) = \boldsymbol{\beta^t} X_i^t V_i^{-1} X_i \boldsymbol{\beta} - 2\boldsymbol{y_i^t} V_i^{-1} X_i \boldsymbol{\beta} + \boldsymbol{y}_i^t V_i^{-1} \boldsymbol{y}_i$$

$$= \boldsymbol{\beta}^t A_i \boldsymbol{\beta} - 2\boldsymbol{y}_i^t B_i^t A_i \boldsymbol{\beta} + \boldsymbol{y}_i^t B_i^t A_i B_i \boldsymbol{y_i} + \boldsymbol{y}_i^t V_i^{-1} \boldsymbol{y}_i - \boldsymbol{y}_i^t B_i^t A_i B_i \boldsymbol{y}_i$$

$$= (\boldsymbol{\beta} - B_i \boldsymbol{y}_i)^t A_i (\boldsymbol{\beta} - B_i \boldsymbol{y}_i) + \boldsymbol{y}_i^t V_i^{-1} \boldsymbol{y}_i - \boldsymbol{y}_i B_i^t A_i B_i \boldsymbol{y}_i$$

$\sum_{i=1}^{n} (\boldsymbol{y}_i - X_i \widetilde{\boldsymbol{\beta}})^t V_i^{-1} (\boldsymbol{y}_i - X_i \widetilde{\boldsymbol{\beta}})$ can be expressed as

$$\sum_{i=1}^{n} (\boldsymbol{y}_i - X_i \widetilde{\boldsymbol{\beta}})^t V_i^{-1} (\boldsymbol{y}_i - X_i \widetilde{\boldsymbol{\beta}})$$

$$= \sum_{i=1}^{n} \boldsymbol{y}_i^t V_i^{-1} \boldsymbol{y}_i - 2\left(\sum_{i=1}^{n} A_i B_i \boldsymbol{y}_i\right)^t \widetilde{\boldsymbol{\beta}} + \widetilde{\boldsymbol{\beta}}^{\boldsymbol{t}} \sum_{i=1}^{n} A_i \widetilde{\boldsymbol{\beta}}$$

$$= \sum_{i=1}^{n} \boldsymbol{y}_i^t V_i^{-1} \boldsymbol{y}_i - \left(\sum_{i=1}^{n} A_i B_i \boldsymbol{y}_i\right)^t \widetilde{\boldsymbol{\beta}}$$

$$= \sum_{i=1}^{n} \boldsymbol{y}_i^t V_i^{-1} \boldsymbol{y}_i - \left(\sum_{i=1}^{n} A_i B_i \boldsymbol{y}_i\right)^t \left(\sum_{i=1}^{n} A_i\right)^{-\mathbf{1}} \left(\sum_{i=1}^{n} A_i B_i \boldsymbol{y}_i\right)$$

$$= \sum_{i=1}^{n} \boldsymbol{y}_i^t V_i^{-1} \boldsymbol{y}_i - K$$

The marginal likelihood can be expressed as

$$\int l d\boldsymbol{\beta} = \prod_{i=1}^{n} (2\pi)^{-\frac{1}{2}} |V_i|^{-\frac{1}{2}} \exp\left\{-\frac{1}{2}\boldsymbol{y}_i^t (V_i^{-1} - B_i^t A_i B_i)\boldsymbol{y}_i\right\}$$

$$\times \int \prod_{i=1}^{n} exp\left(-\frac{1}{2}(\boldsymbol{\beta} - B_i\boldsymbol{y}_i)^t A_i (\boldsymbol{\beta} - B_i\boldsymbol{y}_i)\right) d\boldsymbol{\beta}$$

$$= \prod_{i=1}^{n} (2\pi)^{-\frac{1}{2}} |V_i|^{-\frac{1}{2}} \exp\left\{-\frac{1}{2}\boldsymbol{y}_i^t (V_i^{-1} - B_i^t A_i B_i)\boldsymbol{y}_i\right\}$$

$$\times \int (2\pi)^{-\frac{p}{2}} \left|\left(\sum\nolimits_{i=1}^{n} A_i\right)^{-1}\right|^{-\frac{1}{2}} e^F \, d\boldsymbol{\beta}$$

$$\times \exp\left\{-\frac{1}{2}\sum\nolimits_{i=1}^{n} \boldsymbol{y}_i B_i^t A_i B_i \boldsymbol{y}_i + \frac{1}{2}K\right\}$$

$$\times (2\pi)^{\frac{p}{2}} \left|\left(\sum\nolimits_{i=1}^{n} A_i\right)^{-1}\right|^{\frac{1}{2}}$$

$$= (2\pi)^{\frac{p}{2}} \left|\sum\nolimits_{i=1}^{n} A_i\right|^{-\frac{1}{2}} \prod_{i=1}^{n} (2\pi)^{-\frac{1}{2}} |V_i|^{-\frac{1}{2}} \exp\left\{-\frac{1}{2}\boldsymbol{y}_i^t V_i^{-1} \boldsymbol{y}_i + \frac{1}{2}K\right\}$$

$$= (2\pi)^{\frac{p}{2}} \left|\sum\nolimits_{i=1}^{n} A_i\right|^{-\frac{1}{2}} \prod_{i=1}^{n} (2\pi)^{-\frac{1}{2}} |V_i|^{-\frac{1}{2}} \mathrm{e}^{-\frac{1}{2}\sum_{i=1}^{n} (\boldsymbol{y}_i - X_i\tilde{\boldsymbol{\beta}})^t V_i^{-1} (\boldsymbol{y}_i - X_i\tilde{\boldsymbol{\beta}})}$$

$$= (2\pi)^{\frac{p}{2}} \left|\sum\nolimits_{i=1}^{n} A_i\right|^{-\frac{1}{2}} L_p,$$

where $F = \frac{1}{2}\left(\boldsymbol{\beta} - \tilde{\boldsymbol{\beta}}\right)^t \left(\sum_{i=1}^{n} A_i\right)\left(\boldsymbol{\beta} - \tilde{\boldsymbol{\beta}}\right)$. To sum up, restricted log-likelihood is obtained

$$\mathrm{l_r} = l_p - \frac{1}{2}\log\left|\sum_{i=1}^{n} X_i^t V_i^{-1} X_i\right| + \frac{p}{2}\log(2\pi). \qquad (6)$$

The variance components are estimated by maximizing (6). And then, the $\boldsymbol{\beta}$ is estimated as a form of weighted least square, $\widehat{\boldsymbol{\beta}} = \left(\sum_{i=1}^{n} X_i^t \hat{V}_i^{-1} X_i\right)^{-1}\left(\sum_{i=1}^{n} X_i^t \hat{V}_i^{-1} \boldsymbol{y}_i\right)$ where $\hat{V}_i$ is the variance matrix with the estimated $\sigma^2_{\mathrm{inter}}$ and $\sigma^2_{\mathrm{intra}}$. These two steps are iterated until the convergence.

2.3 Hypothesis and Power function

The goal of CDs is to verify that there exist treatment effects or not. That is we only are interest of $\tau_1, \dots, \tau_{T-1}$. The null and alternative hypotheses are given by

$$H_0: \tau_1 = \cdots = \tau_{T-1} = 0 \; v.s. H_1: Not\ H_1. \tag{7}$$

Wald test statistic is available in order to do test hypotheses (7). The Wald test statistic is given by

$$W = \left(C\widehat{\boldsymbol{\beta}}\right)^t \left[C\left(\sum_{i=1}^n X_i^t \widehat{V}_i X_i\right)^{-1} C^t\right]^{-1} \left(C\widehat{\boldsymbol{\beta}}\right) \tag{8}$$

where C is contrast matrix,

$$C = \begin{bmatrix} 0 & 1 & 0 & \cdots & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & \cdots & 0 & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & 1 & 0 & 0 & 0 \end{bmatrix}_{[(T-1)\times(1+2T-2)]}, \tag{9}$$

and (8) is distributed as chi-squared distribution with $rank(C)$ degrees of freedom. Using the contrast matrix C with rank $T-1$, hypotheses (7) are rewritten as

$$H_0: C\boldsymbol{\beta} = 0 \; v.s. H_1: Not\ H_1. \tag{10}$$

If $W \geq \chi_\alpha^2(T-1)$, then the null hypothesis in (7) is rejected. The power function can be obtained as calculating the probability of rejection area under the alternative. The expected value and variance of

$C\widehat{\boldsymbol{\beta}}$, under the alternative, can be obtained as $\mathrm{E}(C\widehat{\boldsymbol{\beta}}) = C\boldsymbol{\beta}$ and $Var(C\widehat{\boldsymbol{\beta}}) = C\left(\sum_{i=1}^{n} X_i^t \hat{V}_i X_i\right)^{-1} C^t$, respectively. Each $\boldsymbol{y}_i$ is distributed as Normal and $C\widehat{\boldsymbol{\beta}}$ is a linear combination for $\boldsymbol{y}_i$. To sum up, $C\widehat{\boldsymbol{\beta}}$ is distributed as $VN\left(C\boldsymbol{\beta}, C\left(\sum_{i=1}^{n} X_i^t \hat{V}_i X_i\right)^{-1} C^t\right)$. To get the distribution of Wald statistic under the alternative, the following theorem 2.1 is needed.

Theorem 2.1 Let y be distributed as $MVN(\mu, \Sigma)$, let A be a symmetric matrix of rank r, and let $\lambda = \mu^t A \mu$. Then $\boldsymbol{y}^t A \boldsymbol{y}$ is distributed as $\chi^2(r, \lambda)$ if and only if $A\Sigma$ is idempotent.

Using the midterm of (8), we have

$$\left[C\left(\sum_{i=1}^{n} X_i^t \hat{V}_i X_i\right)^{-1} C^t\right]^{-1} C\left(\sum_{i=1}^{n} X_i^t \hat{V}_i X_i\right)^{-1} C^t = I.$$

From the Theorem 2. 1, under the alternative, Wald statistic is distributed as $\chi^2(T-1, \lambda)$, where $\lambda = (C\boldsymbol{\beta})^t \left[C\left(\sum_{i=1}^{n} X_i^t \hat{V}_i X_i\right)^{-1} C^t\right]^{-1} (C\boldsymbol{\beta})$. Note that the λ depend on n, that is the λ is the function of n. Now, the power function for (10) is computed as

$$Power[\alpha, \lambda(n)] = P(W^* \geq \chi_\alpha^2(T-1) | H_1), \qquad (11)$$

where W^* is the random variable for W under the alternative. Note that power function (11) is the function of λ and α. λ impacts on the left hand side of probability in (11), and α does on the right hand side of probability. For the simplicity, equation (11) is rewritten as

$$Power[\alpha, \lambda(n)] = 1 - \boldsymbol{\chi}^{2,T-1}(\chi^2_\alpha(T-1)|\lambda(n)), \qquad (12)$$

where $\boldsymbol{\chi}^2_\alpha(\cdot\,|\lambda)$ is the cumulative probability function for a non-central chi-square distribution with $(T-1)$ degrees of freedom and non central parameter λ.

2.4 Sample size calculation for cross-over designs

To compute a sample size, we first need to decide a significance level α, and desired power, and the effect sizes $\tau_1, \dots, \tau_{T-1}$ from which the non-central parameter λ can be computed. We can get the sample size for each sequence by solving the following equation (13) numerically.

$$Desired\ power = argmin_n(Power[\alpha, \lambda(n)])\ for some fixed\ \alpha. \qquad (13)$$

Chapter 3

Examples

In this section, we illustrate our method via two examples. Each sample size is calculated at the significance level $\alpha = 0.05$ and the desired power 0.8. Sample size depends on the certain factors such as effect size, common variance, and the within-subject variation. For some fixed common variance, the greater effect size, the less sample is needed. A variance of response value is given as

$$Var(y_{ijk}) = \sigma_{inter}^2 + \sigma_{intra}^2 = \sigma^2. \quad (14)$$

A variance of response value is explained by the inter-subject variation and the intra-subject variation. For verifying which factors impact on the sample size, sample size is calculated while changing effect sizes,

common variance, and contribution rate of within-subject variation. In addition, in order to prepare for unexpected situation, sample size considered dropout rate as 20% is also computed.

3.1 Sample size calculation for cross-over design with three treatments

The first example is to calculate sample size for the cross-over design with three treatments. The sample size n for each sequence is first computed. To prepare unexpected situation, the 20% dropout rate is considered, and $6n/0.8$ subjects will be recruited. Finally, subjects are randomly assigned to each sequence by $n/0.8$ individuals. Fixing the common variance as $\sigma^2 = 10^2$, the effect sizes are considered as $\boldsymbol{\tau}^{(1)} = (0, 2.5, 5)^t$, $\boldsymbol{\tau}^{(2)} = (0, 2, 4)^t$, $\boldsymbol{\tau}^{(3)} = (0, 1.5, 3)^t$, and $\boldsymbol{\tau}^{(4)} = (0, 1, 2)^t$. In order to know the role of within-subject variation, the contributions of within-subject variation are treated as 30%, 50%, and 70% for the every effect size $\boldsymbol{\tau}^{(1)}$, $\boldsymbol{\tau}^{(2)}$, $\boldsymbol{\tau}^{(3)}$, and $\boldsymbol{\tau}^{(4)}$. To verify how effect sizes impact on the sample size, from $\boldsymbol{\tau}^{(1)}$ to $\boldsymbol{\tau}^{(4)}$, the effect sizes decrease for the fixed common variance. The calculated sample sizes are given in Table 3 where nd is the sample size after reflecting the 20% drop-out rate.

TABLE 3 The results of sample size calculation for cross-over design with three treatments for each sequence.

Effect size	Contribution of within-subject	Sample size(n)	Sample size(nd)
$\tau^{(1)}$	30%	4	5
	50%	7	9
	70%	9	12
$\tau^{(2)}$	30%	7	9
	50%	11	14
	70%	13	17
$\tau^{(3)}$	30%	11	14
	50%	18	23
	70%	25	32
$\tau^{(4)}$	30%	25	32
	50%	41	52
	70%	57	72

There is the trend that the sample size increases as the contribution of within-subject variation increases. When the effect size is less than 10% for common stand deviation, large sample sizes are needed relatively.

3.2 Sample size calculation for cross-over design with four treatments

The second example is to calculate sample size for the cross-over design with four treatments. The sample size n for each sequence is first computed. To prepare unexpected situation, the 20% dropout rate is considered, and $12n/0.8$ subjects will be recruited. Finally, subjects are randomly assigned to each sequence by $n/0.8$ individuals. Fixing the common variance as $\sigma^2 = 10^2$, the effect sizes are considered as $\boldsymbol{\tau}^{(1)} = (0, 2.5, 5, 7.5)^t$, $\boldsymbol{\tau}^{(2)} = (0, 2, 4, 6)^t$, $\boldsymbol{\tau}^{(3)} = (0, 1.5, 3, 4.5)^t$ and $\boldsymbol{\tau}^{(4)} = (0, 1, 2, 3)^t$. In order to know the role of within-subject variation, the contributions of within-subject variation are treated as 30%, 50%, and 70% for the every effect size $\boldsymbol{\tau}^{(1)}$, $\boldsymbol{\tau}^{(2)}$, $\boldsymbol{\tau}^{(3)}$, and $\boldsymbol{\tau}^{(4)}$. To verify how effect sizes impact on the sample size, from $\boldsymbol{\tau}^{(1)}$ to $\boldsymbol{\tau}^{(4)}$, the effect sizes decrease for the fixed common variance. There is the trend that the sample size increases as the contribution of within-subject variation increases.

TABLE 4 The results of sample size calculation for cross-over design with four treatments for each sequence.

Effect size	Contribution of within-subject	Sample size(n)	Sample size(nd)
$\tau^{(1)}$	30%	1	2
	50%	2	3
	70%	2	3
$\tau^{(2)}$	30%	2	3
	50%	3	4
	70%	3	4
$\tau^{(3)}$	30%	3	4
	50%	4	5
	70%	5	7
$\tau^{(4)}$	30%	5	7
	50%	9	12
	70%	12	15

3.3 Results

There is the trend that the sample size increases as the contribution of within-subject variation increases, that is as the contribution of between-subject variation decreases. The meaning of reducing between-subject variation is the loss of information from a subject. The more larger sample size which is computed can be thought as making up for the loss of information from subjects.

As the number of treatment increases, there is the trend that the power is overestimated. It is because the possibility of rejecting the null hypothesis is higher than the cross-over design with three treatments.

Chapter 4

Discussion

Determining the sample size is important in clinical trial. In clinical trial, a sufficient number of subjects has relationship with convincing the validity and the success of an intened trial. In the statistical view, if the sample size increases, the power also increases. However, due to a high cost and difficulties of recruiting subjects for clinical trials, determining sample size n is necessary. Wang et al. [1] proposed the method of determining the sample size for cross-over design. But their method have limiation to be applied to cross-over design with multiple treatments. In this paper, extending the Wang's method, we proposed a new method to be applied to cross-over design with multiple treatments. Our method have a few advantages. The first

one is that covariates can be considered as a little bit correcting the model (1). The second one is that our method can be applied to non-orthogonal cross-over design as well as orthogonal cross-over design. To illustrate our method, we computed the sample size with our several exmple. The first example is about the cross-over design with three treatments. The secon example is on the cross-over design with four treatments. In each example, the sample size is calculated, changing the contribution of within-subject variation and effect sizes. The sample size computed increases as the contribution of within-subject variation increases, that is as the contribution of between-subject variation decreases. The meaning of reducing between-subject variation is the loss of information from a subject. The sample size which is computed largely can be thought as making up for the loss of information from subjects.

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초 록

임상 실험 연구에서 적당한 표본크기를 계산하는 것은 중요하다. 표본 크기가 충분할 때 연구자들은 의도된 실험의 결과를 확신할 수 있기 때문이다. 하지만 임상 실험에 참가하는 피험자를 모집하는 것 자체도 어렵고, 비용도 만만치 않다. 이러한 문제 때문에 최적의 표본크기를 산정하는 것은 필수이다.

교차 설계는 다 집단을 비교하는 실험에서 많이 이용된다. 교차 설계는 각 피험자가 모든 처리를 경험하기 때문에, 피험자가 가지고 있는 처리효과외의 요인들을 제거할 수 있기 때문이다. 또한, 각 기간 사이에 충분한 이전 처리 효과가 제거될 시간을 줌으로써, 각 처리 군마다 필요한 피험자를 한 명으로부터 모두 확보되는 효과를 가져주고, 결국 총 표본의 크기를 감소시킬 수 있는 장점도 있다.

교차 설계의 표본 크기를 계산하는 방법에 대한 연구는 모두가 집단이 2 개인 경우에 한정되어 있다. 그 중 t-test 기반 표본 크기 산출법이 널리 이용되고 있다. T-test 기반이기 때문에 집단이 3 개 이상이 될 경우부터는 적용하기 어려운 문제가 있다. 본 연구에서는 집단이 2 개인 경우에도 계산이 가능하고, 보다 많은

집단이 있을 때에도 표본의 크기를 계산할 수 있는 방법을 제안한다.

주요어: 교차 설계, 표본 크기 계산법, 최적 표본 크기

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