

**RELATIVE EFFICIENCY OF ADJUSTED AND
UNADJUSTED ANALYSES
WHEN BASELINE DATA ARE PARTIALLY MISSING**

**RELATIVE EFFICIENCY OF ADJUSTED AND
UNADJUSTED ANALYSES
WHEN BASELINE DATA ARE PARTIALLY MISSING**

By

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Abstract

Many medical studies are performed to investigate the effectiveness of new treatments (such as new drugs, new surgery) versus traditional (or placebo) treatments. In many cases, researchers measure a continuous variable at baseline and again as an outcome assessed at follow up. The baseline measurement usually has strong relationship with post treatment measurement. Consequently, the ANCOVA model using baseline as covariate may provide more powerful and precise results than the ANOVA model.

However, most epidemiologic studies will encounter the problem of missing covariate data. As a result, the patients with missing baseline measurements will be excluded from the data analysis. Hence, there exists a tradeoff between the ANOVA with full data set and the ANCOVA with partial data set.

This study focuses on the variance of the estimator of treatment means difference. In practical situation, the standard error of the estimator obtained from the ANCOVA model with partially missing baseline relative to the standard error obtained from the ANOVA with full data relies on the correlation between baseline and follow-up outcome, the proportion of the missing baseline, and the difference of the group means on the

baseline. In moderate sample size studies, it is also affected by the sample size.

The theoretically required minimum correlations for the ANCOVA model were calculated to obtain the same precision with the ANOVA model assuming the missing proportion, sample size and difference of group means on covariate are available. The minimum correlation can be obtained through checking the reference table or figures.

The figures of asymptotic relative efficiencies provide the asymptotic variance and the length of the confidence intervals of the estimated difference obtained from the ANCOVA model relative to the ANOVA model for all the range of the correlation between baseline and follow up.

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Chapter 1

Introduction

1.1 Project Overview

The main interest of the present project is to compare the precision of the standard Analysis of Variance (ANOVA) model with full data to the Analysis of Covariance (ANCOVA) model with partially missing baseline measurements (covariate).

In clinical trials, researchers often apply the ANOVA model on post-treatment measurements of the primary outcome (dependent variable) to investigate the effectiveness of new treatment (such as new drugs, new surgery) versus standard (or placebo) treatment. If pre-treatment measurements (baseline) are also available, the ANCOVA model using baseline as covariate can provide more powerful and precise results than the ANOVA model. However, most epidemiologic studies will encounter the problem of missing covariate data. In addition, software packages typically used to analyze data will delete any cases with a missing covariate to perform a complete case analysis [2]. As a result, the patients with missing baseline measurements will be excluded from the data analysis. The analysis solely based on partial sample size will generate

lower power than the analysis based on the complete data. Hence, there exists a tradeoff between the ANOVA with full data set and the ANCOVA with partial data set. On one hand, the ANCOVA model generally provides greater precision and eliminates the bias given the baseline measurements if there exists a baseline (covariate) which is highly correlated with the dependent variable in the model. On the other hand, it may decrease the precision and power because analysis is only based on partial data set.

The subsequent part of this chapter will touch on the motivation of this study and discuss the application of Pre-post test Design in Clinical Trial. Then a randomized controlled trial (RCT) will be demonstrated. The last part of this chapter introduces the main application and developing history of the ANCOVA model.

Chapter 2 introduces some related formulas and assumptions about the ANOVA and ANCOVA model. It also derives formulas about the relative precision of treatment effects between the standard ANOVA model and the ANCOVA with partially missing data. At the end of the chapter, some reference tables and figures are provided to help medical researchers make a decision between the ANOVA and the ANCOVA models in practice.

Chapter 3 tests the theoretical results from chapter 2 on the examples of MOMET data and Quality of Life data for the knee surgery clinical trial. Both the ANOVA and the ANCOVA models are applied to the two data sets and the results generated by the statistical software (SAS) are compared. Then, it compares the results based on statistical

computation with results from reference tables and figures.

Chapter 4 discusses the effect of sample size and mean difference of covariate on minimum required correlation. The improvements of this study over previous studies are demonstrated based on the calculation results.

Chapter 5 contains conclusions based on the theoretical and practical results, summarizes several key points in this study.

1.2 Motivation of This Study

One of the principal applications of the ANCOVA model is to increase precision in randomized experiments. If a covariate (baseline), which has strong correlated relationship with the dependent variable (post-treatment measurement), exists in the model, it will greatly increase the model precision. In other words, it can reduce the sample size of the trial under the specified conditions (such as, statistical power, significance level and minimum important difference).

On the other hand, it does not always benefit from using the ANCOVA model. If the baseline missing proportion is high, the relationship between baseline and post-treatment measurement is weak (not a good predictor), or the cost of mining baseline data is very high, it is less desirable to choose the ANCOVA procedure with baseline measurement as covariate. This study focuses on the effects of the first two conditions (baseline missing proportion and correlation between baseline and post-treatment

measurements) on the precision of estimate of treatments difference.

In reality, there are lots of reasons for missing baseline data, such as patients' refusal or inability to answer questions, technical difficulty of examination, and budget restriction of time and money. In this study, all the discussions are based on the situation of missing baseline at random. Accordingly, the clinical research often bears the problem of randomly missing baseline data and researchers need to assess tradeoff between the two models if both moderate correlation and a certain amounts of randomly missing baseline data exist at the same time.

The main purpose of this study is to provide a practical reference (tables and figures) to choose the more precise statistical procedure between the standard ANOVA and the ANCOVA with partially missing baseline under different situations, such as sample size, proportion of missing baseline, the mean difference of covariate, and correlation coefficient between the baseline and the dependent variable. Based on the knowledge from other clinical trials or previous experience, we may be able to estimate the value of the proportion of missing baseline or correlation coefficient for a particular kind of clinical trials. If the baseline missing proportion is available, we can obtain the minimum required correlation to achieve more precise estimate using the ANOCVA procedure through checking the reference tables and figures. On the other hand, if the correlation coefficient is available, we can find the maximum missing proportion and the ANCOVA model can provide more precise estimate.

1.3 Introduction of The Knee Surgery Trial

Background

A torn meniscus is one of most common injury of the knee joint [10]. The surgery procedures to repair the meniscus include open and arthroscopic techniques using sutures and bioabsorbable implants [5]. The technique of suturing is standard and well-known surgery procedure. Its effectiveness has already been proved. The technique of Bioabsorbable implants is more recently developed. Advantages of bioabsorbable implants consist of a less technically demanding repair and a lower risk of neurovascular injury [5]. The purpose of this clinical trial is to test whether the new technique of bioabsorbable implants has same effectiveness with the standard surgery of suturing to repair meniscal injury.

Study Design

This is a parallel-group, randomized, single center clinical trial with five orthopaedic surgeons. 100 patients undergoing meniscal injury were randomly assigned into two intervention groups with 51 patients in bioabsorbable implants group and 49 patients in inside-out suturing group. The sample size is calculated based on 80% power to detect a 15% risk difference in favor of sutures group with 5% type I error [5].

Outcome Measures

The outcomes include retear rate, disease-specific quality of life measurement with the Anterior Cruciate Ligament Quality of Life Outcome Measure (ACL-QOL) [9] and Western Ontario Meniscal Evaluation Tool (WOMET) [8]. The discussion in this

study is solely based on WOMET and ACL-QOL data. The two data sets both involve measuring a continuous variable at baseline and again as an outcome assessed at 1-year follow up. Since the baseline is measured before the treatments are administered, the treatments do not affect the baseline. In addition, the partially missing baseline at random occurred in both data sets. All of these features above satisfy the requests of this study.

1.4 Introduction of ANCOVA

The method of analysis of covariance (ANCOVA) was introduced by Fisher (1932) in *Statistical Methods for Research Workers*. This technique is the integration of Analysis of Variance (ANOVA) and the analysis of regression model. It is often used to test the null hypothesis that the sample means from different treatment populations are same. Its application comprises (1) *To increase the precision in randomized experiments;* (2) *To adjust for sources of bias in observational studies;* (3) *To throw light on the nature of treatment effects in randomized experiments;* (4) *To study regressions in multiple classifications* [6]. In general, the main advantage of the ANCOVA over the ANOVA model is to reduce the variability and achieve greater precision. However, if the treatments also affect the covariate, the ANCOVA procedure will not only reduce the confounding but also eliminate a part of the treatment effect.

This study explores the relative precision of the estimator of the treatment effect between the ANCOVA and the ANOVA models. Most medical studies come across the problem of missing covariate data (baseline) and exist difference between group means in covariate. Therefore, the practical precision of the difference in the treatment effects not

only depends upon correlation between covariate and dependent variable and sample size, but also depends upon baseline missing proportion and the difference in group means in covariate. The detailed situation will be discussed in Chapter 2.

1.5 The Use of Baseline in Clinical Trial

The medical baseline is the initial information gathered before the interventions are applied on the patients. Baseline measurement is used as the reference point to determine the patients' response to the treatment. In many randomized trials researcher measure a continuous variable at baseline and again as an outcome assessed at follow up. The baseline measurement usually has strong relationship with post treatment measurement. Consequently, it is often used to be covariate in the model to increase the precision and reduce the bias.

There are several possible approaches for how such data can be entered into the statistical analysis of such trials. One of them can apply the ANOVA model on the gain score ($Y - X$) or the fraction gain score ($\frac{Y-X}{Y}$) between post-treatment and baseline. Both approaches have acceptable power when the correlation between baseline and dependent variable is high. When the correlation is low, the two approaches are not desirable. The statistical power based on these two approaches is even much lower than the ANOVA approach with low correlation [3].

Another common approach is the randomized block design, in which the patients are first partitioned into subgroups based on the range of the baseline. This method can

achieve the desired precision of estimating the treatment effects. If the relation between dependent variable and covariate variable is linear, the blocking and the ANCOVA are about equally effective [11]. The drawback of the method is that a part of the information of baseline is lost by using blocks because the continuous baseline is converted to a categorical variable and the individual baseline values are replaced by the common values of the blocks. This study elaborates on the ANCOVA approach using baseline as covariate.

Chapter 2

Methodology

2.1 Analysis of Variance Model

Introduction

The Analysis of Variance (ANOVA) model is a versatile statistical tool to study the relation between a dependent variable and one or more independent variables. Like regression models, it is appropriate for both observational data and experimental data. Further more, the independent variable in the ANOVA model may be qualitative [7]. It can be categorized into single-factor and multifactor, or fixed effects and random effects based on the different classification criterion. It is generally employed in comparison of several population means. For the special case (comparison of two population means), it is equivalent to a two-sample T test. The discussion in this study is solely based on the fixed effects single-factor ANOVA model.

Fixed Effects Single-Factor ANOVA Model

There are two completely equivalent formulations of the fixed effects single-factor

ANOVA model. One is the cell means model, given by

$$Y_{ij} = \mu_i + \varepsilon_{ij} \quad (2.1)$$

The alternative one is the factor effects model. It is identical with the first one except using the different parameter. The second formulation is used in this study since it is expressed in terms of factor effects (treatments effects) and overall mean. It is given as follows:

$$Y_{ij} = \mu + \tau_i + \varepsilon_{ij} \quad (2.2)$$

Where $i = 1, 2, \dots, f$ and $j = 1, 2, \dots, n_i$.

μ = grand mean of treatment population,

τ_i = affect of treatment i,

ε_{ij} = experiment error.

The Assumptions and Features of the Model

The grand mean μ is constant for all measurements of all treatment distributions. The treatment effect τ_i is constant for all measurements only within population i and the sum of the treatment effects is equal to Zero. The experimental errors ε_{ij} represent all the uncontrolled sources of variation and are unique for every experimental unit. They are assumed to be independent and distributed as $N(0, \sigma_y^2)$. Y_{ij} are also independent $N(\mu_i, \sigma_y^2)$ because they just are linear functions of ε_{ij} .

Variance of Treatment Effects in ANOVA

Based on the factor effects model (2.2), the i th sample mean and total sample mean can be expressed as below:

$$\bar{Y}_i = \mu. + \tau_i + \bar{\varepsilon}_i.$$

$$\bar{Y}_{..} = \mu. + \bar{\varepsilon}_{..}$$

The statistic $(\bar{Y}_i - \bar{Y}_{..})$ is the difference between the i th sample mean and total sample mean which is an unbiased estimator of the i th treatment effect, i.e. $\hat{\tau}_i = (\bar{Y}_i - \bar{Y}_{..})$. It is given by

$$(\bar{Y}_i - \bar{Y}_{..}) = (\mu. + \tau_i + \bar{\varepsilon}_i - \mu. - \bar{\varepsilon}_{..}) = \tau_i + (\bar{\varepsilon}_i - \bar{\varepsilon}_{..})$$

$$E(\bar{Y}_i - \bar{Y}_{..}) = E(\tau_i) + E(\bar{\varepsilon}_i - \bar{\varepsilon}_{..}) = \tau_i$$

As a result, the treatment means difference $(\bar{Y}_i - \bar{Y}_j)$ is an unbiased estimator of unadjusted difference $(D = \tau_i - \tau_j)$ of treatment effects, i.e. $\hat{D} = \bar{Y}_i - \bar{Y}_j$. This study focuses upon the variance of the difference of treatment effects.

Analysis of Variance

The total variability without using any information can be decomposed into two components: deviation of estimated factor level mean around overall mean and deviation around estimated factor level mean. It is given by

$$Y_{ij} - \bar{Y}_{..} = \bar{Y}_i - \bar{Y}_{..} + Y_{ij} - \bar{Y}_i.$$

If squaring and summing them on both sides, we can obtain the following:

$$\sum_i \sum_j (Y_{ij} - \bar{Y}_{..})^2 = \sum_i n_i (\bar{Y}_{i.} - \bar{Y}_{..})^2 + \sum_i \sum_j (Y_{ij} - \bar{Y}_{i.})^2 \quad (2.3)$$

The term on the left hand side is denoted by SSTO for total sum of squares. The first term on the right hand side is denoted by SSTR for treatment sum of squares. The second term on the right is denoted by SSE for error sum of squares. The formula (2.3) can be written equivalently as:

$$SSTO_Y = SSTR_Y + SSE_Y \quad (2.4)$$

Table 2.1: Analysis of Variance Table:

Source of Variation	SS	DF	Mean of Square	E{MS}
Between Treatments	SSTR	$f - 1$	$MSTR = \frac{SSTR}{f-1}$	$\sigma_Y^2 + \frac{\sum n_i (\mu_i - \mu)^2}{f-1}$
Within Treatments (Error)	SSE	$N - f$	$MSE = \frac{SSE}{N-f}$	σ_Y^2
Total	SSTO	$N - 1$		

The variance of $\bar{Y}_{i.}$ is given by

$$\sigma_{\{\bar{Y}_{i.}\}}^2 = \frac{\sigma_y^2}{n_i}$$

As we know, $(\bar{Y}_{i.} - \bar{Y}_{j.})$ is an unbiased estimate of treatment difference $D = \tau_i - \tau_j$ and

$\bar{Y}_{i.}$ and $\bar{Y}_{j.}$ are independent. Therefore, the variance of \hat{D} is given as follows:

$$\sigma_{\hat{D}}^2 = \sigma_{\{\bar{Y}_{i.} - \bar{Y}_{j.}\}}^2 = \sigma_y^2 \left(\frac{1}{n_i} + \frac{1}{n_j} \right) \quad (2.5)$$

For simplicity, we assume that there are only two treatments groups (control group and treatment group), i.e., $f = 2$ and the two groups have same size n (i.e. $n_1 = n_2 = \frac{N}{2}$) of the experimental units. The simplified form of formulation (2.5) is defined by

$$\sigma_{\hat{D}}^2 = \frac{4}{N} \sigma_y^2 \quad (2.6)$$

2.2 Analysis of Covariance Model

Assumptions

The Analysis of Covariance is a technique that combines features of the analysis of variance and regression. There are some restrictions and assumptions under the ANCOVA model. They are given as:

1. Response variable has common variance for every treatment groups,
2. The treatments do not affect the covariates, and
3. The regression slopes of all the treatment groups are same and constant.

Fixed Effects Single-Factor ANCOVA Model

The discussion in this study is based on the fixed effects single-factor ANCOVA model. The model is given as following:

$$Y_{ij} = \mu + \tau_i + \beta X_{ij} + \varepsilon_{ij} \quad (2.7)$$

The intercept $(\mu + \tau_i)$ in this model is the estimated value of Y_{ij} at covariate (baseline

measurement) $X = 0$. τ_i is the treatment effect of the i th group. Because the baseline value of 0 may not be meaningful and the predicted value of Y_{ij} at baseline = 0 may not be of interest, the ANCOVA model is often expressed as:

$$Y_{ij} = \mu + \tau_i + \beta(X_{ij} - \bar{X}_{..}) + \varepsilon_{ij} \quad (2.8)$$

where $i = 1, 2, \dots, f$ and $j = 1, 2, \dots, n_i$.

μ = Grand mean of treatment population

τ_i = fixed treatment effect

β = Regression coefficient of the relation between X and Y

X_{ij} = Covariate

ε_{ij} = Experimental error.

In this model, baseline in deviation form $X_{ij} - \bar{X}_{..}$ is used as covariate. The grand mean μ is constant for all measurements of all treatment distributions. The treatment effect τ_i is constant for all measurements within population i with restriction $\sum \tau_i = 0$. Experimental error ε_{ij} represents the uncontrolled sources of variation. They are assumed to be independent and distributed as $N(0, \sigma_\varepsilon^2)$. It follows that Y_{ij} are also independent and normally distributed because Y_{ij} is a linear function of the only random variable ε_{ij} . They are given as following:

$$E\{Y_{ij}\} = \mu + \tau_i + \beta(X_{ij} - \bar{X}_{..})$$

$$\sigma^2 \{Y_{ij}\} = \sigma^2$$

Approach of Least-squares Method

The estimators of the parameters in the model (2.8) can be obtained by Least-squares method. The sum of squared error is defined by

$$\sum_i \sum_j \hat{\varepsilon}_{ij}^2 = \sum_i \sum_j \left[Y_{ij} - \hat{\mu} + \hat{\tau}_i + \hat{\beta}(X_{ij} - \bar{X}_{..}) \right]^2 \quad (2.9)$$

Taking the partial derivative of the formula above with respect to the three parameters μ , τ_i , and β , respectively and setting the results to zero yield three normal equations. Solving the three normal equations gives the least-squares estimators for the three parameters which are given by

$$\hat{\mu} = \bar{Y}_{..}$$

$$\hat{\tau}_i = \bar{Y}_i - \bar{Y}_{..} - \hat{\beta}(\bar{X}_i - \bar{X}_{..})$$

$$\hat{\beta} = \frac{SPE_{XY}}{SSE_X}$$

Where SSE_X and SPE_{XY} represent the Error Sum of Square for the variable X and the Error Sum of Product for the variables X and Y.

The error variation in the ANCOVA model is just the minimum sum of squared error, which can be obtained by replacing the parameters in expression (2.9) by their least-squares estimators. After the replacement, the error variation in the ANCOVA model

is given as

$$SSE_Y^{adj} = \text{Minimum} \sum_i \sum_j \hat{\varepsilon}_{ij}^2 = SSE_Y - \frac{(SPE)^2}{SSE_X}$$

Where SSE_Y^{adj} represent the Error Sum of Square for the variable Y after the regression on covariate variable X.

Alternative Approach

The analysis of variance (ANOVA) model only treats between-group variance as systematic (nonzero) variance and the regression model only treats variance accounted by regression as systematic. The analysis of covariance (ANCOVA) model treats both between-groups and regression variance as systematic components. As a result, the adjusted Total Sum of Square ($SSTO_Y^{adj}$) and adjusted Error Sum of Square (SSE_Y^{adj}) in the ANCOVA model can be represented by the remaining part of the original SSE and SSTO after the regression on covariate variable X. The adjusted SSE and SSTO can be given as following:

$$SSTO_Y^{adj} = SSTO_Y - \frac{(SPTO)^2}{SSTO_X}$$

$$SSE_Y^{adj} = SSE_Y - \frac{(SPE)^2}{SSE_X}$$

In the two formulas above, the second terms on the right hand side represent the regression part of SSTO and SSE on covariate X, respectively. As a consequence, for a given set of data, total error of the ANCOVA model is smaller than the ANOVA model

because some of the within-group variability will be removed by the regression of the dependent variable on covariate. However, error per unit (MSE) may be not since it also lost one degree of freedom for estimating the parameter of regression coefficient. Please see the ANCOVA table below for details.

Table 2.2: Analysis of Covariance Table

Source of Variation	X	XY	Y	DF
Total	$SSTO_X$	$SPTO_{YX}$	$SSTO_Y$	$N - 1$
Treatments	$SSTR_X$	$SPTR_{XY}$	$SSTR_Y$	$f - 1$
Errors	SSE_X	SPE_{XY}	SSE_Y	$N - f$
Errors Reduction			$\frac{SPE_{XY}^2}{SSE_X}$	1
Adjusted Errors			$SSE_Y^{adj} = SSE_Y - \frac{SPE_{XY}^2}{SSE_X}$	$N - f - 1$
Adjusted Treatments			$SSTR_Y^{adj} = SSTR_Y + \frac{SPE_{XY}^2}{SSE_X}$	$f - 1$
Test Statistics	$F = \frac{MSE^{adj}}{MSTR^{adj}}$ follows $F(f - 1, N - f - 1)$			

After the adjustment, the nonpredictable or error variation in the ANCOVA model is given by

$$SSE_Y^{adj} = SSE_Y - \frac{SPE_{XY}^2}{SSE_X} = (1 - r^2) SSE_Y \quad (2.10)$$

Where r is the pooled sample within-group correlation coefficient between X and Y.

Consequently, the predictable variation in the ANCOVA model is given as follows:

$$SSTR^{adj} = SSTR_Y + \frac{SPE_{XY}^2}{SSE_X}$$

The second term of the right hand side of the expression above represents the reduced

variation due to adjustment. Note that there is one less degree of freedom for SSE_Y^{adj} than SSE_Y because one degree of freedom is lost due to estimating the regression coefficient β of the covariate. Therefore, MSE_Y^{adj} is given as following [4]:

$$MSE_Y^{adj} = \frac{SSE_Y}{N-f-1}(1-r^2) = MSE_Y(1-r^2)\frac{N-f}{N-f-1} \quad (2.11)$$

Where $N =$ Sample size of the experimental units

$f =$ The number of treatment groups

Hence, the experimental error variance for the ANCOVA model is given as [4]:

$$\sigma_{adj}^2 = \sigma_Y^2(1-\rho^2)\frac{N-f}{N-f-1} \quad (2.12)$$

Where ρ is the population within-group correlation coefficient between X and Y.

Hence, the gain in precision of model variance by using the ANCOVA model rather than using ANOVA model primarily depends on the correlation between dependent variable and covariate within treatments.

Adjusted Treatment Means

An adjusted mean is the mean of dependent variable scores that would be expected or predicted for a specified group of subjects if the covariate mean of this group is same as the grand covariate mean. Since there may be differences of group means on covariate and the dependent variable is related to the covariate, researchers are often interested in finding out whether one dependent mean is higher than another one because of the difference on covariate of different groups. This confounder can be eliminated by using adjusted mean because the covariance adjustment can remove all the bias under the right

conditions. The formula of the adjusted mean is defined by

$$\bar{Y}_{i.}^{adj} = \bar{Y}_{i.} - \hat{\beta}(\bar{X}_{i.} - \bar{X}_{..}) \quad (2.13)$$

In view of regression analysis, these adjusted treatment means are the estimates of the intercepts $(\mu + \tau_i)$ of the treatment lines. Its variance of $\bar{Y}_{i.}^{adj}$ can be given as [4]

$$\sigma_{\{\bar{Y}_{i.}^{adj}\}}^2 = \sigma_{adj}^2 \left[\frac{1}{n_i} + \frac{(\bar{X}_{i.} - \bar{X}_{..})^2}{SSE_X} \right] \quad (2.14)$$

From the ANCOVA model (2.8), we can obtain sample mean of group i and grand mean without adjustment. They can be expressed as following:

$$\bar{Y}_{i.} = \mu + \tau_i + \beta(\bar{X}_{i.} - \bar{X}_{..}) + \bar{\varepsilon}_{i.}$$

$$\bar{Y}_{..} = \mu + \bar{\varepsilon}_{..}$$

Subtracting the formula of grand mean from the formula of group mean above, we can obtain:

$$\bar{Y}_{i.} - \beta(\bar{X}_{i.} - \bar{X}_{..}) - \bar{Y}_{..} = \tau_i + (\bar{\varepsilon}_{i.} - \bar{\varepsilon}_{..}) \Rightarrow \bar{Y}_{i.}^{adj} - \bar{Y}_{..} = \tau_i + (\bar{\varepsilon}_{i.} - \bar{\varepsilon}_{..})$$

$$E(\bar{Y}_{i.}^{adj} - \bar{Y}_{..}) = E(\tau_i) + E(\bar{\varepsilon}_{i.} - \bar{\varepsilon}_{..}) = \tau_i$$

Therefore, the statistic $(\bar{Y}_{i.}^{adj} - \bar{Y}_{..})$ is an unbiased estimator of the ith treatment effect, i.e.

$\hat{\tau}_i = (\bar{Y}_{i.}^{adj} - \bar{Y}_{..})$. Consequently, the adjusted mean difference $(\bar{Y}_{i.}^{adj} - \bar{Y}_{j.}^{adj})$ is an unbiased

estimator of the difference between the two treatment effects $D_{adj} = \tau_i - \tau_j$. It can be

expressed as

$$E\left(\bar{Y}_{i.}^{adj} - \bar{Y}_{j.}^{adj}\right) = \tau_i - \tau_j$$

The initial (without adjustment) bias due to the systematic difference in X is $\beta(\mu_i - \mu_j)$.

The unadjusted treatment effect is given by

$$E(\bar{Y}_i - \bar{Y}_j) = (\tau_i - \tau_j) + \beta(\mu_i - \mu_j)$$

The error of the difference between the two treatment effects is demonstrated as [4]:

$$S^2_{\{\widehat{\tau_i - \tau_j}\}adj} = S^2_{\{\bar{Y}_{i.} - \bar{Y}_{j.}\}adj} = MSE_Y^{adj} \left(\frac{1}{n_i} + \frac{1}{n_j} + \frac{(\bar{X}_{i.} - \bar{X}_{j.})^2}{SSE_X} \right) \quad (2.15)$$

For simplicity, we assume that there are only two treatment groups (control group and treatment group), i.e., $f = 2$ and the two groups have same size n (i.e. $n = \frac{N}{2}$) of the experimental units. So formula (2.13) can be expressed as

$$S^2_{\{\widehat{\tau_1 - \tau_2}\}adj} = S^2_{\{\bar{Y}_{1.} - \bar{Y}_{2.}\}adj} = MSE_Y^{adj} \frac{4}{N} \left(1 + \frac{N(\bar{X}_{1.} - \bar{X}_{2.})^2}{4SSE_X} \right) \quad (2.16)$$

Assuming a normal distribution for X , $\frac{N(\bar{X}_{1.} - \bar{X}_{2.})^2}{4\sigma_X^2}$ has noncentral chi-square distribution

with one degree of freedom and noncentrality parameter $\lambda = \frac{N(\mu_1 - \mu_2)^2}{4\sigma_X^2}$. Similarly, we could

conclude that $\frac{SSE_X}{\sigma_X^2}$ has central Chi-square distribution with $(N - 2)$ degree of

freedom. Therefore,

$$W = (N - 2) \frac{N(\bar{X}_{1.} - \bar{X}_{2.})^2}{4SSE_X}$$

The above statistic is a noncentral F variable with $(1, N - 2)$ degrees of freedom and

noncentrality parameter λ . Its expectation is given as

$$E(W) = \frac{(N-2)(1+\lambda)}{N-4}$$

As a result, the second term within the brackets in expression (2.16) is noncentral F ratio divided by $(N-2)$. Taking the expected value of the expression (2.16) with respect to Y and X , the variance of the difference of the two adjusted treatments is given as following:

$$\sigma_{\{\hat{\mu}_1 - \hat{\mu}_2\}adj}^2 = \sigma_Y^2(1-\rho^2) \frac{N-2}{N-3} \frac{4}{N} \left(1 + \frac{1+\lambda}{N-4}\right) \quad (2.17)$$

2.3 Precision Comparison

As mentioned in the previous chapter, most of the clinical studies will encounter the problem of missing baseline measurements for the ANCOVA model. Hence, the precision obtained is only based on the partial data set if we apply the ANCOVA model with partially missing baseline measurements. Is it worthwhile comparing the precision from the standard ANOVA model with full data set? The relative efficiency of two estimators is a useful index to compare the precision. It is the reciprocal of the ratio of the corresponding variance of the two estimators.

Now, the proportion of missing baseline data is represented by η . Let $\delta = \frac{(\mu_1 - \mu_2)}{\sigma_X}$ be the standardized difference of group means on covariate X and then $\lambda = \frac{N}{4} \delta^2$. The variance of the difference between adjusted treatment means with partially missing

baseline is given as

$$\sigma_{\{\bar{y}_1 - \bar{y}_2\}adj}^2 = \sigma_Y^2 (1 - \rho^2) \frac{N(1-\eta) - 2}{N(1-\eta) - 3} \frac{4}{N(1-\eta)} \left(1 + \frac{1 + \frac{N(1-\eta)}{4} \delta^2}{N(1-\eta) - 4} \right) \quad (2.18)$$

The variance of the difference of unadjusted treatment means using the standard ANOVA with full data set is given by

$$\sigma_{\{\bar{y}_1 - \bar{y}_2\}}^2 = \frac{4}{N} \sigma_Y^2$$

The relative efficiency of these two estimators is the reciprocal of the ratio of the corresponding variance of the two estimators. It is derived by

$$\varphi = \frac{\sigma_{\{\bar{y}_1 - \bar{y}_2\}}^2}{\sigma_{\{\bar{y}_1 - \bar{y}_2\}adj}^2} = \left\{ (1 - \rho^2) \frac{N(1-\eta) - 2}{N(1-\eta) - 3} \frac{1}{(1-\eta)} \left(1 + \frac{1}{4} \frac{N(1-\eta) \delta^2 + 4}{N(1-\eta) - 4} \right) \right\}^{-1} \quad (2.19)$$

The relative efficiency φ means that the covariance procedure with n sample units in each treatment group can give nearly as precise estimate as the ANOVA procedure with φn sample units in each group. If $\varphi > 1$, the estimator from the ANCOVA model achieves greater precision than the estimator from the ANOVA procedure. In other words, the ANCOVA procedure can provide narrower confidence interval for the estimate and more powerful test than the ANOVA procedure.

In fact, the sample size N is not a major impact on relative efficiency. The details will be discussed later. The asymptotic relative efficiency value, as sample size N goes to infinity, can be used as a useful reference for all the cases with different sample

size (except very small sample size trials). When the sample size goes to infinity, the asymptotic relative precision is given as:

$$\varphi = \left\{ \frac{1-\rho^2}{1-\eta} \left(1 + \frac{\delta^2}{4} \right) \right\}^{-1} \quad (2.20)$$

For completely randomized controlled trials, it is assumed that $\mu_1 = \mu_2$, i.e. $\delta = 0$. The relative precision is given as:

$$\varphi = \left\{ (1-\rho^2) \frac{N(1-\eta)-2}{N(1-\eta)-4} \frac{1}{(1-\eta)} \right\}^{-1}$$

For the completely randomized controlled trials with moderately large sample size ($N > 100$), the asymptotic relative precision is very close to the actuality. It is given as following:

$$\varphi = \left\{ \frac{1-\rho^2}{1-\eta} \right\}^{-1} = \frac{1-\eta}{1-\rho^2}$$

2.4 Reference Table and Figure

If relative efficiency equals to 1, it means that either the ANCOVA model or the ANOVA model has identical precision. Based on this relationship, we can calculate the theoretical minimum required correlation for the ANCOVA model to obtain the same precision with the ANOVA supposing the missing proportion, sample size and difference of group means on covariate are available. The expression of theoretical minimum

required correlation is defined as following

$$\rho = \sqrt{1 - \frac{(1-\eta)((1-\eta)N-3)((1-\eta)N-4)}{((1-\eta)N-2)((1-\eta)N-3 + \frac{1}{4}(1-\eta)N\delta^2)}} \quad (2.21)$$

When the sample size goes to infinity or for large sample size, the asymptotic minimum required correlation is effectively equal to

$$\rho = \sqrt{1 - \frac{1-\eta}{1 + \frac{1}{4}\delta^2}} \quad (2.21 \text{ a})$$

(The effect of sample size on minimum correlation is very minor for moderately large sample size. Please find it in discussion part.)

Following the expression above **(2.21a)**, the asymptotic minimum required correlation for completely randomized controlled trials ($\delta = 0$) is given as

$$\rho = \sqrt{\eta} \quad (2.21 \text{ b})$$

If the actual correlation is higher than this theoretical minimum correlation, using the ANCOVA model can achieve more precise estimate. Otherwise, the ANOVA model will outperform the ANCOVA model.

In this study, the theoretical minimum required correlations are computed for sample size $N=20, 50, 100, 200, 500$, and infinity, the missing proportion $\eta=0\sim.40$ and the standardized difference of group means on covariate $\tau =0, 0.25, 0.50, 0.75$, and 1. The ranges of the parameters are selected based on the practical requirement.

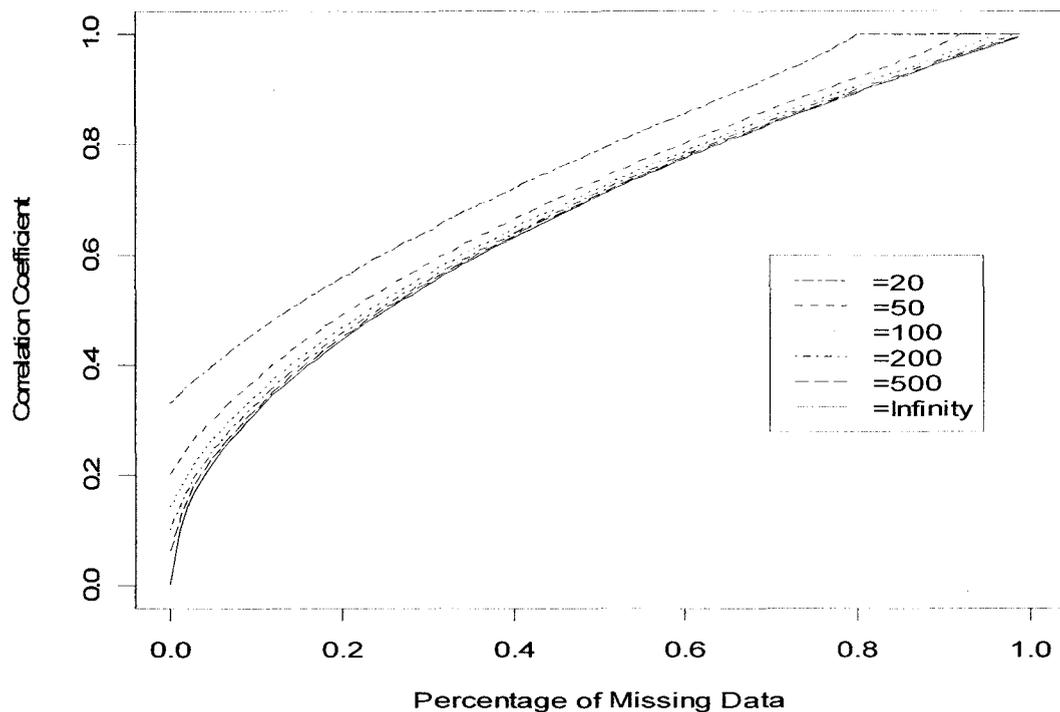
Table 2.3: Minimum Required Correlation for $\delta = 0$

Missing Baseline Proportion η	Minimum Required Correlation ρ					
	N=20	N=50	N=100	N=200	N=500	N=INF
0	0.333	0.204	0.143	0.101	0.063	0
0.02	0.362	0.248	0.201	0.174	0.155	0.141
0.04	0.398	0.286	0.246	0.224	0.210	0.20
0.06	0.415	0.319	0.284	0.265	0.253	0.245
0.08	0.438	0.349	0.317	0.300	0.290	0.283
0.10	0.461	0.377	0.347	0.332	0.323	0.316
0.12	0.483	0.423	0.375	0.361	0.352	0.346
0.14	0.503	0.426	0.401	0.387	0.380	0.374
0.16	0.523	0.449	0.425	0.412	0.405	0.400
0.18	0.542	0.471	0.448	0.436	0.429	0.424
0.20	0.561	0.492	0.470	0.458	0.452	0.447
0.22	0.579	0.512	0.490	0.480	0.473	0.469
0.24	0.596	0.531	0.510	0.500	0.494	0.490
0.26	0.613	0.550	0.530	0.520	0.514	0.510
0.28	0.630	0.568	0.548	0.539	0.533	0.525
0.30	0.645	0.585	0.566	0.557	0.551	0.548
0.32	0.661	0.602	0.584	0.575	0.569	0.566
0.34	0.677	0.619	0.601	0.592	0.587	0.583
0.36	0.692	0.645	0.617	0.608	0.603	0.600
0.38	0.707	0.650	0.633	0.625	0.620	0.616
0.40	0.721	0.665	0.649	0.640	0.636	0.632

The table above demonstrates the theoretical minimum correlation for the completed randomized controlled trials, i.e. $|\delta| = 0$. If we know the missing baseline proportion and sample size for a specified clinical trial, it is very convenient to obtain the theoretical minimum correlation through checking the table. For example, if the sample size is 100 and the proportion of missing baseline is 10 percent in a specific trial, the theoretical minimum correlation for the ANCOVA model is 0.374 to obtain the same precision with

the ANOVA model. If the observed sample correlation is less than the theoretical minimum correlation, the ANCOVA model may achieve less precision than the ANOVA model. Alternatively, if the observed sample correlation is greater than the theoretical minimum correlation, the ANCOVA model will achieve higher precision. Please see other tables for $|\delta| = .25 \sim 1$ in appendix B (Table 2.3~2.6).

Figure 2.1: Minimum required correlations for $\delta = 0$



The figure above is also a good reference tool for precision comparison of two procedures. The ordinate and abscissa represent the correlation coefficient and missing baseline proportion, respectively. The six lines are for sample size=20, 50, 100, 200, 500,

and infinity, respectively.

All the points on the diagonal part of the line indicate that the combinations of correlation coefficient and missing proportion under either the ANOVA or the ANCOVA model achieve same precision. All the combinations of correlation coefficient and missing proportion under the line demonstrate that the ANOVA model achieves higher precision than the ANCOVA. All the points above the line represent the situation in which the ANCOVA model generates higher precision. If the missing proportion is very high with that range, all the points on the top flat part of the line indicate that the ANCOVA will never achieve the same precision as the ANOVA, even if the correlation coefficient is equal to the maximum value 1. Other figures for $|\delta| = .25 \sim 1$ which apply to observational studies are available in appendix A (Figure 2.2~2.5). The more precise figures which include the situations under exactly missing range 0~.40 are available in Appendix A (Figure 2.6~2.10)

2.5 Asymptotic Relative Efficiency

The sample size is not a major impact on the relative efficiency between the adjusted (ANCOVA) and the unadjusted (ANOVA) analyses in moderately large sample ($N > 100$) trials. Hence, the asymptotic results are very close to the actual results from all sizes of the moderately large sample trials. If the variance of the estimate of treatment difference obtained from the ANOVA model is selected as a standard, the variance obtained from the ANCOVA model without missing baseline in terms of the variance

obtained from the ANOVA is given as

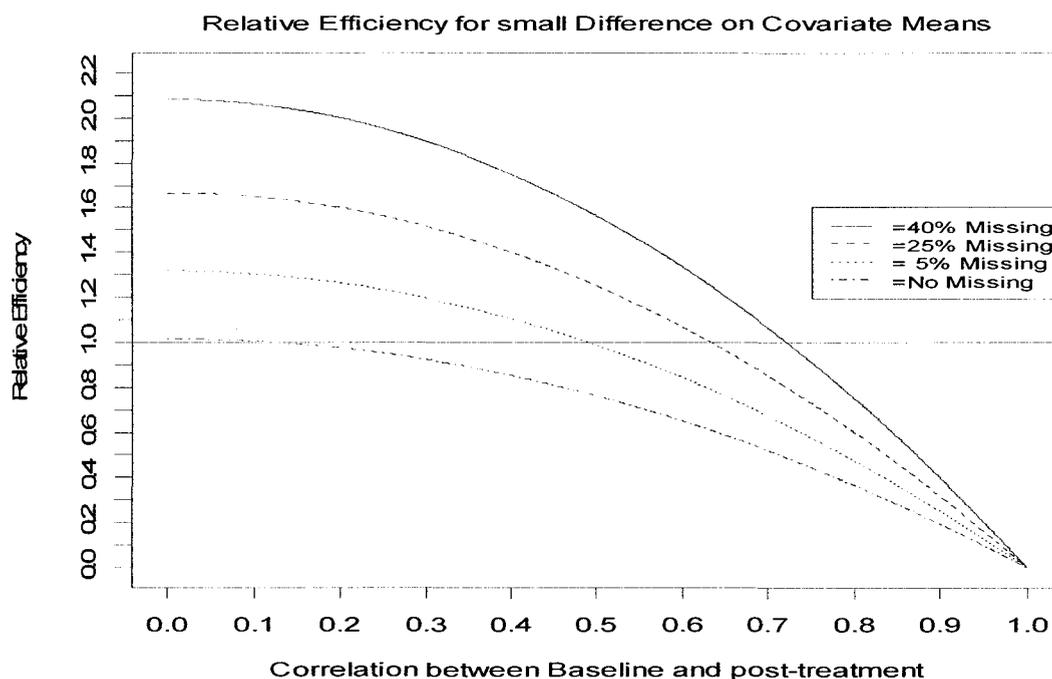
$$(1-\rho^2)\left(1+\frac{\delta^2}{4}\right)$$

The relative variance obtained from the ANCOVA model with partially missing baseline is given as

$$\frac{1-\rho^2}{1-\eta}\left(1+\frac{\delta^2}{4}\right)$$

The asymptotic variances of the estimates of the adjusted means difference obtained from the ANCOVA model relative to the variances obtained from the ANOVA model are graphed in Figure 2.12 for the case with 0.25 standard deviation difference of the means on baseline.

Figure 2.12: Relative efficiency of estimator for treatment effect between ANOVA and ANCOVA models for $\delta=0.25$



The four lines in the figure from the top down represent 40, 25, 5, and zero per cent missing baseline ($\eta = 0.4, 0.25, 0.05, \text{ and } 0$). Only for very small values of correlation ($\rho < 0.12$), the ANCOVA model without missing baseline is less efficient than the unadjusted analysis (ANOVA). Otherwise, the ANCOVA with full data set always obtain greater precision than the ANOVA. The ANCOVA model with 5, 25, and 40 per cent missing baseline is more efficient than the ANOVA model only for $\rho > 0.26, 0.51, \text{ and } 0.64$, respectively.

The points on the chart above the horizontal line $Y=1$ indicate that the standard errors of the estimated difference of the adjusted means obtained from the ANCOVA model are greater than the ANOVA model. Under this situation, using the ANCOVA model will add variation and the ANOVA model is more likely to get a significant result. Conversely, the points below the horizontal line indicate that the ANCOVA model will obtain greater precision than the ANOVA model.

If we know the correlation between baseline and follow up scores, and the proportion of missing baseline in a specific trial, the asymptotic variance of the estimator obtained from the ANCOVA model in terms of the variance from the ANOVA model can be obtained through checking the figures.

For instance, if the correlation coefficient is 0.7 and the proportion of missing baseline is 10 percent, the variance from the ANCOVA model is 0.6 in terms of the

variance obtained from the ANOVA model. In other words, the length of the confidence interval obtained from the ANCOVA model is only 0.6 relative to the confidence interval from the ANOVA model. Consequently, under this situation, the ANCOVA procedure is more likely to detect the significant results than the ANOVA.

This case is to describe the situation for the observational studies with the small size of the difference on covariate means ($\delta = 0.25$). Please see other figures of the cases with no, moderately large, and large differences ($\delta = 0, 0.5, \text{ and } 1$) of group means on covariate in Appendix A (Figure 2.12~2.14).

Chapter 3

Application in Knee Surgery Trial

3.1 Analysis of WOMET Data

A torn meniscus is one of the most common injuries of the knee joint. The surgeries to repair the meniscus include both open and arthroscopic techniques using sutures and more recently bioabsorbable narrows. The knee surgery trial is parallel-group, single center, randomized clinical trial. The purpose of the trial is to compare the effectiveness of bioabsorbable narrows to inside-out Suturing. The outcomes include retear rate, disease-specific quality of life measurement with the Anterior Cruciate Ligament Quality of Life Outcome Measure (ACL-QOL) [9] and Western Ontario Meniscal Evaluation Tool (WOMET) [8]. The discussion in this study is solely based on WOMET and ACL-QOL data. The WOMET is validated, reliable, and responsive patient-based 16-item questionnaire. The scores from WOMET provide a measure of quality of life for patients with meniscal pathology. The scores may range from 0 to 100, the higher values indicating better surgical results. The patients are randomized assigned to two treatment groups (Suture and Arrows). The pre-operative measurement was used as the covariate (baseline). The 12 month post-operative measure was used as the dependent

variable. Please see the details for this trial in reference [5].

Descriptive Analysis of WOMET Data

In WOMET data, there are 100 patients (49 in Suture group, and 51 in Arrows group). Of them, 77 patients have post-operative score, 92 patients have the pre-operative score, and 71 patients have both. Hence, 6 patients who have post-operative scores do not have pre-operative scores. The descriptive summary of the variables are demonstrated in the following table:

Table 3.1: Descriptive Summary of WOMET Data

Variable		Size	Mean	Std Dev
Pre-operative (only)	Total	92	36.92	16.93
	Arrow	46	33.77	15.43
	Suture	46	40.07	17.93
Post-operative (only)	Total	77	66.50	23.19
	Arrow	39	68.68	22.96
	Suture	38	64.27	23.52
Pre-operative (both)	Total	71	36.87	17.68
	Arrow	35	34.55	16.35
	Suture	36	39.13	18.83
Post-operative (both)	Total	71	66.20	23.03
	Arrow	35	66.75	23.18
	Suture	36	65.67	23.52

Analysis Using ANOVA

The hypothesis is that there is no difference in true mean post-treatment scores between Arrows group and Suture group. 77 observations with follow up scores can be used in this analysis. The table below presents the detailed calculation results based on the ANOVA model for MOMET data.

Table 3.2: Analysis of Variance Table for WOMET Data

Source of Variation	SS	DF	Mean of Square	F Value	P Value
Between Treatments	375.38	1	375.38	0.70	0.407
Within Treatments(Error)	40501.38	75	540.02		
Total	40876.76	76			

In the 12th month post-operative, the mean score of Arrows group is 68.68 (95% CI 61.24, 71.62) and 64.27 (95% CI 56.53, 72.00). The difference between groups was not statistically significant (95% CI -6.14, 14.97, P=0.41). The mean square error of the ANOVA model is 540.02. The estimated difference between two treatments is 4.42(95% CI -6.14, 14.97, SE=5.30).

Analysis using ANCOVA

The hypothesis is that there is no difference in true mean post-treatment scores between Arrows group and Suture group after the covariate (baseline) adjustment. There are only 71 observations with both post-operative score and pre-operative score. Firstly, the heterogeneity of slopes for two treatments is not significant (P=0.14). Hence, the assumption of same slopes for two treatments groups is not violated. The table below

presents the detailed calculation results based on the ANCOVA model for MOMET data.

Table 3.3: Analysis of Covariance Table for WOMET Data

Source of Variation	SS	DF	Mean of Square	F Value	P Value
Treatments	20.89	1			
Treatment after Regression	596.63	2	298.32		
Errors	37120.10	69			
Regression Reduction	575.74	1			
Errors after regression	36544.36	68	537.42	0.56	0.58
Total	37140.99	70			

In the 12th month post-operative, the adjusted mean score of Arrows group is 67.13 (95% CI 59.30, 74.98, SE=3.94) and the one of the Suture group is 65.30 (95% CI 57.56, 73.04, SE=3.88). The difference between adjusted group means was not statistically significant (95% CI -9.24, -12.91, P=0.74). The adjusted mean square error of ANCOVA model is 537.42. Before the adjustment, the observed difference between treatment means based on 71 observations is 1.09(95% CI -9.90, 12.07, SE=5.51). After the baseline adjustment, the observed estimate of difference between adjusted treatment mean is 1.83 (95% CI -9.24, 12.91, SE=5.55). Since the baseline scores are worse in the Arrows group, the difference between two treatments given baseline is underestimated by the ANOVA model. Hence, the difference from the ANCOVA model has increased from 1.09 to 1.83.

Precision Comparison

Firstly, the relative efficiency is checked by using the reference table. For

MOMET data, the missing proportion is 0.08 (6/77), the standardized difference in means on covariate is 0.38, and the sample size is 77. The theoretical minimum correlation for this case is approximately 0.370 based on the reference table. The sample correlation coefficient based on MOMET data is given as

$$r = \frac{SPE_{xy}}{\sqrt{SSE_x SSE_y}} = 0.352$$

Based on the results above, the observed sample correlation is slightly smaller than the theoretical minimum correlation based on the table. As a result, the ANOVA model will achieve greater precision than the ANCOVA model for MOMET data if the decision is made merely based on the reference table.

Secondly, the precisions are compared using the analysis results from the ANOVA and the ANCOVA procedures. The standard error of estimated difference between treatment means using the ANOVA model based on 77 observations is 5.30. The standard error of estimated difference between adjusted treatment means using the ANCOVA model based on 71 observations is 5.55. The ANOVA model provides greater precision than the ANCOVA model.

The results based on the two approaches above demonstrate that the theoretical minimum correlation obtained from the reference table is consistent with the practical situation. The table above represents the parameter estimates and their MSE for the ANOVA and the ANCOVA models.

Table 3.4: Estimates of the Parameters and their Standard Errors

ANOVA Model			ANCOVA Model		
Parameter	Estimate	SDE	Parameter	Estimate	SDE
μ	66.47	2.65	μ	66.22	2.75
τ_1	2.21	2.65	τ_1	0.92	2.78
τ_2	-2.21	2.65	τ_2	-0.92	2.78
			β	0.16	0.16
MSE	540.02		MSE_{adj}	537.42	
D	4.42	5.30	D_{adj}	1.83	5.55

In order to unify the standards, the two standard errors should be compared based on the same data set. Hence, the standard error from the ANOVA model is recalculated based on 71 observations instead of based on 77 observations. After the replacement, the new standard error from the ANOVA model is 5.50. The relative efficiency of the two estimators based on the ANOVA and ANCOVA model is 0.99.

3.2 Analysis of ACL-QOL Data

The ACL-QOL is validated, reliable, and responsive patient-based 32-item questionnaire. It provides a subjective measure of quality of life for patients with chronic anterior cruciate ligament deficiency. . The scores may range from 0 to 100, the higher values indicating better surgical results. In the trial, patients are randomized assigned to two treatment groups (Suture and Arrows). The pre-operative measurement was used as the covariate (baseline). The 12 month post-operative measure was used as the dependent variable.

Descriptive Analysis of ACL-QOL Data

In ACL-QOL data, there are 100 patients (49 in Suture group, and 51 in Arrow group). 79 patients have post-operative score, 99 patients have the pre-operative score, and 78 patients have both. The descriptive summary of the variables are addressed in the following table:

Table 3.5: Descriptive Summary of ACL-QLF Data

Variable		Size	Mean	Std Dev
Pre-operative (only)	Total	99	30.90	16.15
	Arrow	50	26.30	13.33
	Suture	49	35.59	17.50
Post-operative (only)	Total	79	61.84	24.04
	Arrow	41	62.47	23.55
	Suture	38	61.08	24.85
Pre-operative (both)	Total	78	31.30	16.86
	Arrow	40	27.38	14.06
	Suture	38	35.44	18.67
Post-operative (both)	Total	78	61.51	24.05
	Arrow	40	61.92	23.58
	Suture	38	61.08	24.85

Analysis using ANOVA

The hypothesis is that there is no difference in true mean post-treatment scores between Arrows group and Suture group. 78 observations can be used in this analysis. The table below presents the detailed calculation results based on the ANOVA model for ACL-QOL data.

Table 3.6: Analysis of Variance Table for ACL-QOL Data

Source of Variation	SS	DF	Mean of Square	F Value	P Value
Treatments	38.05	1	38.05	0.07	0.80
Errors	45031.01	77	584.82		
Total	45069.06	78			

In the 12th month post-operative, the mean score of Arrows group is 62.47 (95% CI 54.95, 69.99) and 61.08 (95% CI 53.27, 68.90). The difference between groups is not statistically significant (95% CI -9.45, 12.23, P=0.80). The mean square error of ANOVA model is 584.82. The observed estimate of difference between treatments is 1.39(95% CI -9.45, 12.23, SE=5.44).

Analysis using ANCOVA

The hypothesis is that there is no difference in true mean post-treatment scores between Arrows group and Suture group after the covariate (baseline) adjustment. There are only 78 observations with both post-operative score and pre-operative score. The heterogeneity of slopes for two treatments is not significant (P=0.90). Hence, the assumption of same slopes for two treatments groups is not violated. The table below presents the detailed calculation results based on the ANCOVA model for ACL-QOL data.

Table 3.7: Analysis of Covariance Table for ACL-QOL Data

Source of Variation	SS	DF	Mean of Square	F Value	P Value
Treatments	13.77	1			
Treatment after Regression	3406.82	2	1703.41		
Errors	44537.72	76			

Regression Reduction	3393.05	1			
Errors after regression	4144.67	75	548.60	3.11	0.051
Total	45069.06	78			

In the 12th month post-operative, the adjusted mean score of Arrows group is 63.52 (95% CI 56.03-71.01 SE=3.76) and the one of the Suture group is 59.41 (95% CI 51.72, 67.09 SE=3.86). The difference between adjusted group means is not statistically significant (95% CI -6.78, 15.00, P=0.45). The adjusted mean square error of ANCOVA model is 548.60. Before the adjustment, the observed difference between treatment means based on 78 observations 0.84(95% CI -10.08~11.76, SE=5.48). After the adjustment, the observed estimate of difference between adjusted treatment mean is 4.11(95% CI -6.78, 15.00, SE=5.47). The situation in ACL-QOL data is similar with WOMET data. Since the baseline scores are worse in the Arrows group, the difference between two treatments given baseline is underestimated by the ANOVA model. Hence, the difference from the ANCOVA model has increased from 0.84 to 4.11.

Precision Comparison

Firstly, the relative efficiency is checked by using the reference table. For ACL-QOL data, the missing proportion is only 0.01 (1/79), the standardized difference between means on covariate is 0.478, and the sample size is 79. The theoretical minimum correlation of this case is approximately 0.304 based on the reference table. The actual sample correlation coefficient of ACL-QOL is 0.276. Based on the results above, the observed sample correlation is slightly smaller than the theoretical minimum correlation

based on the table. The ANOVA model can achieve greater precision than the ANCOVA model for ACL-QOL data if the decision is made merely based on the reference table.

Secondly, the precisions are compared using the analysis results from the ANOVA and the ANCOVA procedures. The standard error of difference between treatment means using ANOVA model based on 79 observations is 5.44. The standard error of the estimated difference between adjusted treatment means using ANCOVA model based on 78 observations is 5.47. The ANOVA model provides greater precision than the ANCOVA model. The results based on the two approaches above demonstrate that the theoretical minimum correlation obtained from the reference table is consistent with the practical situation. The table below presents the parameter estimates and their MSE for the ANOVA and the ANCOVA models

Table 3.8: Estimates of the Parameters and their Standard Errors

ANOVA Model			ANCOVA Model		
Parameter	Estimate	SDE	Parameter	Estimate	SDE
μ	61.78	2.72	μ	61.30	2.65
τ_1	0.69	2.72	τ_1	2.06	2.73
τ_2	-0.69	2.72	τ_2	2.06	2.73
			β	0.41	0.16
MSE	584.82		MSE_{adj}	548.60	
D	1.39	5.44	D_{adj}	4.11	5.47

The two standard errors should be compared based on the same data set to unify the standards. The standard error from the ANOVA model is recalculated based on 78

observations instead of 79 observations. After the replacement, the new standard error from the ANOVA model is 5.48. The relative efficiency of the two estimators based on the ANOVA and ANCOVA model is 1.00.

Chapter 4

Discussion

Effect of Sample Size on Relative Efficiency

For moderately large size trials ($N \geq 100$), the sample size does not have much impact on the relative efficiency between the ANCOVA and the ANOVA procedures. In other words, the theoretical minimum correlations do not have much difference from the trials with different sample size if the missing proportion and standardized mean difference on covariate X are same.

The following table demonstrates the average difference of theoretical minimum correlations between sample size=20, 50, 100, 200,500 and infinity.

Sample size	20	50	100	200	500
Mean-Diff	0.113	0.045	0.023	0.012	0.005

From the table above, we can tell that the average difference of correlations between sample size 100 and infinity is only 0.023. In addition, the difference decreases with increasing sample size. All the lines in the figures (2.1-2.5) are almost parallel to each

other. It demonstrates that the differences of minimum correlations between different sample sizes are almost unchanged. Hence, all the actual differences are very close to the average difference. Consequently, the asymptotic results for moderately large ($N > 100$) trials are very close to the actual results.

Effect of the Difference between Group Means on Covariate

The difference between group means on covariate is a primary factor on the relative efficiency of the estimated difference between the ANOVA model and the ANCOVA model besides the correlation and proportion of missing. For example, the missing proportion in ACL-QOL data is only 0.01 (78/79). However, the standard error of the difference between the adjusted means from the ANCOVA model is still greater than the ANOVA model because there exists a moderately large difference between the group means on baseline scores.

If the baseline scores are worse in the treatment group, the difference between treatment and control groups given baseline will be underestimated by the ANOVA model. This situation occurs in both WOMET and ACL-QOL data. Conversely, the difference will be overestimated if the baseline scores are better in the treatment group.

Achievements of This Study

In some studies, the lost one degree of freedom using to estimate the regression coefficient is often omitted for the ANCOVA procedure. For large sample size trials, the effect of omitting one degree of freedom is negligible. However, for relatively small

sample size trials and relatively low correlation, the magnitude of difference in minimum correlation is appreciable. For a trial with sample size of 20, if the difference of one degree of freedom is omitted, the magnitude of minimum correlation increases from 0.242 to 0.333.

In order to obtain the more precise results in small sample size trials, this study keep the effect of the sample size. As a consequence, keeping the difference in degree of freedom and the effect of sample size not only achieves more precise results but also expands the application scope to small sample size trials with relatively low correlation.

In some studies, the second term in the brackets of the right hand side of equation (2.16) is often neglected or under estimated. Some studies replace this term by its average value, given as following

$$S^2_{\{\tau_1-\tau_2\}adj} = MSE_Y^{adj} \frac{4}{N} \left(1 + \frac{MSTR_X}{(N-2)MSE_X} \right)$$

The second term within the brackets becomes central F ratio divided by $(N-2)$ with degree of freedom $(1, N-2)$ and its expectation is $\frac{1}{N-4}$. If compared with the result $\left(\frac{N\delta^2}{4N-16} + \frac{1}{N-4} \right)$ from this study, the first term which is always positive is omitted. Hence, the second term in equation (2.16) using previous approach is always under estimated. Consequently, the previous procedure leads to consistent underestimation of standard error of difference of adjusted means.

Chapter 5

Conclusion

Researches in previous studies often focus on the size of the model mean squared errors of the ANOVA and the ANCOVA procedures. However, it is not sufficient to detect the relative precision of the estimated difference of treatment effects between the ANOVA model and the ANCOVA model simply based on the model MSE. For instance, if the sample size is 200 and the standardized mean difference on covariate is 0.75, the minimum required correlation is 0.380 even if there is no missing baseline. In other words, the ANCOVA model with correlation 0.38 can achieve the same precision with the ANOVA model. However, the model mean squared error from the ANCOVA model is only 0.85 in terms of MSE obtained from the ANOVA model. Consequently, if the difference between group means on covariate is relatively large, the standard error of the estimator from the ANOCVA model may be larger than the ANOVA model, even if the adjusted MSE of the ANCOVA model is less than the ANOVA model.

The current study considers both the effects of the difference of means on covariate and the missing one degree of freedom in order to obtain more precise results

and expand the application scope to small sample size trials. Based on the application results of the WEMET and ACL-QOL data sets, the theoretical minimum required correlations are consistent with the actual situations.

Before the ANCOVA procedure is applied, it is important to verify that the treatments have no effects on covariate if the covariate was measured after the treatments were applied. If this assumption is violated, the ANCOVA procedure may remove not only the part of the variability of dependent variable but also part of the treatments effects.

The relative variance of the estimated difference between treatment means from the ANCOVA in terms of the variance from the ANOVA models can be obtained through checking the reference tables and figures. If the relative variance from the ANCOVA is less than 1, the ANOVA will lose information. Therefore, using the ANCOVA is more likely to be significant. Conversely, if the relative variance is greater than 1, the ANOVA model is more likely to show a significant result. However, it is incorrect to select the analysis which gives a more significant finding. The method of the analysis should be specified before the administration of the trial.

Finally, the results in this study are theoretical conclusions based on the satisfaction of some ideal conditions. Accordingly, they can be used as a convenient reference but cannot replace the experimental values.

Chapter 6 Appendix

Appendix A: Figures

Figure 2.2: Minimum Required Correlations for $\delta=0.25$

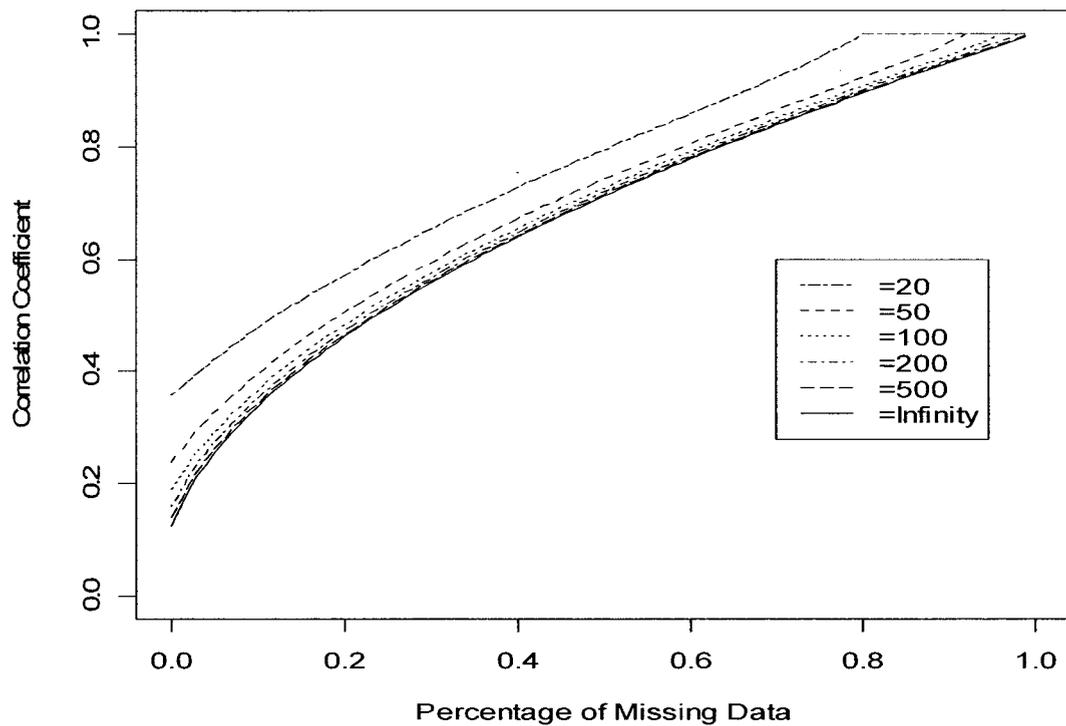


Figure 2.3: Minimum Required Correlations for $\delta=0.5$

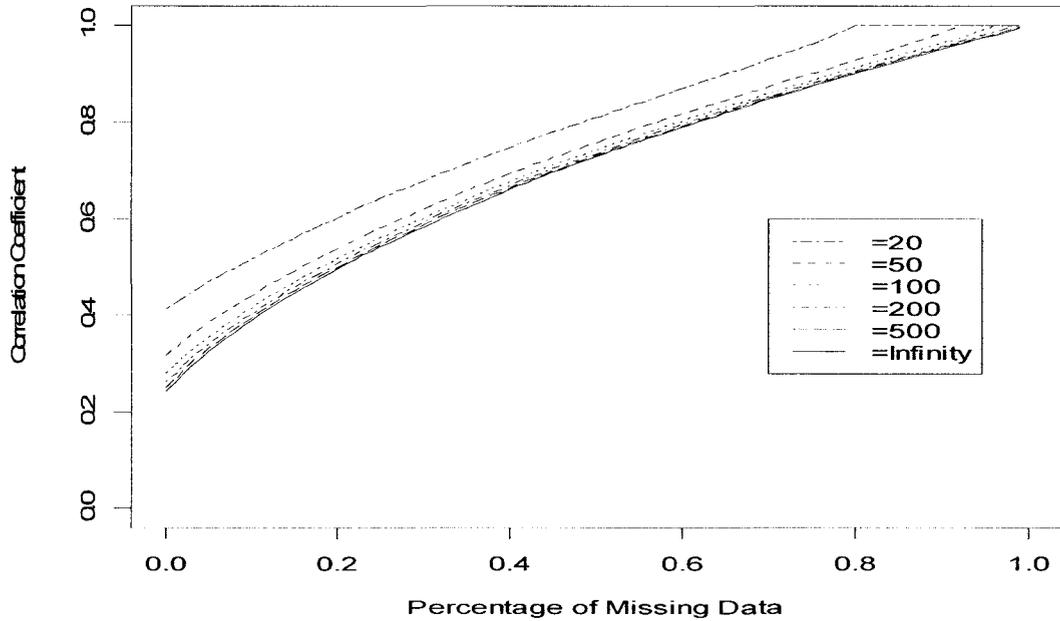


Figure 2.4: Minimum Required Correlations for $\delta=0.75$

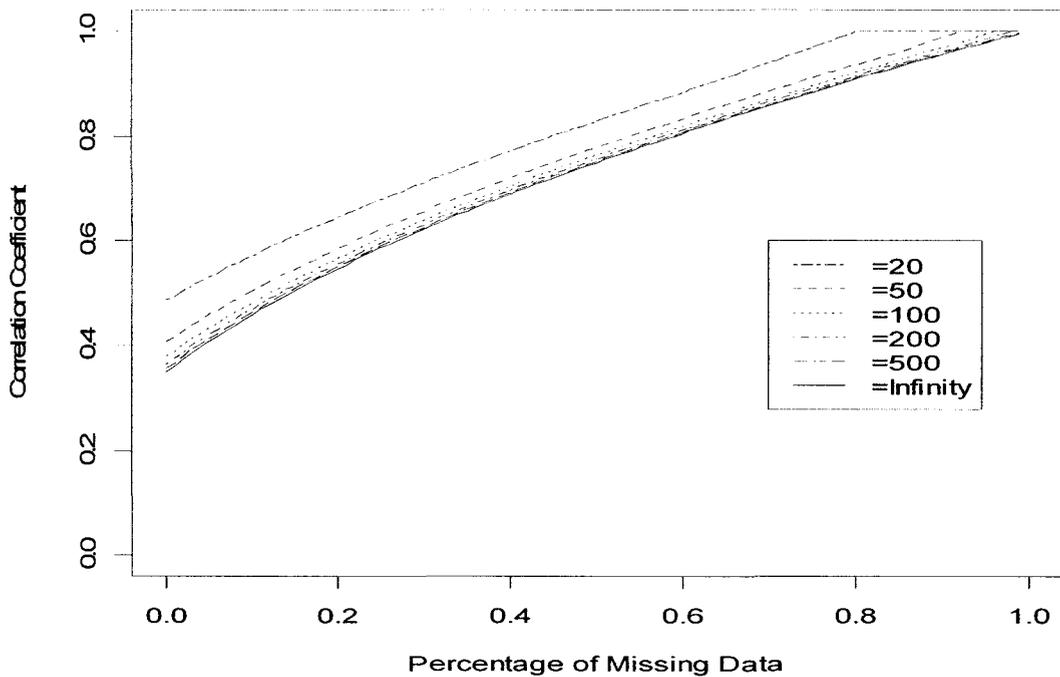


Figure 2.5: Minimum Required Correlations for $\delta=1$

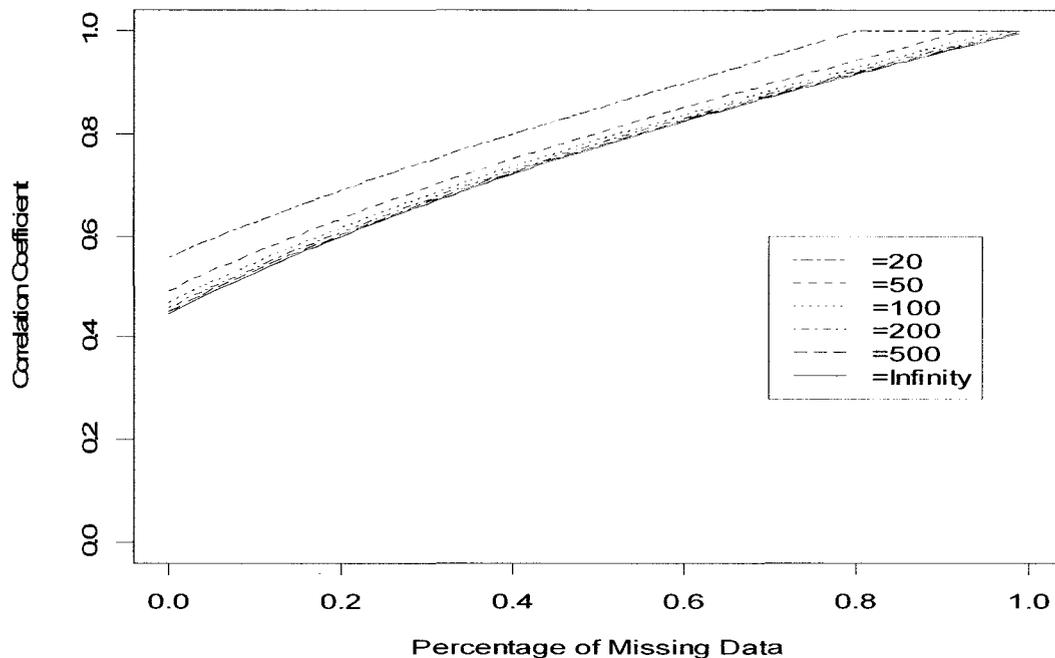


Figure 2.6: Reference in Practical Missing Range for $\delta=0$

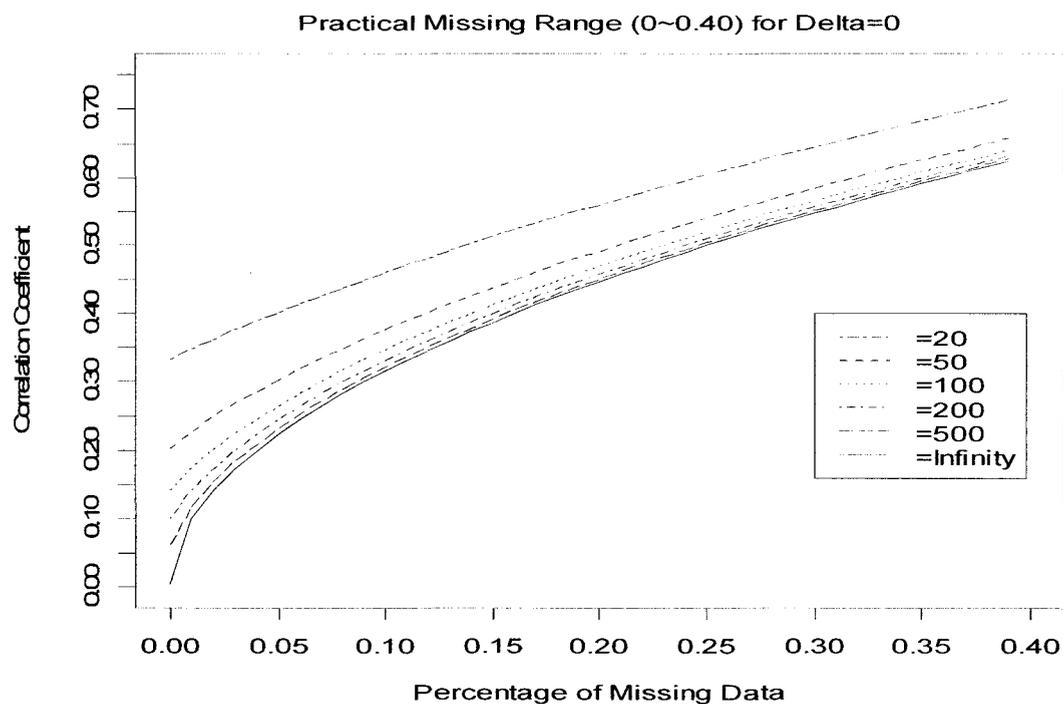


Figure 2.7: Reference in Practical Missing Range for $\delta=0.25$

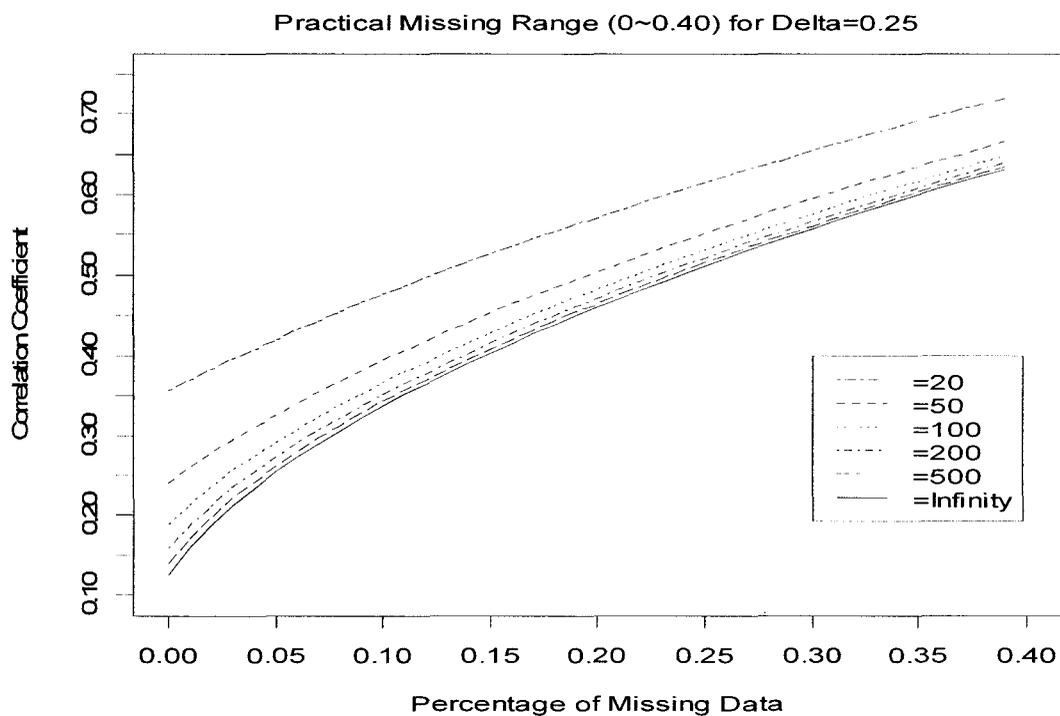


Figure 2.8: Reference in Practical Missing Range for $\delta=0.5$

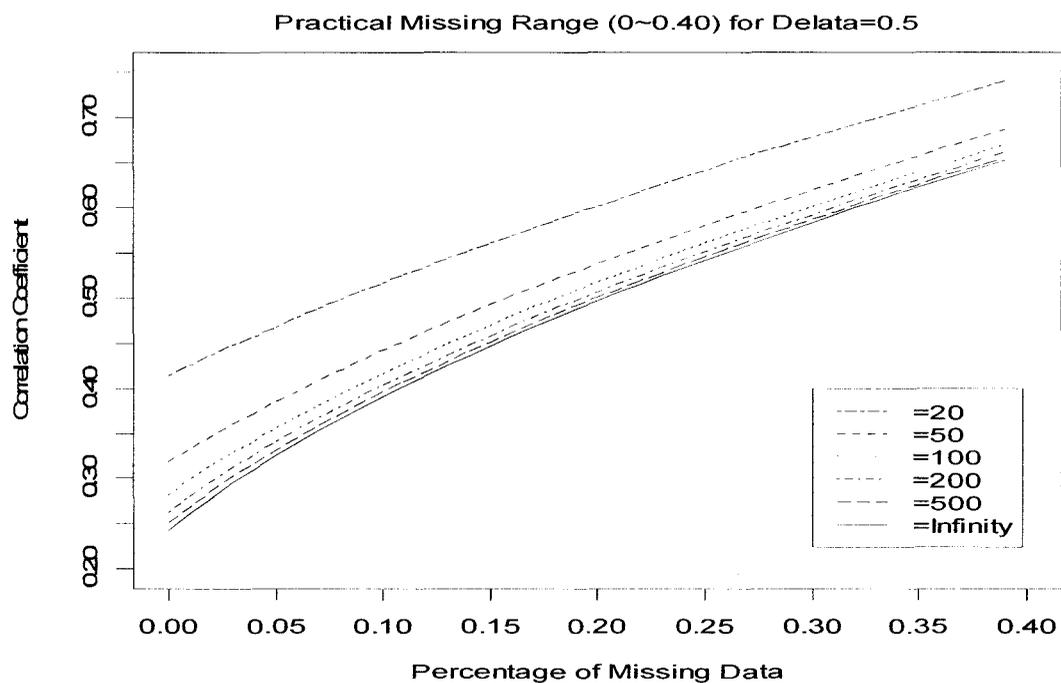


Figure 2.9: Reference in Practical Missing Range for $\delta=0.75$

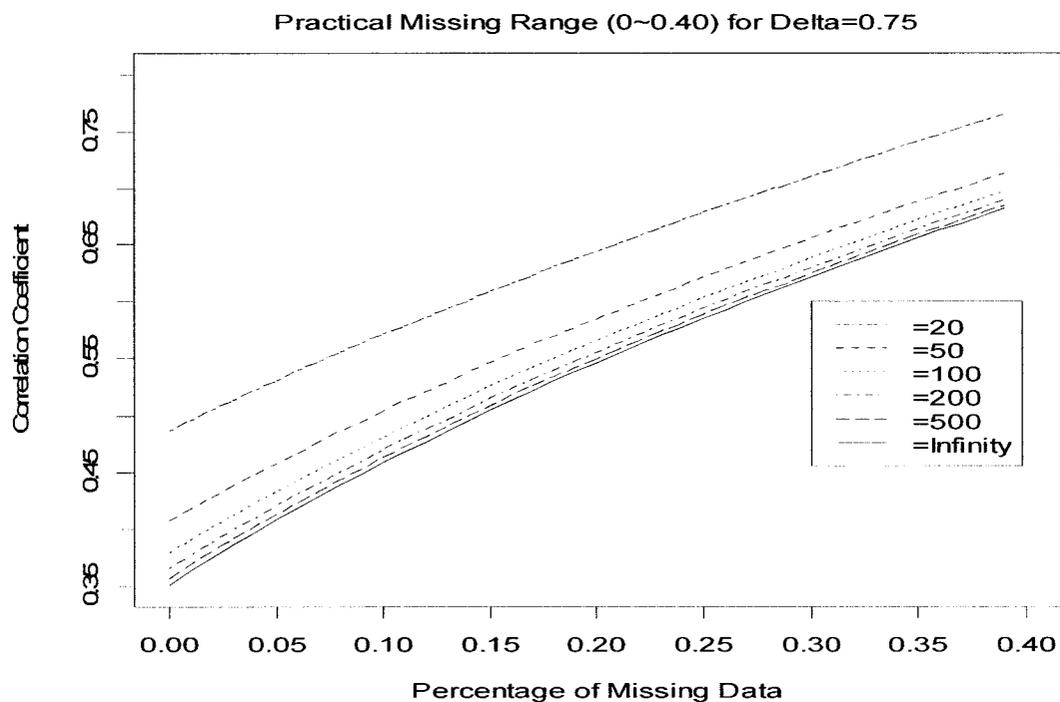


Figure 2.10: Reference in Practical Missing Range for $\delta=1$

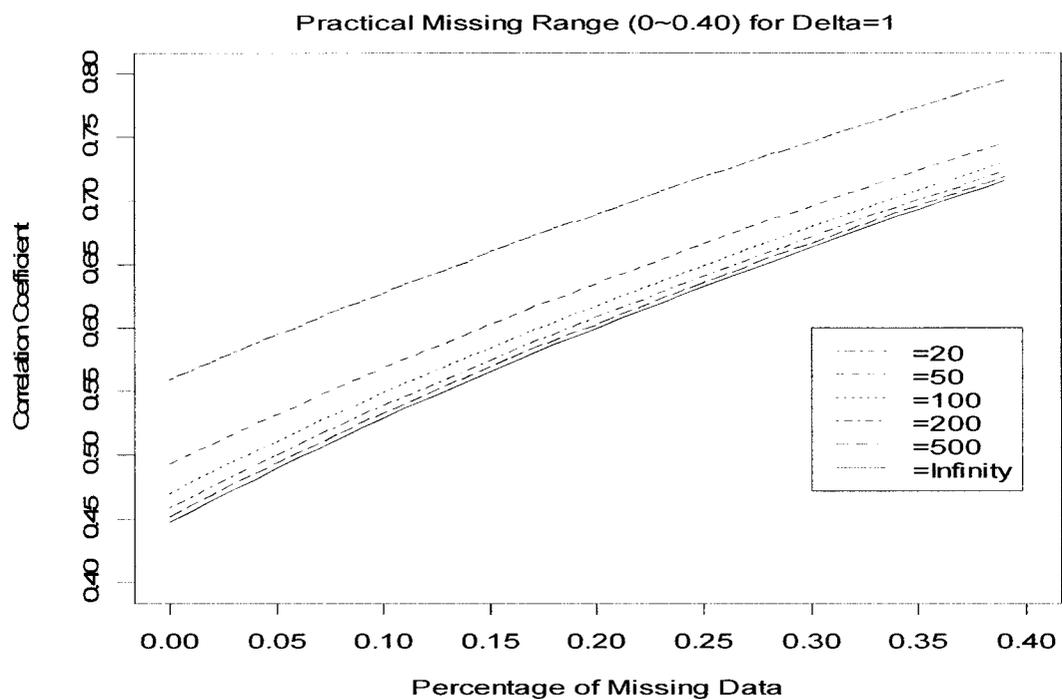


Figure 2.11: Relative efficiency of estimator for treatment effect between ANOVA and ANCOVA models for $\delta=0$

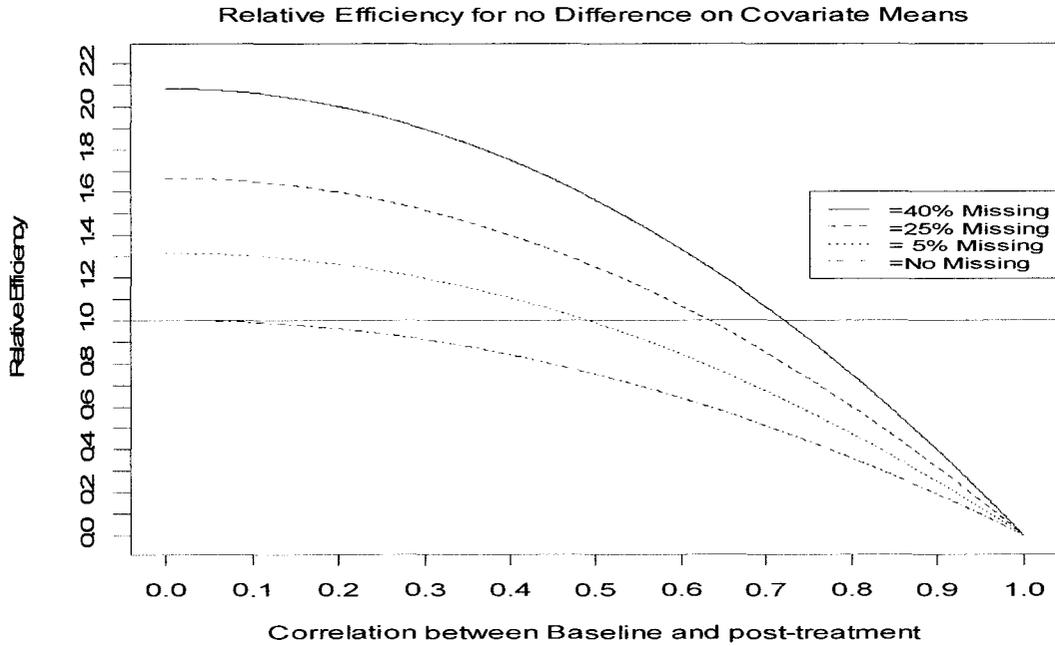


Figure 2.13: Relative efficiency of estimator for treatment effect between ANOVA and ANCOVA models for $\delta=0.5$

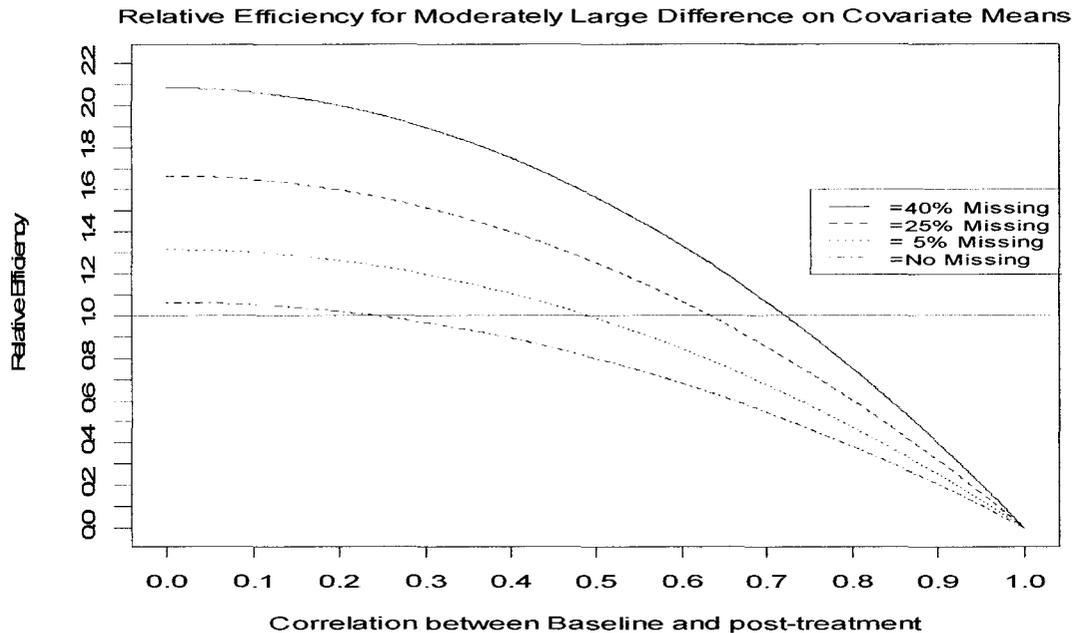
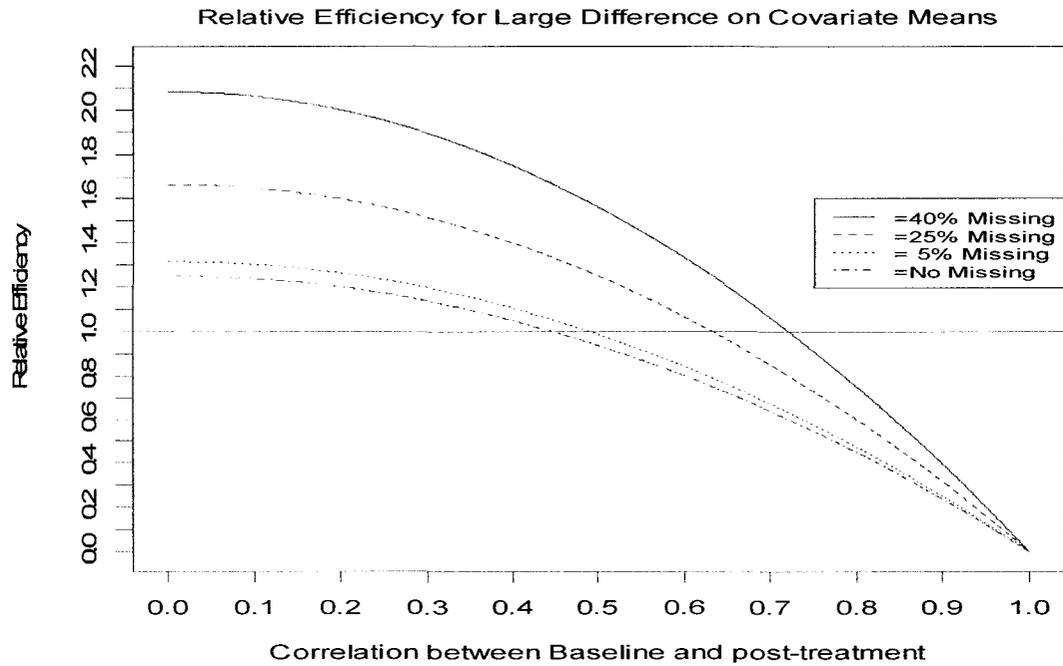


Figure 2.14: Relative efficiency of estimator for treatment effect between ANOVA and ANCOVA models for $\delta=1$



Appendix B: Table

Table 2.3: Minimum Required Correlations for $\delta = 0$

Missing Baseline Proportion η	Minimum Required Correlation ρ					
	N=20	N=50	N=100	N=200	N=500	N=INF
0	0.333	0.204	0.143	0.101	0.063	0
0.02	0.362	0.248	0.201	0.174	0.155	0.141
0.04	0.398	0.286	0.246	0.224	0.210	0.20
0.06	0.415	0.319	0.284	0.265	0.253	0.245
0.08	0.438	0.349	0.317	0.300	0.290	0.283
0.10	0.461	0.377	0.347	0.332	0.323	0.316
0.12	0.483	0.423	0.375	0.361	0.352	0.346
0.14	0.503	0.426	0.401	0.387	0.380	0.374
0.16	0.523	0.449	0.425	0.412	0.405	0.400
0.18	0.542	0.471	0.448	0.436	0.429	0.424
0.20	0.561	0.492	0.470	0.458	0.452	0.447
0.22	0.579	0.512	0.490	0.480	0.473	0.469
0.24	0.596	0.531	0.510	0.500	0.494	0.490
0.26	0.613	0.550	0.530	0.520	0.514	0.510
0.28	0.630	0.568	0.548	0.539	0.533	0.525
0.30	0.645	0.585	0.566	0.557	0.551	0.548
0.32	0.661	0.602	0.584	0.575	0.569	0.566
0.34	0.677	0.619	0.601	0.592	0.587	0.583
0.36	0.692	0.645	0.617	0.608	0.603	0.600
0.38	0.707	0.650	0.633	0.625	0.620	0.616
0.40	0.721	0.665	0.649	0.640	0.636	0.632

Table 2.4: Minimum Required Correlations for $\delta=0.25$

Missing Baseline Proportion η	Minimum Required Correlation ρ					
	N=20	N=50	N=100	N=200	N=500	N=INF
0	0.357	0.239	0.190	0.160	0.140	0.124
0.02	0.384	0.278	0.236	0.213	0.198	0.187
0.04	0.409	0.311	0.274	0.255	0.243	0.234
0.06	0.432	0.341	0.308	0.291	0.280	0.273
0.08	0.455	0.369	0.339	0.323	0.313	0.307
0.10	0.476	0.395	0.367	0.352	0.343	0.337
0.12	0.497	0.419	0.392	0.379	0.371	0.365
0.14	0.517	0.442	0.417	0.404	0.397	0.391
0.16	0.536	0.464	0.440	0.428	0.421	0.416
0.18	0.554	0.485	0.462	0.450	0.443	0.439
0.20	0.572	0.505	0.483	0.472	0.465	0.461
0.22	0.589	0.524	0.503	0.492	0.486	0.482
0.24	0.606	0.542	0.522	0.512	0.506	0.502
0.26	0.623	0.560	0.540	0.531	0.525	0.521
0.28	0.639	0.578	0.558	0.549	0.543	0.540
0.30	0.654	0.595	0.576	0.567	0.561	0.557
0.32	0.670	0.611	0.593	0.584	0.578	0.575
0.34	0.685	0.627	0.609	0.600	0.595	0.592
0.36	0.699	0.642	0.625	0.617	0.611	0.608
0.38	0.714	0.658	0.641	0.632	0.627	0.624
0.40	0.728	0.673	0.656	0.648	0.643	0.640

Table 2.5: Minimum Required Correlation for $\delta=0.5$

Missing Baseline Proportion η	Minimum Required Correlation ρ					
	N=20	N=50	N=100	N=200	N=500	N=INF
0	0.414	0.318	0.282	0.263	0.251	0.242
0.02	0.437	0.347	0.314	0.297	0.286	0.279
0.04	0.458	0.373	0.343	0.327	0.317	0.311
0.06	0.479	0.397	0.369	0.354	0.346	0.340
0.08	0.498	0.421	0.394	0.380	0.372	0.366
0.10	0.517	0.442	0.417	0.404	0.396	0.391
0.12	0.535	0.463	0.439	0.427	0.419	0.414
0.14	0.553	0.483	0.460	0.448	0.441	0.437
0.16	0.570	0.502	0.480	0.469	0.462	0.458
0.18	0.587	0.521	0.499	0.488	0.482	0.478
0.20	0.603	0.539	0.518	0.507	0.501	0.497
0.22	0.618	0.556	0.536	0.526	0.520	0.516
0.24	0.634	0.573	0.553	0.543	0.537	0.534
0.26	0.649	0.589	0.570	0.560	0.555	0.551
0.28	0.663	0.605	0.586	0.577	0.571	0.568
0.30	0.678	0.620	0.602	0.593	0.588	0.584
0.32	0.692	0.635	0.617	0.609	0.603	0.600
0.34	0.706	0.650	0.632	0.624	0.619	0.615
0.36	0.720	0.664	0.647	0.639	0.634	0.631
0.38	0.733	0.678	0.662	0.653	0.649	0.645
0.40	0.746	0.692	0.676	0.668	0.663	0.660

Table 2.6: Minimum Required Correlation for $\delta=0.75$

Missing Baseline Proportion η	Minimum Required Correlation ρ					
	N=20	N=50	N=100	N=200	N=500	N=INF
0	0.487	0.408	0.380	0.366	0.357	0.351
0.02	0.505	0.429	0.402	0.389	0.380	0.375
0.04	0.522	0.449	0.424	0.411	0.403	0.398
0.06	0.539	0.468	0.444	0.432	0.424	0.419
0.08	0.555	0.486	0.463	0.452	0.444	0.440
0.10	0.571	0.504	0.482	0.471	0.464	0.459
0.12	0.587	0.521	0.500	0.489	0.482	0.478
0.14	0.602	0.538	0.517	0.506	0.500	0.496
0.16	0.616	0.554	0.534	0.524	0.517	0.513
0.18	0.631	0.570	0.550	0.540	0.534	0.530
0.20	0.645	0.585	0.566	0.556	0.550	0.546
0.22	0.658	0.600	0.581	0.571	0.566	0.562
0.24	0.672	0.614	0.596	0.587	0.581	0.578
0.26	0.685	0.628	0.610	0.601	0.596	0.593
0.28	0.698	0.642	0.625	0.616	0.611	0.607
0.30	0.711	0.656	0.638	0.630	0.625	0.622
0.32	0.723	0.669	0.652	0.644	0.639	0.635
0.34	0.736	0.682	0.665	0.658	0.652	0.649
0.36	0.748	0.695	0.678	0.670	0.666	0.662
0.38	0.760	0.707	0.691	0.683	0.679	0.676
0.40	0.772	0.720	0.704	0.696	0.691	0.688

Table 2.7: Minimum Required Correlation for $\delta=1$

Missing Baseline Proportion η	Minimum Required Correlation ρ					
	N=20	N=50	N=100	N=200	N=500	N=INF
0	0.560	0.493	0.470	0.459	0.452	0.447
0.02	0.574	0.509	0.487	0.476	0.469	0.465
0.04	0.588	0.524	0.503	0.492	0.486	0.482
0.06	0.601	0.540	0.519	0.508	0.502	0.498
0.08	0.615	0.554	0.534	0.524	0.518	0.514
0.10	0.628	0.568	0.549	0.539	0.533	0.529
0.12	0.641	0.582	0.563	0.554	0.548	0.544
0.14	0.653	0.596	0.577	0.568	0.562	0.559
0.16	0.666	0.609	0.591	0.582	0.576	0.573
0.18	0.678	0.622	0.604	0.595	0.590	0.587
0.20	0.690	0.635	0.617	0.609	0.603	0.600
0.22	0.701	0.648	0.630	0.621	0.617	0.613
0.24	0.713	0.660	0.643	0.634	0.629	0.626
0.26	0.724	0.672	0.655	0.647	0.642	0.639
0.28	0.736	0.684	0.667	0.660	0.654	0.651
0.30	0.747	0.695	0.680	0.671	0.666	0.663
0.32	0.758	0.707	0.691	0.683	0.678	0.675
0.34	0.768	0.718	0.702	0.695	0.690	0.687
0.36	0.779	0.729	0.714	0.706	0.702	0.699
0.38	0.790	0.740	0.725	0.717	0.713	0.710
0.40	0.800	0.751	0.736	0.728	0.724	0.721

Table 2.8: Effect of Sample Size on Min-Required Correlation

Mean Difference	Sample size	Mean-Diff	Max- Diff	Min-Diff	95% CI	STD
0	20	0.132	0.248	0.089	0.116~0.148	0.050
	50	0.056	0.127	0.033	0.046~0.067	0.032
	100	0.030	0.074	0.016	0.023~0.037	0.022
	200	0.016	0.042	0.008	0.011~0.020	0.015
	500	0.007	0.018	0.003	0.004~0.010	0.009
0.25	20	0.125	0.232	0.089	0.113~0.136	0.036
	50	0.051	0.115	0.033	0.045~0.058	0.020
	100	0.026	0.066	0.016	0.022~0.030	0.011
	200	0.013	0.036	0.008	0.011~0.015	0.006
	500	0.005	0.015	0.003	0.005~0.006	0.002
0.50	20	0.113	0.172	0.087	0.106~0.121	0.023
	50	0.045	0.076	0.033	0.042~0.049	0.012
	100	0.023	0.040	0.016	0.021~0.025	0.006
	200	0.011	0.020	0.008	0.010~0.012	0.003
	500	0.005	0.008	0.003	0.004~0.005	0.001
0.75	20	0.102	0.136	0.084	0.098~0.107	0.015
	50	0.040	0.057	0.032	0.038~0.043	0.007
	100	0.020	0.029	0.016	0.019~0.021	0.004
	200	0.010	0.015	0.008	0.009~0.011	0.002
	500	0.004	0.006	0.003	0.004~0.004	0.001
1	20	0.092	0.112	0.079	0.089~0.095	0.010
	50	0.036	0.046	0.030	0.035~0.038	0.005
	100	0.018	0.023	0.015	0.017~0.019	0.002
	200	0.009	0.012	0.007	0.009~0.009	0.001
	500	0.004	0.005	0.003	0.003~0.004	0.001

Appendix C: SAS and R Code

SAS Code

SAS Code for WOMET Data

```
/*MANIPULATE WOMTET DATA*/
/*IMPORT WOMET AND OPERATIVE DATA SETS */
PROC IMPORT DATAFILE='C:\Documents and Settings\Felix Feng\My
Documents\project\womet.xls' OUT=PROJECT.WOMET_RAW REPLACE;
RUN;
PROC IMPORT DATAFILE='C:\Documents and Settings\Felix Feng\My
Documents\project\operative.xls' OUT=PROJECT.OPERA_RAW
REPLACE;
RUN;

/*MODIFY WOMTET DATA*/
DATA WOMET(DROP=SOCRE_STAN);
  SET PROJECT.WOMET_RAW (KEEP=PATIENT_NO __ LABEL_VISIT
  SOCRE_STAN);
  SCORE=SOCRE_STAN;
  SCORE=ROUND (SCORE, 0.01);
RUN;
DATA OPERATIVE(DROP=DEVICE __ ARROW_OR_SUTURE __);
  SET PROJECT.OPERA_RAW;
  TREATMENT=DEVICE __ ARROW_OR_SUTURE __;
RUN;

/*SELECT OBSERVATIONS AND CREATE NEW DATA SETS*/
DATA WOMET1 (KEEP=PRESCORE PATIENT_NO__);
  SET WOMET;
  IF LABEL_VISIT="Pre-op";
  PRESCORE=SCORE;
  IF PRESCORE >=0;
RUN;
DATA WOMET2(KEEP=YEAR_1 PATIENT_NO__);
  SET WOMET;
  IF LABEL_VISIT="1 Year";
  YEAR_1=SCORE;
  IF YEAR_1 >=0; RUN;
```

```

DATA WOMET3 (KEEP=YEAR_2 PATIENT_NO__);
  SET WOMET;
  IF LABEL_VISIT="2 Year";
  YEAR_2=SCORE;
  IF YEAR_2 >=0;
RUN;

```

```

/*SORT AND MERGE DATA SETS*/
%MACRO SORT(SET=);
PROC SORT DATA=&SET;
  BY PATIENT_NO__;
RUN;
%MEND SORT;

```

```

%SORT(SET=WOMET1);
%SORT(SET=WOMET2);
%SORT(SET=WOMET3);
%SORT(SET=OPERATIVE);
DATA PROJECT.WOMET;
  MERGE WOMET1 WOMET2 WOMET3 OPERATIVE;
  BY PATIENT_NO__;
RUN;

```

```

/* START TO ANALYSIS DATA */
/*DESCRIPTION ANALYSIS*/
OPTIONS NODATE;
PROC MEANS DATA=PROJECT.WOMET;
  VAR PRESCORE YEAR_1;
  CLASS TREATMENT;
RUN;
PROC TTEST DATA=PROJECT.WOMET;
  TITLE 'UNIVARIATE STATISTICS TEST';
  CLASS TREATMENT;
  VAR PRESCORE YEAR_1;
RUN;
PROC CORR DATA=PROJECT.WOMET;
  VAR PRESCORE YEAR_1;
RUN;

```

```

/* TEST FOR SLOPE=0 */
PROC REG DATA=PROJECT.WOMET;
  MODEL YEAR_1=PRESCORE;
RUN; QUIT;

```

```

/*TEST EQUAL SLOPE FOR TWO GROUPS */
PROC GLM DATA=PROJECT.WOMET;
  CLASS TREATMENT;
  MODEL YEAR_1=PRESCORE TREATMENT PRESCORE*TREATMENT;
RUN; QUIT;

/* PRECISION IN ANOVA MODEL*/
PROC GLM DATA=PROJECT.WOMET;
  TITLE 'TEST DIFFERENCE BETWEEN TREATMENTS USING ANOVA MODEL';
  CLASS TREATMENT;
  MODEL YEAR_1=TREATMENT /SOLUTION;
  LSMEANS TREATMENT /PDIFF STDERR;
  ESTIMATE 'DIFF BEWN TREATMENT' TREATMENT 1 -1;
RUN;
QUIT;

/* PRECISION IN ANCOVA MODEL*/
PROC GLM DATA=PROJECT.WOMET;
  TITLE 'TEST DIFFERENCE BETWEEN TREATMENTS USING ANCOVA MODEL';
  CLASS TREATMENT;
  MODEL YEAR_1=TREATMENT PRESCORE /SOLUTION;
  LSMEANS TREATMENT /PDIFF STDERR;
  ESTIMATE 'SLOPE' PRESCORE 1;
  ESTIMATE 'DIFF BEWN TREATMENT' TREATMENT 1 -1;
  OUTPUT OUT=WOMET_RESID R=RESIDUAL P=PREDICT
RSTUDENT=R_STUDENT;
RUN; QUIT;

/*ABTAIN A DATA BOTH PRE AND POST AVAILBEL*/
DATA WOMET_71OBS;
  SET PROJECT.WOMET;
  IF YEAR_1=. THEN DELETE;
  IF PRESCORE=. THEN DELETE;

/*WOMET71 FOR IMPORT TO R*/
DATA PROJECT.WOMET71;
  SET WOMET_71OBS (KEEP=PRESCORE YEAR_1 TREATMENT);
RUN;
PROC EXPORT DATA= Project.Womet71
  OUTFILE= "C:\womet71.csv"
  DBMS=CSV REPLACE;
RUN;

/* TO OBTAIN THE COEFFICIENTS AND THEIR MSE */

```

```

DATA WOMET_REG;
  SET PROJECT.WOMET;
  IF TREATMENT=1 THEN TREATMENT1=1;
  ELSE TREATMENT1=-1;
RUN;
PROC MEANS DATA=WOMET_REG MEAN;
VAR PRESORE;
OUTPUT OUT=PROJECT.WOMET_REG MEAN=MEAN_X;
RUN;
DATA PROJECT.WOMET_REG;
  IF _N_=1 THEN SET PROJECT.WOMET_REG;
  SET WOMET_REG;
RUN;
DATA PROJECT.WOMET_REG;
  SET PROJECT.WOMET_REG (KEEP=PRESORE YEAR_1 TREATMENT
TREATMENT1 MEAN_X);
  DIFF=PRESORE-MEAN_X;
RUN;
PROC REG DATA=PROJECT.WOMET_REG;
  MODEL YEAR_1=TREATMENT1;
RUN; QUIT;
PROC REG DATA=PROJECT.WOMET_REG;
  MODEL YEAR_1=TREATMENT1 DIFF;
RUN; QUIT;

/*MODEL DIAGNOSTIC */
PROC GLOT DATA=WOMET_RESID;
  TITLE ' ';
  PLOT R_STUDENT*PREDICT;
  PLOT R_STUDENT*TREATMENT;
RUN; QUIT;

PROC UNIVARIATE DATA=WOMET_RESID;
  VAR R_STUDENT;
  HISTOGRAM/ CFILL=GRAY NORMAL KERNEL;
  QQPLOT /NORMAL (MU=EST SIGMA=EST);
RUN;

```

SAS Code for ACL-OLF Data

```

/*MANIPULATE ACL-OLF DATA*/
/*IMPORT ACL-OLF AND OPERATIVE DATA SETS */
PROC IMPORT DATAFILE='C:\Documents and Settings\Felix Feng\My

```

```

Documents\project\Mohtadi_QofLife.xls' OUT=PROJECT.QOF_RAW
REPLACE;
PROC IMPORT DATAFILE='C:\Documents and Settings\Felix Feng\My
Documents\project\operative.xls' OUT=PROJECT.OPERA_RAW
REPLACE;
RUN;

/*MODIFY WOMTET DATA*/
DATA QOF (DROP=OVERALL_MEAN_SCORE_);
  SET PROJECT.QOF_RAW (KEEP=PATIENT_NO__LABEL_VISIT
OVERALL_MEAN_SCORE_);
  SCORE=OVERALL_MEAN_SCORE_+0;
  SCORE=ROUND(SCORE,0.01);
RUN;
DATA OPERATIVE(DROP=DEVICE__ARROW_OR_SUTURE__);
  SET PROJECT.OPERA_RAW;
  TREATMENT=DEVICE__ARROW_OR_SUTURE__;
RUN;

/*SELECT OBSERVATIONS AND CREATE NEW DATA SETS*/
DATA QOF1 (KEEP=PRESCORE PATIENT_NO__);
  SET QOF;
  IF LABEL_VISIT="Pre-op";
  PRESCORE=SCORE;
  IF PRESCORE >=0;
RUN;
DATA QOF2 (KEEP=YEAR_1 PATIENT_NO__);
  SET QOF;
  IF LABEL_VISIT="1 Year";
  YEAR_1=SCORE;
  IF YEAR_1 >=0;
RUN;
DATA QOF3 (KEEP=YEAR_2 PATIENT_NO__);
  SET QOF;
  IF LABEL_VISIT="2 Year";
  YEAR_2=SCORE;
  IF YEAR_2 >=0;
RUN;

/* SORT AND MERGE DATA SETS*/
%MACRO SORT(SET=);
PROC SORT DATA=&SET;
  BY PATIENT_NO__;
RUN;
%MEND SORT;

```

```

%SORT(SET=QOF1);
%SORT(SET=QOF2);
%SORT(SET=QOF3);
%SORT(SET=OPERATIVE);
DATA PROJECT.QOF;
  MERGE QOF1 QOF2 QOF3 OPERATIVE;
  BY PATIENT_NO__;
RUN;

```

```

/* DATA ANALYSIS PART */
/*DESCRIPTION ANALYSIS*/
OPTIONS NODATE;
PROC MEANS DATA=PROJECT.QOF;
  VAR PRESORE YEAR_1;
RUN;
PROC TTEST DATA=PROJECT.QOF;
  TITLE 'SIMPLE STATISTICS TEST';
  CLASS TREATMENT;
  VAR PRESORE YEAR_1;
RUN;
PROC CORR DATA=PROJECT.QOF;
  VAR PRESORE YEAR_1;
RUN;

```

```

/* TEST IF SLOPE=0 */
PROC REG DATA=PROJECT.QOF;
  MODEL YEAR_1=PRESORE;
RUN; QUIT;

```

```

/*TEST EQUAL SLOPE FOR TWO GROUPS */
PROC GLM DATA=PROJECT.QOF;
  CLASS TREATMENT;
  MODEL YEAR_1=TREATMENT PRESORE PRESORE*TREATMENT;
RUN; QUIT;

```

```

/* PRECISION IN ANOVA MODEL */
PROC GLM DATA=PROJECT.QOF;
  TITLE 'TEST DIFFERENCE BETWEEN TREATMENTS USING ANOVA MODEL';
  CLASS TREATMENT;
  MODEL YEAR_1=TREATMENT/SOLUTION;
  LSMEANS TREATMENT /PDIFF STDERR CL;
  ESTIMATE 'DIFF BEWN TREATMENT' TREATMENT 1 -1;
RUN;QUIT;

```

```

/* PRECISION IN ANCOVA MODEL */
PROC GLM DATA=PROJECT.QOF;
  TITLE 'TEST DIFFERENCE BETWEEN TREATMENTS USING ANCOVA MODEL';
  CLASS TREATMENT;
  MODEL YEAR_1=TREATMENT PRESORE /SOLUTION;
  LSMEANS TREATMENT /PDIFF STDERR CL;
  ESTIMATE 'SLOPE' PRESORE 1;
  ESTIMATE 'DIFF BEWN TREATMENT' TREATMENT 1 -1;
  OUTPUT OUT=WOMET RESID R=RESIDUAL P=PREDICT
RSTUDENT=R_STUDENT;
RUN; QUIT;

/* ANOVA MODEL USING ONLY 78 OBS TO BUILD THE ANCOVA TABLE*/
DATA PROJECT.QOF78;
  SET PROJECT.QOF(keep=prescore year_1 treatment);
  IF YEAR_1=. THEN DELETE;
  IF PRESORE=. THEN DELETE;
RUN;
PROC GLM DATA=PROJECT.QOF78;
  CLASS TREATMENT;
  MODEL YEAR_1=TREATMENT;
RUN; QUIT;
PROC GLM DATA=PROJECT.QOF78;
  CLASS TREATMENT;
  MODEL PRESORE=TREATMENT;
RUN; QUIT;

PROC GLM DATA=PROJECT.QOF78;
  TITLE 'TEST DIFFERENCE BETWEEN TREATMENTS USING ANOVA MODEL';
  CLASS TREATMENT;
  MODEL YEAR_1=TREATMENT /SOLUTION;
  LSMEANS TREATMENT /PDIFF STDERR CL;
  ESTIMATE 'DIFF BEWN TREATMENT' TREATMENT 1 -1;
RUN;QUIT;

/* EXPORT SAS DATA TO R */
PROC EXPORT DATA= PROJECT.QOF78
  OUTFILE= "C:\qof78.csv"
  DBMS=CSV REPLACE;
RUN;

/* TO OBTAIN THE COEFFICIENTS AND THEIR MSE */
DATA QOF_REG;
  SET PROJECT.QOF;

```

```

        IF TREATMENT=1 THEN TREATMENT1=1;
        ELSE TREATMENT1=-1;
RUN;
PROC MEANS DATA=QOF_REG MEAN;
VAR PRESORE;
OUTPUT OUT=PROJECT.QOF_REG MEAN=MEAN_X;
RUN;
DATA PROJECT.QOF_REG;
  IF __N_=1 THEN SET PROJECT.QOF_REG;
  SET QOF_REG;
RUN;
DATA PROJECT.QOF_REG;
  SET PROJECT.QOF_REG(KEEP=PRESORE YEAR_1 TREATMENT
TREATMENT1 MEAN_X);
  DIFF=PRESORE-MEAN_X;
RUN;
PROC REG DATA=PROJECT.QOF_REG;
  MODEL YEAR_1=TREATMENT1;
RUN; QUIT;
PROC REG DATA=PROJECT.QOF_REG;
  MODEL YEAR_1=TREATMENT1 DIFF;
RUN; QUIT;

/* calculation SSE for X USING 99 OBSEVATION*/
PROC GLM DATA=PROJECT.QOF;
CLASS TREATMENT;
MODEL PRESORE=TREATMENT;
RUN; QUIT;
/* calculation SSE for X USING 78 OBSEVATION*/
PROC GLM DATA=QOF_78OBS;
CLASS TREATMENT;
MODEL PRESORE=TREATMENT;
RUN; QUIT;

```

R Code

```
/* Calculation for Minimum Required Correlations */
correlation<-function(n,eta,tau){
sqrt(1-(1-eta)*((1-eta)*n-3)*((1-eta)*n-4)/(((1-eta)*n-2)*((1-eta)*n-3+(1-eta)*n*tau^2/))
eta<- seq(0,0.40,by=0.02)
correlation1_20 <-correlation(20,eta,0)
correlation1_50 <-correlation(50,eta,0)
correlation1_100 <-correlation(100,eta,0)
correlation1_200 <-correlation(200,eta,0)
correlation1_500 <-correlation(500,eta,0)
correlaiton_inf<-function(eta,tau){sqrt(1-(1-eta)/(1+tau^2/4))}
eta<- seq(0,0.40,by=0.02)
correlation1_inf <-correlaiton_inf(eta,0)
correlation1_inf

/* Figure for Minimum Correlation */
figure<-function(n,eta,tau){
sqrt(1-(1-eta)*((1-eta)*n-3)*((1-eta)*n-4)/(((1-eta)*n-2)*
((1-eta)*n-3+(1-eta)*n*tau^2/4) ))}
eta<- seq(0.00001,0.9999,by=0.01)
c1_20 <-figure(20,eta,0)
c1_20[81:100] <-1
c1_50 <-figure(50,eta,0)
c1_50[93:100] <-1
c1_100 <-figure(100,eta,0)
c1_100[97:100] <-1
c1_200<-figure(200,eta,0)
c1_200[99:100] <-1
c1_500<-figure(500,eta,0)
```

```

figure_inf<-function(eta,tau){
sqrt(1-(1-eta)/(1+tau^2/4))}
eta<- seq(0.00001,0.9999,by=0.01)
c1_inf <-figure_inf(eta,0)
eta_a<- seq(0.00001,0.39999,by=0.01)
c1_20a <-figure(20,eta_a,0)
c1_50a <-figure(50,eta_a,0)
c1_100a <-figure(100,eta_a,0)
c1_200a<-figure(200,eta_a,0)
c1_500a<-figure(500,eta_a,0)
c1_infa <-figure_inf(eta_a,0)
par(mfrow=c(1,1))
plot(0:1,0:1,xlab="Percentage of Missing Data",ylab="Correlation Coefficient"
, type="n")
lines(eta,c1_20,lty=6,col=6)
lines(eta,c1_50,lty=2,col=5)
lines(eta,c1_100,lty=3,col=3)
lines(eta,c1_200,lty=4,col=4)
lines(eta,c1_500,lty=5,col=2)
lines(eta,c1_inf,lty=1,col=1,lwd=1.5)
box()
legend(0.7,0.6,c("=20","=50","=100","=200","=500","=Infinity"),
cex=1.0,lty=c(6,2,3,4,5,1))
plot(0:0.8,0:0.8,xlim=c(0,0.4),ylim=c(0,0.75),axes=False,ann=False,
main="Practical Missing Range (0~0.40) for Delta=0 ",type="n")
lines(eta_a,c1_20a,lty=6,col=6)
lines(eta_a,c1_50a,lty=2,col=5)
lines(eta_a,c1_100a,lty=3,col=3)
lines(eta_a,c1_200a,lty=4,col=4)

```

```

lines(eta_a,c1_500a,lty=5,col=2)
lines(eta_a,c1_infa,lty=1,col=1,lwd=1.5)
axis(2,at=seq(0,0.80,0.05))
axis(1,at=seq(0,0.4,0.05))
mtext("Percentage of Missing Data", side=1, line=3)
mtext("Correlation Coefficient", side=2, line=3)
mtext("Practical Missing Range (0~0.40) for Delta=0", side=3, line=1,cex=1)
box()
legend(0.3,0.4,c("=20","=50","=100","=200","=500","=Infinity"),
cex=1.0,lty=c(6,2,3,4,5,1))

```

/* Figure and Calculation of Relative Efficiency */

```

effi_m<- function(rau,tau,eta){
(1-rau^2)/(1-eta)*(1+tau^2/4)}
rau_1<- seq(0,1,0.001)
effi_m1<-effi_m(rau_1,1, 0.05)
effi_m2<-effi_m(rau_1,1, 0.25)
effi_m3<-effi_m(rau_1,1, 0.40)
effi_c <-function(rau,tau){
(1-rau^2)*(1+tau^2/4)}
effi_c1<-effi_c(rau_1,1)
plot(0:2.5,0:2.5,xlim=c(0,1),ylim=c(0,2.2),
axes=False,ann=False,
main="Practical Missing Range (0~0.40) for Tau=0 ",type="n")
lines(rau_1,effi_m3,lty=1,col=1)
lines(rau_1,effi_m2,lty=2,col=2)
lines(rau_1,effi_m1,lty=3,col=3)
lines(rau_1,effi_c1,lty=4,col=4)
axis(2,at=seq(0,2.2,0.1))

```

```

axis(1,at=seq(0,1.0,0.1))
mtext("Correlation between Baseline and Post-treatment", side=1, line=3)
mtext("Relative Efficiency", side=2, line=3)
mtext("Relative Efficiency for Large Difference on Covariate Means",
side=3, line=1,cex=1)
box()
abline(h=1)
legend(0.75,1.6,c("=40% Missing ", "=25% Missing ", "= 5% Missing ",
"=No Missing"),cex=0.8,lty=c(1,2,3,4))

```

/* Calculation for the Effect of Missing One Degree of Freedom */

```

correlation<-function(n,eta,tau){
sqrt(1-(1-eta)*((1-eta)*n-3)*((1-eta)*n-4)/(((1-eta)*n-2)*
((1-eta)*n-3+(1-eta)*n*tau^2/4))}
eta<- seq(0,0.40,by=0.02)
correlation1_20 <-correlation(20,eta,0)
correlation1_50 <-correlation(50,eta,0)
correlation1_100 <-correlation(100,eta,0)
correlation1_200 <-correlation(200,eta,0)
correlation1_500 <-correlation(500,eta,0)
correlation1<-function(n,eta,tau){
sqrt(1-(1-eta)*((1-eta)*n-4)/((1-eta)*n-3+(1-eta)*n*tau^2/4))}
eta<- seq(0,0.40,by=0.02)
correlation11_20 <-correlation1(20,eta,0)
correlation11_50 <-correlation1(50,eta,0)
correlation11_100 <-correlation1(100,eta,0)
correlation11_200 <-correlation1(200,eta,0)
correlation11_500 <-correlation1(500,eta,0)

```

/* Import WOMET Data in SAS Format and Calculation for ANCOVA Table */

```
womet<-read.csv("c:/womet4.csv",header=TRUE,sep=" ",
colClasses=c("numeric","numeric","character"))
mean(womet$YEAR_1,na.rm=T)
womet71<-read.csv("c:/womet71.csv",header=TRUE,sep=" ",
colClasses=c("numeric","numeric","character"))
mean_x<-mean(womet71$PRESCORE,na.rm=T)
mean_y<-mean(womet71$YEAR_1,na.rm=T)
sum_xy <-sum(womet71$PRESCORE*womet71$YEAR_1)
spto <- sum_xy-sum(womet71$PRESCORE)*sum(womet71$YEAR_1)/71
sum_x1 <- sum(womet71$PRESCORE[womet71$TREATMENT==1])
sum_x2 <- sum(womet71$PRESCORE[womet71$TREATMENT==2])
sum_y1 <- sum(womet71$YEAR_1[womet71$TREATMENT==1])
sum_y2 <- sum(womet71$YEAR_1[womet71$TREATMENT==2])
spe <- sum_xy-(sum_x1*sum_y1/35+sum_x2*sum_y2/36)
```

/* Import ACL-OLF Data in SAS Format and Calculation for ANCOVA Table */

```
qof78<-read.csv("c:/qof78.csv",header=TRUE,sep=" ",
colClasses=c("numeric","numeric","character"))
mean_x<-mean(qof78$PRESCORE,na.rm=T)
mean_y<-mean(qof78$YEAR_1,na.rm=T)
sum_xy <-sum(qof78$PRESCORE*qof78$YEAR_1)
spto <- sum_xy-sum(qof78$PRESCORE)*sum(qof78$YEAR_1)/78
sum_x1 <- sum(qof78$PRESCORE[qof78$TREATMENT==1])
sum_x2 <- sum(qof78$PRESCORE[qof78$TREATMENT==2])
sum_y1 <- sum(qof78$YEAR_1[qof78$TREATMENT==1])
sum_y2 <- sum(qof78$YEAR_1[qof78$TREATMENT==2])
spe <- sum_xy-(sum_x1*sum_y1/40+sum_x2*sum_y2/38)
```

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