THE IMPACT OF DIFFERENT ESTIMATION PROCEDURES ON NET MONETARY BENEFIT IN CLINICAL TRIALS: A SIMULATION STUDY

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ABSTRACT OF THE DISSERTATION

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Background: Growth in health care spending has led to greater use of cost-effectiveness analysis (CEA) in assessing health technologies. Traditional CEA uses the incremental cost-effectiveness ratio (*ICER*), a measure with statistical issues and limitations with missing data. Better analytic methods for CEA are needed to inform health care policy decisions.

Objectives: The study evaluated estimates of cost-effectiveness from three models using incremental net monetary benefit (*INMB*) rather than *ICER*. Estimates were compared under different conditions of missingness. Data were simulated to include missing at random (MAR) and missing not at random (MNAR) nonresponse mechanisms as defined by Little and Rubin (2002).

Methods: The parameter of interest was *INMB*. Models were ANCOVA, mixed effects (ME), and joint mixed effects and log of time-to-dropout (joint ME), a selection model.

Because the joint ME model incorporates correlation between time-to-dropout and random effects of the longitudinal model of *NMB* into one model, the hypothesis was it would produce the best estimate. Simulated treatment effect provided a "true" *INMB* for model evaluations that included bias (absolute difference from "true"), precision (ratio of variances), and cost-effectiveness acceptability curves with willingness-to-pay (λ) values from \$0 to \$100k. Base case used a threshold criterion for dropout. Sensitivity analyses assessed impact of higher missingness. Post-hoc analysis used a trajectory criterion for dropout.

Results: Base case analyses resulted in ANCOVA and ME models producing the least biased estimates. At λ = \$50k, bias was \$1.3k, \$1.4k, and \$2.3k, and precision was 1.27, 0.90, and 1.24 for ME, ANCOVA, and joint ME, respectively. ANCOVA estimates were best in sensitivity analyses although estimates were poor. The joint ME model performed best in the post hoc analysis.

Conclusions: The models performed differently under alternative missingness conditions and were sensitive to nonresponse mechanisms. All estimates were poor when missingness was high, therefore, primary prevention of missing data should be a goal of research. MNAR nonresponse mechanisms are more complicated than implied by Little and Rubin's definitions as shown by results with threshold versus trajectory criteria for dropout. Further research is needed with selection models in CEA and *INMB* as the measure of cost-effectiveness.

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CHAPTER 1. INTRODUCTION

Health care spending in the United States continues to rank highest in the world. In 2004, U.S. per capita health care spending was $6,102 (US $PPP, i.e., purchasing power parity), which was 2.5 times greater than the median ($2,552) for all thirty industrialized member countries of the Organization for Economic Cooperation and Development (Anderson et al., 2007). U.S. national health expenditures, as a share of gross domestic product, grew from 13.7% in 1993 to 16.0% in 2006, and are projected to reach 19.5% by 2017 (Keehan et al., 2008). The primary factors estimated to drive growth in personal health care spending are medical prices and utilization, population growth, and age-sex mix (Keehan et al., 2008). Since the early 1990s, the cost and utilization of hospital care has accounted for approximately one-third of the total national health expenditures every year, and spending on pharmaceuticals has grown from 5.6 to 10.0 percent of total national health expenditures between the years 1993 and 2004 (U.S. Department of Health and Human Services, 2006).

Continual growth in health care spending has increased payers' interest in cost-effective medical technologies. Analytic methods that facilitate comparisons of medical technologies on cost-effectiveness may help to inform health care policy decisions. The focus of the current study, therefore, was to evaluate different modeling approaches for measuring cost-effectiveness. The study used data that were simulated to include data problems frequently present in clinical trial databases and that pose analytical and interpretation challenges.

Health care spending has also been an issue outside of the United States. In many ways, health authorities around the world are further advanced than in the United States regarding consideration of economic evidence for purchasing and pricing decisions. The National Institute for Clinical Excellence (NICE) in the United Kingdom has been conducting regular reviews of the "best available evidence" for the National Health Service (NHS) since 1999. NICE reviews include economic appraisals of alternative treatments, and the results of these evaluations become guidelines to the NHS on what treatments physicians should choose. Canada, Australia, the Netherlands, Finland, and Portugal are just a few of the other industrialized countries that have begun conducting health technology assessments similar to what is being done in the United Kingdom.

Although health technology assessments are not yet formalized in the United States, there is increasing awareness that resource allocation must be addressed in a systematic manner. For example, the American Academy of Managed Care Pharmacy (AMCP) issued a guideline to pharmaceutical manufacturers for submitting clinical and economic dossiers for formulary consideration (Academy of Managed Care Pharmacy, 2005). The guideline requests that submissions include a modeling report that should present economic models and/or incremental cost-effectiveness analyses. More recently, the Centers for Medicare and Medicaid Services issued a draft guidance document on a new approach to reimbursement policy called "coverage with evidence development" (CED) (Centers for Medicare and Medicaid Services, 2006). The guidance links coverage decisions to evidence-based medicine and clinical research, with one of the goals being to produce savings for the Medicare program.

Good evidence development requires appropriate analytical methods for comparing alternative health interventions. The incremental cost-effectiveness ratio (ICER) has been the standard measure for determining the cost-effectiveness of one treatment compared to another. The ICER is defined as the ratio of the difference in costs to the difference in effectiveness between two treatment alternatives.

Mathematically, the ICER is represented as $ICER = \frac{(\mu_{C1} - \mu_{C0})}{(\mu_{E1} - \mu_{E0})} = \frac{\mu_{\Delta C}}{\mu_{\Delta E}}$. The terms μ_{C1} and μ_{C0} denote the expected values of cost (usually total direct medical costs) for a new experimental treatment, T_1, and a standard of care treatment, T_0. The terms μ_{E1} and μ_{E0} denote the expected values of effectiveness for the treatments T_1 and T_0, respectively. The value of the ICER can be interpreted as the additional investment that is needed for each additional unit of health that is expected from investing in T_1 rather than T_0. When the ICER is less than the maximum price, λ, that society is willing to pay to achieve one more unit of health benefit, then T_1 should be chosen over T_0. That is, if ICER < λ then the new treatment is considered to be a good value.

The ICER, however, has some limitations as a statistic. As a ratio of two asymptotically normal variables, the ICER has a Cauchy distribution. The mean for the Cauchy distribution does not exist and the variance is indefinite, therefore, bootstrap methods or other techniques are necessary to approximate the variance of the ICER for significance testing (Zethraeus et al, 2003). An alternative to the ICER that overcomes the problem of estimating uncertainty when the variance is indefinite is to estimate the incremental net-monetary-benefit (*INMB*) (Stinnett & Mullahy, 1998). The *INMB* is calculated as the maximum value that the payer is willing to pay for one more unit of

effectiveness (λ) times the net effectiveness, minus the net cost. The *INMB* is represented as $INMB = \lambda\mu_{\Delta E} - \mu_{\Delta C}$. The *INMB* reformulates the components of an ICER and the value of λ into a continuous variable that can be expressed in monetary or health units, and is normally distributed in large samples. In regression models with net monetary benefit ($NMB_{ij} = \lambda\mu_{Eij} - \mu_{Cij}$, for patient *i* and treatment *j*) as the dependent variable, the *INMB* would be represented by the parameter estimate for the treatment main effect term (assuming no interaction terms involving treatment). $INMB > 0$ is mathematically the same decision procedure as comparing the ICER to λ. Moreover, the p-value associated with the parameter estimate for the main treatment effect (again, assuming no interaction terms involving treatment) is the probability associated with the statistical test of $INMB = 0$ (Hoch et al, 2002; Van Hout et al, 1994). Therefore, the *INMB* offers an alternative approach to analyzing treatment cost-effectiveness within a regression model framework.

Clinical trials and observational studies are common sources of data for cost-effectiveness evaluations, and a challenge of cost-effectiveness analysis in the context of these studies occurs when there is a significant amount of missing follow-up data. Common reasons for subjects to drop out of clinical studies are death, adverse events, improvement or lack of improvement in symptoms, and other reasons unrelated to the trial procedures. In the presence of missing data, biased estimates of the average total costs and effectiveness will result if a simple sample average is taken. Biased estimates of the average total costs and effectiveness will also result if only completely observed cases are analyzed. Different probability distributions of the patterns of missing

observations in a dataset may require alternative analytical approaches in order to produce unbiased estimates of the treatment effect.

If missingness in a clinical trial does not depend on the values of the response variable, observed or missing, nor on the values of any other variables in the data set, the missing response data are said to be missing completely at random (MCAR) (Little, 1995; Little & Rubin, 2002; Fairclough, 2002). When the missing response data are MCAR, ordinary least squares regression and analysis of covariance (ANCOVA) methods on the subset of completely observed data can be used to obtain valid estimates, although there can be a loss of power from excluding the incomplete observations (Laird, 1988; Lin, 2000). If missingness depends on the values of the observed response variable and covariates, but does not depend on what the values would have been if the data had been captured after dropout, then the missing response data are said to be missing at random (MAR) (Little, 1995; Little & Rubin, 2002; Fairclough, 2002). With MAR data, likelihood-based models and mixed-effects (ME) regression approaches will produce unbiased inferences (Rubin, 1976; Little & Rubin, 2002). The greatest analytical challenge is when the missingness depends on what the response values would have been if the data had been captured after dropout. This type of missing response is referred to as nonignorable or missing not at random (MNAR) (Little, 1995; Little & Rubin, 2002). Response data that are MNAR can occur, for example, when the missingness is associated with greater decline in health status (Fairclough, 2002). MNAR nonresponse should be suspected in long-term studies of certain medical conditions and should be accounted for when performing cost evaluations from these studies. When missing data are MNAR, it is necessary to model both the observed data and the nonresponse

mechanism in order to obtain valid parameter estimates (Rubin, 1976; Laird, 1988; Little, 1995; Little & Rubin, 2002). A joint mixed-effects and log of time-to-dropout (joint ME) model is a model that has been proposed for nonignorable nonresponse (Schluchter, 1992; Ribaudo et al., 2000; Fairclough, 2002; Fairclough et al., 2004). The joint ME model has been used in analyses of quality of life (Fairclough et al., 1998; Ribaudo et al., 2000; Fairclough et al., 2002 and 2003), however, it has not been applied to cost-effectiveness analyses. The current study attempted to use the joint ME model and compared its results to the results of more commonly used models.

1.1 Study Objectives

The objectives of this study were to evaluate and compare estimates of incremental net monetary benefit (cost-effectiveness) from ANCOVA, ME, and joint ME models under different simulated conditions of nonresponse. The dependent variable in the models was total one-year *NMB*, and the parameter of interest was the treatment group effect on *NMB* (*INMB*). The data used in the analysis were simulated from the data structures of an actual clinical trial, and included simulated MAR and MNAR nonresponse mechanisms. Using a simulated dataset allowed for the "true" *INMB* to be calculated and then used in the evaluation of model estimates. The bias and precision of the model estimates were assessed. Sensitivity analyses were performed to determine how the estimates were affected by various levels of MAR and MNAR missing data.

CHAPTER 2. BACKGROUND

Chapter two provides background information to support the choice of *NMB* as the outcome measure and rationales for the selection of methods used in this study. The chapter begins with a description of the ROSE Study, the original naturalistic clinical trial that is the basis for the simulated data in the current study. Section 2.2 provides a description of the incremental cost-effectiveness ratio (*ICER*), the standard measure for determining cost-effectiveness. Section 2.3 explains how an alternative measure (the *INMB*), is derived from components of the *ICER* and the advantages the *INMB* has as a cost-effectiveness measure compared to the *ICER*. The basic concepts of cost-utility analysis are presented in Section 2.4. Because this dissertation deals with the issue of estimation in the presence of missing data, definitions of nonresponse mechanisms are discussed in Section 2.5. Finally, a review of many of the available methods for analyzing incomplete data is provided in Section 2.6.

2.1 Original Data Source

The study that provided the source data for simulation was a one-year, multi-center, randomized, naturalistic clinical trial, also referred to as the Risperidone Outcomes Study of Effectiveness (ROSE) (Mahmoud et al., 2004; Mahmoud et al., 1999). The ROSE Study was conducted between 1995 and 1997 with the objective to compare clinical, health-related quality of life (HRQOL), and economic outcomes for patients with schizophrenia who were treated with the newly available (at that time) antipsychotic medication, risperidone, or with conventional antipsychotics that were the standard of care. Outcome measures included HRQOL, rehospitalization for the

management of relapse, use of psychiatric services, and the cost of psychiatric care.

Twenty-one sites in 17 states participated in the study. Sites included departments of clinical psychiatric research, university hospitals, community mental health clinics, and physician offices at Veterans Affairs, state, county, and private facilities. Patients were eligible to participate if they were experiencing a relapse of schizophrenia at the time of enrollment. Patients could be randomized in the hospital or in an outpatient setting. Patients who were randomized in an outpatient setting were required to meet criteria for relapse that included an exacerbation of symptoms (as determined by a Clinical Global Impression score of at least moderately psychotic, and at least moderate presentation of two of the following psychotic symptoms: delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution), accompanied by an increase in the use of psychiatric services such as use of emergency room or crisis team services, admission to a crisis bed, or unscheduled office/clinic visits. A total of 684 patients were randomized to receive either risperidone (experimental group; N=354) or conventional antipsychotic therapy (control group; N=330) as initial treatment following relapse. Because the frequency of psychiatric hospitalization may be an important predictor of therapeutic outcome in patients with schizophrenia, patients were stratified prior to randomization according to whether they had had one versus two or more previous hospitalizations in the two–year period before entry to the study. All randomized patients were followed for one year regardless of changes in treatment. Study visits were scheduled at month 0 (baseline), and months 4, 8, and 12 following randomization. Patients who withdrew consent prior to study completion were asked to return for a termination visit.

The interviewer version of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) was used to assess physical and mental HRQOL (Ware & Sherbourne, 1992). Data were collected on the frequency and duration of acute psychiatric hospitalizations for the management of relapse, use of nonhospital acute services (i.e., partial hospitalization or acute residential treatment, emergency room visits, encounters with crisis teams, and use of crisis beds), visits for routine mental health services (i.e., psychiatrist, nonphysician medication and therapy, and case management), and the use of other selected neuroleptic medications. Data were collected directly from medical records, pharmacy records, discharge summaries, or other primary sources of documentation by full-time study coordinators. Estimates of the costs for each type of service were derived from secondary sources. In the current study, these costs have been corrected for inflation and are adjusted to 2005 dollars using the Medical Component of the Consumer Price Index. Original and adjusted costs are presented in Table 2.1-1.

Table 2.1-1 Costs of services from the ROSE Study

Health Care Service (Unit)	Source (Year)	Original Cost Scalar	2005 Adjusted Cost Scalar[a]
Hospitalization for the management of relapse (hospital day)	Medicare Cost Reports (1993)	$575	$916
Partial hospitalization (hospital day)	U.S. Department of Defense's CHAMPUS program (1995)	$240 (full-day) $120 (half-day)	$346 (full-day) $173 (half-day)
Residential treatment (treatment day)	U.S. Department of Defense's CHAMPUS program (1995)	$240 (full-day) $120 (half-day)	$346 (full-day) $173 (half-day)
Emergency room (visit)	Medicare's Resource-Based Relative Value Scale (RBRVS) (1995)	$133	$192
Encounter with crisis team (day)	Medicare's RBRVS (1996)	$205	$290
Crisis bed (day)	Cost of ER or crisis team encounter plus 50% of a hospital day (1995)	$205 +$287	$709
Mental health physician office visit[b] (visit)	Medicare's RBRVS (1995)	$49	$71
Psychotherapy (visit)	Medicare's RBRVS (1995)	$40	$58
Treatment for side effects (visit or medication)	75% of mental health physician office visit (1995)	$37	$51
Disease-related medications (prescription)	Average wholesale price from Pharmacist's Redbook (1997)	By medication	By medication

[a] Adjusted costs are the original cost values adjusted to 2005 U.S. dollars using the Medical Component of the Consumer Price Index.

[b] Includes psychiatrist, nonphysician medication and therapy, and case management.

Selected results from the ROSE Study are shown in Table 2.1-2. The final number of patients analyzed was 675 due to nine patients being dropped from the analysis because of questionable data collection procedures at one of the study sites. Site of care varied at time of randomization, with 442 patients randomized as inpatients and 233 patients randomized as outpatients. The study population included patients with health insurance benefits through Medicaid and Medicare, including patients with dual

eligibility for benefits from both programs (risperidone 73.3%, conventional antipsychotics 71.1%). Early dropout from the study occurred in 14.7 and 19.1% of risperidone- and conventional antipsychotics-treated patients, respectively. The difference between the groups in early dropout was primarily due to loss to follow-up: risperidone 5.4% compared to conventional antipsychotics 10.0%.

Table 2.1-2 Insurance type, dropouts, month 12 SF-36, and annual costs from the ROSE Study

	Risperidone N=349	Conventional antipsychotics N=326
Insurance type, %		
Medicaid/Medicare	73.3	71.1
Veterans Administration	15.8	17.5
Other	10.9	11.4
Early dropout, %	14.7	19.1
Lost to follow-up	5.4	10.0
Withdrew consent	4.4	4.2
Death	1.4	1.2
Other[a]	3.4	3.6
Month 12 SF-36 MCS[b], mean (SD)[c]	40 (12.6)	37 (13.3)
Annual costs, mean (SD)[c,d]	$23,709 (25,254)	$21,746 (24,870)

[a] Includes dropout due to side-effects and lack of efficacy.
[b] MCS is the Mental Component Summary from the SF-36.
[c] $p < .05$ from ANCOVA controlling for study center, prior hospitalizations, and whether patient was randomized in hospital or in an outpatient setting.
[d] All costs in the original study were adjusted to 1996 U.S. dollars using the Medical Component of the Consumer Price Index.

Twelve-month results from the ROSE Study showed that patients randomized to risperidone had significantly better SF-36 mental component summary (MCS) scores compared to patients randomized to conventional therapy, suggesting greater effectiveness with risperidone (Table 2.1-2). However, patients randomized to conventional therapy had significantly lower total costs at month 12 (Mahmoud et al, 2004; Mahmoud et al, 1998).

The relationships between costs, utilities (derived from the SF-36), patient age, and prior hospitalizations in the ROSE Study were maintained in the process of generating the simulated dataset for the current study, thus creating more realistic data than are frequently used in simulation studies. Simulated data are often based on a chosen distribution for the dependent variable and covariates without consideration for the correlations between variables. Although such data may be adequate for comparing methods, they are probably not representative of real clinical trial data and results from those studies may not provide information on the performance of methods when applied to real data. The simulation procedure used in this study is described in Chapter 3.

2.2 The Incremental Cost-effectiveness Ratio

This section provides a description of the incremental cost-effectiveness ratio (*ICER*), which is the standard measure used in cost-effectiveness analysis. The *ICER* is represented as the ratio of the difference in expected costs of two treatments to the difference in the expected effects.

$$ICER = \frac{(\mu_{C1} - \mu_{C0})}{(\mu_{E1} - \mu_{E0})} = \frac{\mu_{\Delta C}}{\mu_{\Delta E}} \tag{2.1}$$

The terms μ_{C1} and μ_{C0} denote the expected values of cost for a new experimental treatment, T_1, and a standard of care treatment, T_0. The terms μ_{E1} and μ_{E0} denote the expected values of effectiveness for the treatments T_1 and T_0, respectively. When the *ICER* is less than the maximum price that society is willing to pay (λ) to achieve one more unit of health effect, then T_1 should be chosen over T_0. In other words, when $\mu_{\Delta C} / \mu_{\Delta E} < \lambda$, the choice should be treatment T_1.

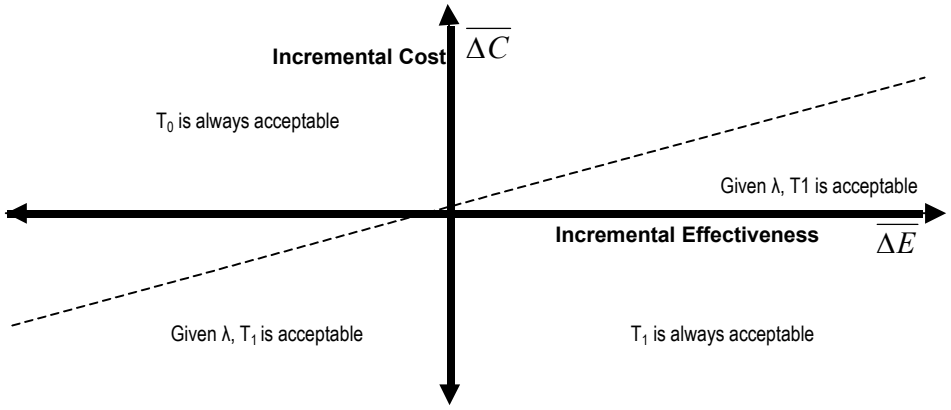
True population means are not known, therefore, the *ICER* is estimated using the sample means for cost, $\overline{C}_1$ and $\overline{C}_0$, and effectiveness, $\overline{E}_1$ and $\overline{E}_0$.

$$\hat{ICER} = (\overline{C}_1 - \overline{C}_0)/(\overline{E}_1 - \overline{E}_0) = \overline{\Delta C}/\overline{\Delta E}$$

The uncertainty in these treatment group estimates of cost and effectiveness needs to be reflected in the confidence intervals around the *ICER*. However, calculating confidence intervals around an *ICER* is not simple because ratios of asymptotically normal variables are Cauchy distributed, and the mean of a Cauchy distribution does not exist and the variance is indefinite (DeGroot, 1975). Consequently, bootstrap methods or other techniques, such as the delta method by O'Brien et al. (1994), nonparametric bootstrapping (Efron & Tibshirani, 1986; Efron & Tibshirani, 1993), or use of Fieller's theorem (Chaudhary & Stearns, 1996), are necessary to approximate the variance of the *ICER* for significance testing. Part of the reason for this complexity is that when there is significant uncertainty regarding the sign of an intervention's incremental cost and/or incremental effectiveness, constructing interpretable confidence intervals around the *ICER* is challenging, regardless of the method used (Stinnett & Mullahy, 1998).

The cost-effectiveness plane (Figure 2.2-1), first introduced by Black (1990), helps to illustrate the challenges in interpretation of the *ICER* and confidence intervals around the *ICER*.

Figure 2.2-1 The cost-effectiveness plane



Adapted from Black (1990) and Stinnett & Mullahy (1998)

The horizontal axis measures the incremental effectiveness, $\overline{\Delta E}$, and the vertical axis measures the incremental cost, $\overline{\Delta C}$, of T_1 versus T_0. The slope of the dashed line represents λ, the threshold of the societal or payer willingness to pay value. The decision rules for choosing T_1 or T_0 involve determining where the *ICER* falls relative to λ in each of the quadrants.

Quadrant	Decision Rule	Sign of *ICER*
Upper right	Choose T_1 if and only if $ICER < \lambda$	+
Lower right	Choose T_1	-
Lower left	Choose T_1 if and only if $ICER > \lambda$	+
Upper left	Choose T_0	-

The rule generally states that if the *ICER* falls below the dashed line, then T_1 is acceptable. One problem with interpretation of the *ICER* is that it has a positive value in the upper right and lower left quadrants and a negative value in the lower right and upper left quadrants. A negative *ICER* in the lower right quadrant is favorable for T_1 because in

this quadrant T_1 is more effective and less costly than the alternative treatment (T_1 is dominant). However, in the upper left quadrant, a negative *ICER* is favorable for T_0 (T_0 is dominant or T_1 is dominated). Thus, just knowing that the *ICER* is negative is insufficient to determine cost-effectiveness.

One does not usually calculate an *ICER* in the situations when a treatment is dominant. However, if one were to present the estimated *ICER*, interpretation would also require information about the magnitudes of the numerator and denominator. This is because a large negative *ICER* can be due to either greater cost savings in the numerator or lower incremental effectiveness in the denominator. Regardless of the sign of the *ICER*, information about the magnitudes of the numerator and denominator is always useful and should be reported.

The interpretation problem for the *ICER* extends to the upper right and lower left quadrants. For positive *ICER*s, a value that is *less* than λ is favorable for T_1 in the upper right quadrant (incremental effectiveness greater than zero). However, in the lower left quadrant (incremental effectiveness less than zero) a positive *ICER greater* than λ is favorable for T_1. In other words, the decision rule for the *ICER* depends on the sign of the effect difference. Because of these problems, if the joint probability distribution of costs and effects extends to more than one quadrant of the cost-effectiveness plane, any inferences based on the distribution of the *ICER* and its confidence intervals will be ambiguous (Stinnett & Mullahy, 1998).

2.3 Net Monetary Benefit

The *INMB* was selected as the measure of treatment cost-effectiveness in the current study because it has statistical properties that allow it to be analyzed within the

structure of regression models. This section explains how the *INMB* is derived from the concepts and components of the *ICER*. Also presented is a discussion of the interpretation, advantages, and limitations of the *INMB* as an alternative to the *ICER*.

A fundamental problem with ratios, and therefore with the *ICER*, is that the mean of ratios is not equal to the ratio of means. This means that the overall incremental cost-effectiveness ratio cannot be constructed from the difference between average cost-effectiveness ratios from the different treatment groups $\left(\frac{\overline{C}_1}{\overline{E}_1} \text{ and } \frac{\overline{C}_0}{\overline{E}_0}\right)$ in a clinical trial, i.e., $\frac{\overline{C}_1}{\overline{E}_1} - \frac{\overline{C}_0}{\overline{E}_0} \neq \frac{\overline{C}_1 - \overline{C}_0}{\overline{E}_1 - \overline{E}_0}$ (Stinnet & Paltiel, 1997). Alternatively, the overall incremental net monetary benefit ($\hat{INMB}$) can be constructed from the difference in mean net monetary benefit from the different treatment groups ($\overline{NMB}_1$ and $\overline{NMB}_0$) as shown in Equation 2.2. The *NMB* of a treatment is the difference between the treatment's effect (*E*) valued in dollars (λ), and its cost (*C*) ($NMB = \lambda E - C$). The estimated *incremental* net monetary benefit, $\hat{INMB}$, can be calculated as the difference between the sample estimates of two treatment groups' (T_1 and T_0) mean effect ($\overline{E_1}$ and $\overline{E}_0$) and cost ($\overline{C}_1$ and $\overline{C}_0$) differences:

$$\begin{aligned} \hat{INMB} &= \overline{NMB}_1 - \overline{NMB}_0 \\ &= (\lambda\overline{E}_1 - \overline{C}_1) - (\lambda\overline{E}_0 - \overline{C}_0) \\ &= \lambda(\overline{E_1} - \overline{E}_0) - (\overline{C}_1 - \overline{C}_0) \\ &= \lambda\Delta\overline{E} - \Delta\overline{C}\,. \end{aligned} \tag{2.2}$$

Further, the $\hat{INMB}$ is a linear combination of the two asymptotically normal random variables, $\Delta\overline{E}$ and $\Delta\overline{C}$, making the $\hat{INMB}$ a continuous variable that is asymptotically normal by the central limit theorem (Hoch et al., 2002).

From the previous section, the threshold criterion for cost-effectiveness is achieved when the *ICER* equals λ, i.e., $\overline{\Delta C} / \overline{\Delta E} = \lambda$. Recall the decision rule for values of the *ICER* that are favorable for T_1:

when $\overline{\Delta E} > 0$ (right quadrants), $ICER = \overline{\Delta C} / \overline{\Delta E} < \lambda$ is favorable for T_1, and

when $\overline{\Delta E} < 0$ (left quadrants), $ICER = \overline{\Delta C} / \overline{\Delta E} > \lambda$ is favorable for T_1.

By rearranging the components of either inequality, and multiplying the second by -1, one obtains $\lambda\overline{\Delta E} - \overline{\Delta C} > 0$. This inequality describes the area under the λ line. The expression on the left-hand side of the inequality describes a treatment's net monetary benefit relative to another treatment. The decision rule for the $\hat{INMB}$ is to choose T_1 over T_0 if $\hat{INMB} > 0$. While the decision rule for the *ICER* is dependent on the sign of the effectiveness difference, the decision rule for the $\hat{INMB}$ is not.

The linear relationship between group mean effects and costs and the $\hat{INMB}$ shown above in Equation 2.2, allows the *NMB* measure to be used as the dependent variable in an ordinary least squares (OLS) regression model (Hoch et al., 2002). If the data were completely observed with no repeated measures (e.g., in a single cross-section at a time point of a study with two treatment groups), the estimated coefficient associated with treatment from a standard regression model would estimate the *INMB* attributable to T_1 as compared to T_0.

$$NMB_i = \lambda E_i - C_i = \alpha + \beta \ GROUP_i \quad + \varepsilon_i \qquad (2.3)$$

Equation 2.3 shows how NMB_i, derived from the observed effect (E_i) and cost (C_i) for the i^{th} patient, can be modeled; α is the intercept term, β the parameter for treatment group (GROUP*)* on *NMB*, and ε the random error term. The parameter estimate for β is the estimate of the *INMB*. Factors for time and group-by-time interaction could be added to account for repeated measures, and covariates could be added to adjust for group differences in potentially confounding factors.

A limitation of the *NMB* measure for estimating cost-effectiveness is that the value society is willing to pay (λ) for one more unit of health effects is unknown. To address this, Stinnett & Mullahy (1998) have recommended conducting analyses at different levels of λ and reporting $\hat{INMB}$ as a function of λ. Stinnett & Mullahy further recommend using the notation, $\hat{INMB}_\lambda$ to indicate the value of λ corresponding to the estimate. This notation is used in the current study.

2.4 Cost-Utility Analysis

The current study used quality-adjusted life years (QALYs) as the measure of treatment effectiveness in the calculation of the *INMB*. QALYs were selected as the effectiveness measure because it is the measure recommended by the U.S. Public Health Service Panel (USPHSP) on Cost-Effectiveness in Health and Medicine (Gold et al., Chap.1, 1996) for use in Reference Case analyses. A Reference Case analysis allows for comparability of study results across multiple studies in order to inform resource allocation decisions. The Panel recommends the QALY as an effectiveness measure

because it incorporates morbidity and mortality consequences in a single measure. This section provides an explanation of QALYs. The cost-effectiveness literature in schizophrenia is also reviewed to illustrate how cost-effectiveness in the therapeutic area of schizophrenia has been an ongoing concern for over a decade.

Cost-effectiveness analysis (CEA) involves comparing the economic consequences of a given treatment to an alternative, using a measure of effectiveness, such as years of life gained, hospitalizations avoided, or QALYs. Cost-utility analysis (CUA) is a specific form of cost-effectiveness evaluation that compares the economic consequences of two or more treatments using some variant of QALYs as the measure of effectiveness. Although CEA is a more general term, the two terms CEA and CUA are used interchangeably throughout this dissertation.

A QALY is an effectiveness measure that is a sum of time units adjusted by health utility weights. Utility is an economic term meaning preference or value. Utility weights are measures of patients' valuations of different health states and outcomes, valued relative to one another on a scale from 0 to 1. When utility weights are multiplied by the time spent in the health state and expressed in years of perfect health, the resulting measure is a QALY. An advantage of the QALY as an effectiveness measure is it combines quality and quantity of life into one measure. QALYs can capture the impact of side effects and the psychological concerns with illness that may be important as well as the value of a treatment.

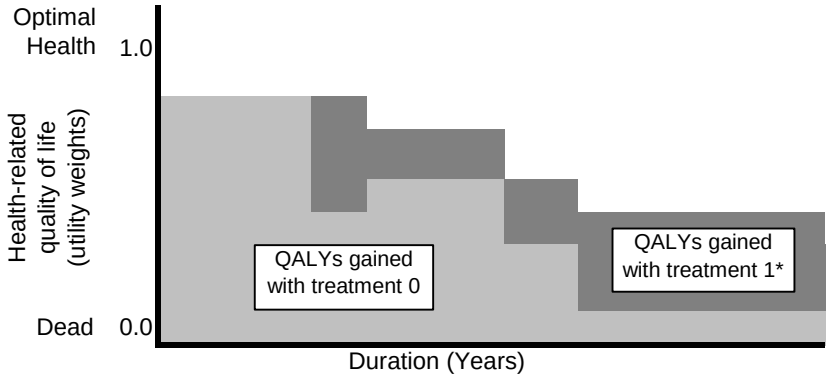
In more detail, the first step to calculating QALYs is to measure and assign utilities to health states. Utility weights are interval-scaled measures (i.e., equal intervals on the preference scale have equivalent interpretations). The two extremes of the scale

are typically optimal health (assigned the value 1.0) and death (assigned the value 0). Numerical preference weightings are assigned to states between these two extremes. Each health state is comprised of different health domains, such as physical functioning and role limitations. Developing a health utility score for each health state involves combining the effect of each domain into a single metric. A variety of scaling methods, such as rating scale, standard gamble, time trade-off, and person trade-off, are used for assigning numerical preference weightings. Standard gamble (SG) is the classical method for measuring health preferences. Derived from utility theory, SG was first presented by von Neumann and Morgenstern (1953). The approach is to offer two alternative scenarios to an individual for evaluation. The first is a treatment with two possible outcomes: either the individual is returned to normal health and lives for an additional *t* years (with probability *p*), or the person dies immediately (with probability 1 - *p*). The second alternative is a chronic illness (state *i*) that will happen with certainty if chosen, and that will result in an additional *t* years of life. The probability *p* is varied until the individual is indifferent to the two alternatives. At this point in the process, the preference value for state *i* is set equal to *p* (Drummond et al., 1987). Brazier et al. (2002) used a variant of standard gamble to estimate the preference-based utility weights that were used in the current study.

The weighted average number of QALYs is the sum over all health states of the utility weight for each health state multiplied by the duration in years (or fractions of years) spent in that health state. QALYs for one treatment alternative can be illustrated by the area under a curve (Figure 2.4-1). The difference in QALYs between two

treatments is the difference between the areas under their two curves (Gold et al., Chap.4, 1996).

Figure 2.4-1 QALYS gained from treatment 1 versus treatment 0



* QALYs gained with treatment 1 is the sum of the two shaded areas.

Adapted from Gold et al., Chap. 4 (1996)

Despite the advantages of combining quality and quantity of life into a single measure, pros and cons of the QALY as an effectiveness measure have been debated by many (from Gold et al., Chap 4., 1996; Donaldson et al., 1988; Weinstein, 1988; Loomes & McKenzie, 1989; Mehrez & Gafni, 1989; Carr-Hill, 1989; Cox et al., 1992; Gafni & Birch, 1993; Mehrez & Gafni, 1993; Culyer & Wagstaff, 1993; Fryback, 1993; Johannesson et al, 1993; and Broome, 1993). The different choices of scaling method and sources of utility values (patients, health care providers, general public) have raised concerns that the precise meaning of the utility scores may depend on the method and values used, and that different methods could produce a variety of results for the same health state from the same respondents (Brinsmead & Hill, 2003).

The variant of standard gamble employed by Brazier et al. (2002) and used in the current study was one method for mapping SF-36 scores to utilities. In Brazier's study, a

representative sample of members from the general population in the United Kingdom evaluated health states defined by the SF-6D (an instrument derived from the SF-36) using a variant of SG developed by a team at McMaster University (Furlong et al., 1990). The interviews involved displaying the probabilities on a chance board, both numerically and in the form of a pie chart. The health states included physical functioning, role limitations, social functioning, pain, mental health, and vitality. These domains, and particularly, role limitations, social functioning, and mental health, are important for the current study population because schizophrenia is a disease that seriously impairs patients' lives in these areas.

In the current study, QALYs were calculated by mapping the SF-36 to utilities using the function developed by Brazier. Although using Brazier's method may not be ideal (because it required applying U.K.-derived utilities to SF-36 scores of U.S. patients), this method was considered to be an adequate approximation because the primary objective was to compare modeling approaches for *NMB* estimation under conditions of missing data (and not to perfect the estimation of QALYs).

Three CUA studies in schizophrenia have been published over a period that spans more than a decade. In each of these studies, cost-effectiveness was evaluated by comparing an atypical to a conventional antipsychotic. Chouinard & Albright (1997) performed a CUA comparing the antipsychotic medications, risperidone and haloperidol. Standard gamble preference ratings were used from psychiatric nurses who rated patients' symptomatology profiles as mild, moderate, or severe. The three severity levels (or health states) were derived from a cluster analysis of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) from a Canadian multi-center risperidone

trial. Mean utility values and 95% confidence intervals for the three health states were 0.61 ± 0.069 (mild); 0.36 ± 0.073 (moderate); and 0.29 ± 0.071 (severe). The utilities were applied to data from 130 patients in the same trial, where each patient was placed into one of the three severity categories. Costs were reported in 1995 Canadian dollars, with an incremental cost-utility ratio of $24,250 per QALY for patients treated with risperidone versus haloperidol.

The second CUA, by Oh et al., (2001), was conducted to compare treatment outcomes for the atypical antipsychotic, clozapine, to the standards of care treatments of haloperidol and chlorpromazine. An incidence-based deterministic decision analysis was used to model treatment outcomes over one year. Probabilities of clinical outcomes were estimated from a random effects meta-analysis of three randomized clinical trials with a combined total of 157 patients. The utility weights were obtained from a sample of seven schizophrenia patients using standard gamble methodology. Costs were reported in 1995 Canadian dollars, with results indicating that clozapine was estimated to save $38,879 per year while producing 0.04 additional QALYs, compared to chlorpromazine.

The third study was a recently published cost-effectiveness analysis from the National Institutes of Mental Health-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (Rosenheck et al., 2006). The CATIE Trial was a randomized, double-blind, 18-month study of the relative effectiveness of four of the atypical antipsychotics (olanzapine, quetiapine, risperidone, and ziprasidone) that were available on the market in 2002, and one conventional antipsychotic (perphenazine). The study was conducted to address questions regarding how to best allocate medication spending for patients with schizophrenia. The study enrolled and followed 1,493 patients

for up to 18 months. The CUA included various methods for deriving utilities, however, the main cost utility analysis was based on QALYs as derived from a mapping function of the PANSS subscale scores and side effects. Costs were based on resource use that was self-reported by the patients. All costs were represented in 2002 US dollars. Analyses included an intention-to-treat (ITT) analysis using all available follow-up data, and an analysis of patients who remained on their initially assigned treatment. Costs were analyzed with a mixed-effects model with terms for treatment group, baseline value of the dependent cost variable (which included costs in the month prior to the study), time, site, history of recent clinical exacerbation, and baseline characteristics-by-time interactions. Costs were log-transformed. A similar mixed-effects model was used for the effectiveness analysis.

Results from the ITT analysis showed that 31.8% of patients had dropped out of the study by month 6, with significant differences in the proportion of participants across randomized treatments. At 18 months, the percent of patients who had dropped out had increased to 54.3%, and differences in participation across the treatment groups were no longer significant. Average monthly health care costs in the ITT analysis were lowest for the patients randomized to perphenazine ($1,131) (significant overall and in all pair-wise comparisons), and among the atypical antipsychotics ranged from $1,433 for olanzapine to $1,730 for ziprasidone. There were no significant differences in QALYs across all treatment groups (range: 0.72 for perphenazine to 0.70 for risperidone).

Only 25.9% of all patients completed 18 months with their initially assigned treatment. Average monthly health care costs were similar to the ITT results with costs being lowest for the patients randomized to perphenazine ($959) (significant overall and

in all pair-wise comparisons), and costs among patient who remained on treatment with an atypical antipsychotic ranging from $1,404 for olanzapine to $1,770 for ziprasidone. There were no significant differences in QALYs across all treatment groups (range: 0.73 or perphenazine to 0.71 for risperidone). Because results for the perphenazine group were consistently and significantly less expensive and not less effective than the next most effective treatment, *ICER*s were not calculated. One of the important outcomes of the CATIE trial, as it relates to the current study, was the high dropout rate in this patient population.

These three studies illustrate the ongoing interest in evaluating the cost-effectiveness of available treatments for schizophrenia. The CATIE cost-effectiveness study highlights how missing data pose a challenge for cost evaluations. Analytic methods that improve these evaluations may be valuable for future schizophrenia research, as well as for research in other therapeutic areas.

2.5 Patterns and Mechanisms of Nonresponse

The current study compared different analytic methods for estimating treatment cost-utility in the presence of missing response data. In longitudinal clinical trials, there can be numerous reasons why data are missing, and choosing an appropriate method for analysis begins with understanding the mechanisms that lead to the missing data. This section provides an overview of the different types of missing data, definitions of mechanisms of nonresponse, and whether the assumptions for each mechanism can be checked.

Missing or censored data can occur in a variety of situations. (1) One situation is when a study's timeframe is not long enough to observe all events, such as death or total health care costs until death. In this type of censoring, the data for individuals who experience the event after the end of the study are considered administratively censored. The current study does not deal with this type of missing data. (2) Another type of censored data occurs when some individuals drop out before the study's timeframe has elapsed. For example, if a study's objective is to estimate total health care costs over one year, then the data for individuals who withdraw or die prior to completing the study are dropouts and are considered censored. The missing data pattern for these patients is referred to as monotone or terminal dropout. A monotone pattern of missing data is the pattern created in the current study via the simulation process. (3) Another pattern, referred to as nonmonotone or intermittent dropout, occurs when a patient misses an assessment in between other nonmissing assessments. Nonmonotone patterns can occur along with monotone patterns within a dataset from a clinical trial. Examples of what these two types of patterns would look like from the ROSE Study, with assessments taken at months 0, 4, 8, and 12, are shown in Table 2.5-1.

Table 2.5-1 Monotone and nonmonotone missing data patterns

	Monotone				Nonmonotone			
Month:	0	4	8	12	0	4	8	12
	X	X	X	.	X	X	.	X
	X	X	.	.	X	.	X	X
	X	.	.	.	X	.	.	X

X = observed response; **.** = missing response

With the monotone pattern, no observations are made on a patient after a certain time point. The patient is considered a dropout after the last observed

assessment. In the case of the nonmonotone pattern, subsequent observations are made on a patient following a missing observation or multiple missing observations. The nonmonotone pattern generally represents missingness due to factors unrelated to patients' health status, such as forgetting an appointment or missing an assessment due to lack of transportation. The monotone pattern is more problematic because the reasons for missingness are more likely to be related to the outcome of interest. This pattern may be seen in clinical trials of chronic illnesses where patients drop out because they either respond or fail to respond to treatment. In the case of the current study, patients with schizophrenia may drop out due to uncontrolled (or controlled) symptoms, which could contribute to lower (or higher) health status, costs, and presumably be associated with the response variable, net monetary benefit. Because a monotone missing data pattern is more likely to reflect relationships between missingness and the outcome variable, the current study focuses on this pattern of missingness.

Rubin (1976) first formalized a theory about the relationships between observed response data and the reasons for missingness, and he referred to these relationships as missing data mechanisms. His theory defined three major classes of missing data mechanisms that differ by how the missingness is related to the outcome of interest. The three classes are (1) data missing completely at random (MCAR), (2) data missing at random (MAR), and (3) data missing not at random (MNAR). The definitions used in this dissertation and the notation used in the following explanation of these nonresponse mechanisms are the same as those originally proposed by Rubin (1976), Little and Rubin (1987), and updated by Little (1995) and Little & Rubin (2002).

Let $\boldsymbol{y}_{ij} = (y_{i1}, \ldots, y_{iK})$ denote a (1 *x K*) data vector of the responses (dependent variable, *Y*) for patient *i* ($i = 1, \ldots, n$) at times *j* ($j = 1, \ldots, K$). Observed and missing responses for patient *i* are denoted as ($\boldsymbol{y}_{obs,i}$, $\mathbf{y}_{mis\,i}$). Observed and missing data for variable *Y* are denoted as Y_{obs} and Y_{mis}. Let $\boldsymbol{X}_i$ be fixed covariates that are assumed to be fully observed, such as patient age, country of residence, times of measurement ($t_{i1}, \ldots, t_{iK}$), and treatment group assignment. When the missing data have a monotone pattern of missingness, M_i represents a single missing indicator that takes the value $M_i = j$ if $y_{i1}, \ldots, y_{ij-1}$ are observed and $y_{ij}, \ldots, y_{iK}$ are missing, and takes the value $M_i = 0$ for complete cases. The missing data mechanism describes the relationship between the observed data and the probability of data being missing, and is represented by the conditional distribution of M_i given $\boldsymbol{y}_i$, and $\boldsymbol{X}_i$, denoted as $f(M_i \mid \boldsymbol{y}_i, \boldsymbol{X}_i)$. Table 2.5-2 provides a summary of the three missing data mechanisms.

Table 2.5-2 Summary of the three major classes of missing data mechanisms

	Notation	Missingness is dependent on…	Missingness is independent of…
MCAR Missing completely at random	$\Pr(M_i \mid \boldsymbol{y}_i, \boldsymbol{X}_i) = \Pr(M_i)$		• Observed responses • Missing responses • Covariates
Covariate dependent dropout	$\Pr(M_i \mid \boldsymbol{y}_i, \boldsymbol{X}_i) = \Pr(\boldsymbol{X}_i)$	• Covariates	• Observed responses • Missing responses
MAR Missing at random	$\Pr(M_i \mid \boldsymbol{y}_i, \boldsymbol{X}_i) = \Pr(\boldsymbol{y}_{obs,i}, \boldsymbol{X}_i)$	• Observed responses • Covariates	• Missing responses
MNAR Missing not at random (nonignorable)	$\Pr(M_i \mid \boldsymbol{y}_i, \boldsymbol{X}_i) = \Pr(\mathbf{y}_{mis})$	• Missing responses	

Adapted from Rubin (1976), Little and Rubin (1987), Little (1995), Little & Rubin (2002), and Fairclough (2002).

MCAR. Missing data are said to be MCAR if missingness does not depend on values of the observed or missing response variable. Further, missingness should not depend on values of any other variables in the data set (Table 2.5-2). This is the strongest assumption of the three missing data mechanisms. When this assumption is satisfied, the probability of missingness is entirely independent of the response variable, and data for complete cases can be regarded as a simple random sample from the total study data set. Examples include missing data due to a patient moving or the study staff forgetting to provide the assessment. It is uncommon for this assumption to hold for the majority of missing data in a trial. Another mechanism, referred to as covariate-dependent dropout,

allows the probability of missingness to be dependent on covariates. Covariate-dependent dropout has been classified as a special case of MCAR by some authors (Diggle & Kenward, 1994; Fairclough, 2002), and as MAR by others (Allison, 2002). An example of this mechanism of nonresponse would be if missingness depended upon the age, gender, or ethnic group of the patients.

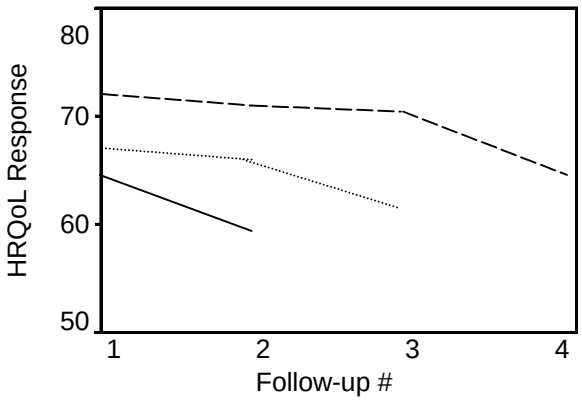
MAR. An assumption that is less restrictive than MCAR and covariate-dependent dropout is one where the missingness depends on values of the previously observed response variable and covariates, but does not depend on what the values would have been among the missing response data (Table 2.5-2). When missing data for the response variable are MAR, the pattern of missingness is predictable from the observed data in the study. An example of MAR by study design would be a study that required patients to discontinue if the value of the response variable at their last assessment exceeded some threshold value, such as blood pressure equal to or above 160/92 mm Hg, indicating stage 2 hypertension. Another example of MAR data would be when response data are missing for patients whose health status was observed to be declining at previous study visits.

MNAR. If the probability of missingness depends on what the response values would have been if the individuals who dropped out could have been assessed, then the missing data mechanism is referred to as missing not at random or nonignorable missing (Table 2.5-2). When data are MNAR, a systematic difference exists between respondents and nonrespondents who have the same values for the previously observed responses or covariates, and the missing data pattern cannot be predicted from the collected data. Data

may be MNAR if patients drop out of a study due to a decline in health status that began to occur since the time of their last study visit.

Determining whether missing data are MCAR or MAR can be accomplished by using logistic regression to examine the associations between the probability of missingness and the values of the observed response, Y_{obs}, and covariates, X. If the MCAR assumption holds, there should be no associations between Y_{obs} and X and the probability of a missing response. An approach for checking the MAR assumption is to graphically display average observed responses by cohorts of patients defined by their pattern of missing data. An example from Fairclough (2002) is presented in Figure 2.5-1.

Figure 2.5-1 Average FACT-Lung TOI scores stratified by time of drop out



(Fairclough, 2002)

The graph shows that individuals who dropped out earlier had lower scores on a HRQOL scale at baseline, and their response scores were lower just prior to dropout, compared to individuals who remained in the study longer. If the missingness depends on previously observed data, as in this example, then the missing data mechanism is not MCAR. When the nonresponse mechanism is MNAR, it is more difficult to test by examination of the

data because the unobserved data are not available (Laird, 1988; Fairclough, 2002). Despite this difficulty, examination of the data for patterns of missingness should be done to help inform the choice of analysis method. For the current study, the ROSE Study data were examined with the above graphical approach to determine if a possible relationship existed between pattern of missingness and the *NMB* response variable. These graphical analyses are described further in Chapter 3, Methods.

It would be uncommon for longitudinal clinical trials with many patients to have missing data that are entirely based on one nonresponse mechanism. If a study had missing data that were all MCAR, then analysis methods that require complete cases, such as ordinary least squares regression, could be used (Laird, 1988; Lin, 2000). These methods are valid under the MCAR assumption because the completely observed cases are a simple random sample from the total study data. Realistically, data are usually missing for a variety of causes, such as subject characteristics, beliefs, and behaviors, and nonvoluntary reasons such as severe morbidity and mortality. Nonvoluntary reasons are more likely to lead to MAR or MNAR nonresponse mechanisms. Likelihood-based models will produce valid inferences, assuming that the missing data are MAR and the probability of missing is independent of the unobserved response data, conditional on the observed response data and covariates (Rubin, 1976; Little & Rubin, 2002). (Another way to think about the second assumption is that the parameters of the dropout process must be distinct from the parameters of interest, i.e., treatment effect). With nonignorable nonresponse or (MNAR), however, it is necessary to model both the observed data and the nonresponse mechanism because the time of dropout is correlated with the treatment effect (Rubin, 1976; Laird, 1988; Little, 1995; Little & Rubin, 2002).

Because MAR and MNAR data pose the greatest analytic challenges and because clinical trial data are subject to multiple nonresponse mechanisms, the base case of the current study used data that were simulated to reflect both MAR and MNAR nonresponse mechanisms occurring within one dataset.

2.6 Methods for Analysis of Incomplete Data

Analyses of data with missing or censored observations can suffer from loss of power to detect meaningful differences if incomplete cases are dropped from the analysis. Alternatively, analyses may result in biased estimates if the nonresponse mechanism is not accounted for when the full sample is retained in the analysis. This section reviews many different approaches for addressing these problems in cost and cost-effectiveness evaluations. Section 2.7 provides a review of modeling approaches that specifically deal with the issues of MNAR data.

Kaplan-Meier and Cox proportional hazards models are standard methods for handling censored data in survival analysis. Quesenberry et al. (1989) used the Kaplan-Meier estimator to estimate distributions of lifetime hospitalizations and inpatient days from administrative claims data for individuals with AIDS from 1981 to 1987. A patient's lifetime number of hospitalizations and inpatient days were censored if the patient withdrew from the health plan before the end of the study period or survived beyond the end of the study period. Hiatt et al. (1990) expanded upon the work of Quesenberry et al. by applying the same approach to the estimation of lifetime health care utilization and costs for a sample of cases from the original study. Unit costs were assigned to all health care services provided to these patients. The Kaplan-Meier

estimate of the mean number of lifetime inpatient days was 38.7 days, and estimated mean lifetime costs were $32,816. The authors did not provide any means for assessing the accuracy of these estimates except to compare them to estimates based on complete cases (i.e., persons who had died). The complete case estimates were lower than the product-limit estimates, with 34.2 days for the mean number of lifetime inpatient days, and $29,021 for the mean lifetime costs.

Fenn et al. (1995) investigated how different methods for estimating costs and effectiveness with censored data can affect the estimated *ICER*s. Mean costs and life-years gained (LYG) using data from a placebo-controlled clinical trial were estimated using three different approaches: (1) means based on the full sample of missing and complete cases (2) means based on complete cases; and (3) means based on product-limit estimators. *ICER*s were calculated for all combinations of the three approaches in the numerator and denominator to demonstrate the unpredictable results that can be achieved when combining biased estimates of costs and effectiveness. Using complete cases for estimating costs with any of the three approaches for estimating effectiveness yielded the lowest *ICER*s (range £55 to £83 / LYG), and using the full sample for estimating costs with any of the three approaches for estimating effectiveness yielded the highest *ICER*s (range £109 to £168 / LYG). The *ICER* with product-limit estimates for both costs and effectiveness fell within the range of values (£145.2 / LYG). The authors concluded that the product-limit approach should be used for estimating both components of an incremental cost-effectiveness ratio. However, no simulation studies were performed to demonstrate that this approach is actually more precise.

Lin et al., (1997) explained how the strategies used by Quesenberry, Hiatt, and Fenn, that treat cumulative costs as right censored survival times, are incorrect unless all patients accumulate costs at a common rate over time. In practice, rates of cost accumulation are not homogeneous. Survival methods require independence between the outcome variable and the censoring variable, and cumulative costs at survival and censoring times are correlated even if the survival and censoring times are independent. This correlation is due to the heterogeneity in the rates of cost accumulation across individuals. In other words, individuals who incur costs rapidly tend to generate higher cumulative costs at all time points including survival-censoring times, as compared to those with lower accumulation rates.

To avoid this correlation problem, Lin and colleagues (1997) proposed a nonparametric approach for estimating total costs from incomplete data due to administrative censoring and drop out. The basic concept behind the method was that total costs for patients who are censored in the same small time interval are more homogeneous than the total costs for all patients. The method involved partitioning the study period into equal-length time intervals. The probability of surviving until the start (or end) of the interval was calculated for each patient, and the average cost per patient was calculated for each interval, conditional on surviving until the start (or end) of the interval. The probabilities and average cost were multiplied together for each interval, and summed over all intervals to estimate the average cost per patient over the study period. The method was applied to simulated data for a 10-year study with 10 one-year intervals. The total 10-year cost was the outcome of interest. Estimates from the partition method were compared to naïve estimates using full sample and complete cases,

and to Kaplan-Meier estimates. Monte Carlo simulations were conducted with different levels of censoring, and survival times were generated from two different distributions (uniform and exponential). The estimators were assessed by comparing to the "true" mean costs from the two survival distributions. Performance measures included bias (defined as the percent difference between known and estimated parameters), variance estimation (defined as sampling standard error of the estimator and sampling average of the standard error estimator), and normal approximation (defined as sampling coverage probability of the 95% confidences interval). The partition method produced nearly unbiased estimates of total costs, except some bias was present under moderate censoring. The naïve estimators performed far worse than the partition method estimator under all conditions, with a large negative bias observed in the full sample estimator under moderate censoring, and a downward bias observed in the complete case estimator. The bias of the Kaplan-Meier estimator was substantial and varied in direction depending on the simulation conditions. Although the partition method provided better estimates compared to product-limit estimators, it was not intended to deal with nonignorable missing data. Further, adjustment for covariates (as in a regression model) was not possible. Nevertheless, a simulation study such as Lin's and colleagues is informative because the study included a "true" parameter with which comparisons of method results could be made. The current study uses a "true" parameter for the purpose of comparing methods.

Lin (2000) further developed the Kaplan-Meier partition method with a semi-parametric marginal model for repeated measures that allowed for adjustment of covariates, and compared two models in another simulation study. The first model was

based on a least squares normal equation, adapted for censored observations by weighting the complete observations by their inverse probabilities of inclusion in the data set. The second model was a variant of the first that allowed for the effects of covariates on censoring and involved J separate estimates of costs, one for each of J time intervals. Monte Carlo simulations were conducted with different levels of censoring, different distributions for survival times (uniform and exponential), and varying sample sizes. Performance of the two models was assessed by comparing means of the parameter estimates for treatment group, $\hat{\beta}$, with the known value, $\beta=0$. Both models produced unbiased estimators under uniform and exponential distributions for survival, and for all conditions of censoring and sample size. The model that adjusted for covariates and used J separate estimates of costs was more efficient and more accurate in small samples. This model may be appropriate for situations when the covariates can predict the probability of data being missing (i.e., covariate dependent dropout), however, it may not provide unbiased estimates under conditions of nonignorable missing data.

Oostenbrink & Al (2005) conducted an extensive simulation study to compare methods for estimating total costs from incomplete data due to dropout. Nine approaches were assessed: six so-called naïve methods (complete case, mean imputation, linear extrapolation, last value carried forward (LVCF), predicted regression, and hot-decking), and three so-called principled approaches (the nonparametric partition method of Lin et al. (1997), the expectation maximization (EM) algorithm, and multiple imputation). The principled methods accounted for missing data and the uncertainty that they introduce. Definitions of the nine methods are provided in Table 2.6-1.

Table 2.6-1 Definitions of methods evaluated by Oostenbrink & Al (2005) for estimating total costs when data are incomplete

Naïve Methods	**Definition**
Complete case	Excludes data from patients who drop out or withdraw before end of study.
Mean imputation	Imputes for each missing value of costs the mean of the observed cost values.
Linear extrapolation	Extrapolates costs for patients who drop out by multiplying each patient's observed cost per day by the study duration in days.
Last value carried forward (LVCF)	Imputes for each missing value of costs the last observed value of the particular patient.
Predicted regression	Imputes the most likely value for each missing cost observation using ordinary least squares regression.
Hot-decking	Imputes values based on a procedure that places each patient into one of several somewhat homogeneous imputation strata. Missing cost observations are imputed by random selection from the observed values of patients who were placed into the same imputation stratum.
Principled Methods	**Definition**
Lin et al's nonparametric method	Estimates total costs per patient based on a procedure that divides the study period into equal-length time intervals. Probability (P) of surviving until an interval, and average cost (C) in the interval conditional on surviving until that interval are calculated. P and C are multiplied together for each interval, summed over all intervals to estimate the average cost per patient over the study period.
Expectation algorithm (EM)	Estimates total costs per patient based on an iterative procedure that begins with a complete case estimate. Initial estimate is used to fill in the missing values and total costs are re-estimated. This last step is repeated until the parameter value converges. The EM method assumes the data to be distributed multivariate normal.
Multiple imputation	Missing values are replaced with *m* simulated values, creating *m* plausible versions of the data set. Each version is analyzed by complete case analysis. The *m* results are combined into a single estimate of total costs that includes uncertainty due to the missing data.

The simulation procedure started with the creation of a complete case sample, followed by imposing three nonresponse mechanisms on the complete data. The nonresponse mechanisms were MCAR, MAR, and MNAR. MCAR data were generated

at each time interval by randomly selecting a number of patients still observed and from that time point forward. All data were set to missing for those patients. The proportion of patients with observed data was set to gradually decline from 100% at the first time interval (t = 1) to 70% by the last time interval (t = 10). MAR data were generated with the probability of dropout during time interval t being associated with the following: positive association with costs during the previous time interval t-1, negative association with HRQOL at time interval t-1, increase in costs between intervals t-2 and t-1, decrease in HRQOL between intervals t-2 and t-1, and age at baseline. This procedure simulates a mechanism for the missing data that guarantees the missing data can be predicted from the observed data. For MNAR data, the probability of dropout was associated with increased costs and worse HRQOL after dropout rather than before, based upon the observed values in the complete case sample.

A simulation consisted of the creation of a complete sample, the creation of three dropout samples, application of the nine analysis methods to the three dropout samples, and 3000 iterations to obtain stabilized estimates. Results from the combined 3000 iterations were then compared to the "true" cost value that was derived from 50000 samples of complete data. Oostenbrink & Al used similar performance measures to those used by Lin (2000): absolute and relative bias (difference in mean costs between the "true" mean costs and the estimators), sampling standard error for the estimator (SSE, which is the standard deviation of the mean costs for the 3000 iterations), sampling average of the standard error estimator (SEE, which is the mean of the standard errors of the 3000 iterations), and sampling coverage probability of the 95% confidence interval (the proportion of iterations for which the 95% confidence interval includes the "true"

mean costs). Three additional sets of simulations were conducted to assess the impact of dropout rate and sample size on the estimators. The dropout rate was varied between 18% and 60% in two additional sets of simulations, and sample size was increased to N=400 with a dropout rate of 30% in a third simulation.

All naïve methods performed poorly. The EM algorithm and multiple imputation methods produced unbiased estimates of the mean and standard error when applied to log-normal distributed costs under the MAR mechanism. These methods produced biased results when log-normal costs were enlarged with costs of events, suggesting that large variations in costs within a patient overtime presents a challenge for estimation of costs with incomplete data. None of the methods evaluated were able to deal with the MNAR mechanism. Oostenbrink & Al (2005) concluded that the distribution of the data and the nonresponse mechanisms are the most important factors to consider in the analysis of incomplete costs data due to drop out. The authors recommended that further simulation studies based on real data should be conducted.

The above studies illustrate some of the potential biases in cost estimation when data are incomplete. As Lin et al. (1997) demonstrated in their simulation study, the direction of bias will be downwards for full sample estimates that do not account for censoring because there is no adjustment for costs incurred after censoring. For estimates based on complete cases, the direction of bias could be up or down, depending on the type of censoring. With administrative censoring (nonmonotone missing data pattern) the bias in a complete case estimate will be towards the costs for individuals with shorter survival because longer survival times are more likely to be censored, and with

incomplete data due to drop out (monotone missing data pattern) the bias will be towards the costs for individuals who complete the study (Lin, 2000).

2.7 Models for Data Missing not at Random

A common method for analyzing incomplete longitudinal data is generalized estimating equations (GEE). GEE uses a generalization of maximum likelihood estimation for analyzing correlated repeated measures data. These equations use all available data but assume that the missing data are MCAR (Zeger and Liang, 1992). This assumption is not likely to hold in longitudinal clinical trials involving patients with complex, chronic medical conditions. In longitudinal clinical trial databases, the assumptions of MAR and/or MNAR for the nonresponse mechanisms are more realistic. This section discusses pattern-mixture and selection models that specifically deal with the issues of MNAR data. A review of the literature revealed that all applications of these models have been in the analysis of treatment efficacy or effectiveness (using HRQOL measures); no cost-effectiveness studies with these models were found. Several publications of these modeling approaches are reviewed.

Pattern-mixture and selection models are two classifications of models that can provide less biased estimates of model parameters when data are MNAR. The advantage that these models offer over mixed-effects models is that they model both the pattern of missingness and the observed data (Little & Rubin, 1987; Little, 1993). The two approaches evolve from different factorizations of the joint distribution of the dependent variable, Y (which includes both Y_{obs} and Y_{mis}), the missing-data indicator, M, and the

covariates, *X*. The pattern-mixture model factorization, according to Glynn, Laird, and Rubin (1986, 1993) and Little (1993), can be specified as

$$f(Y, M \mid X) = f(Y \mid M, X)\, f(M \mid X) \tag{2.4}$$

The pattern-mixture approach models the within-subject regression lines stratified by the pattern of missing values (Equation 2.4). The factor, $f(M \mid X)$, models the marginal proportions of each missing data pattern as functions of between–subject covariates (Little, 1995). The factor, $f(Y \mid X)$, specifies the missing data mechanism that does not depend upon the missing data (Y_{mis}). Therefore, pattern mixture models require only that the proportion of subjects within each pattern of missing data be known. These models do not require specification of a model for the nonresponse mechanism (Fairclough, 2002).

Pattern-mixture models stratify the sample by pattern of missing data, then model the differences in the distribution of the response (i.e., dependent) variable over these patterns. Each pattern has a different set of estimated parameters and variances. The true distribution of the response variable for the entire patient population is estimated as a mixture of the distributions from each of the patterns. An example of strata for patterns of missing data based on time point of assessment as in the current study would be: patients with all *NMB* missing except month 0 (stratum 1), patients with only months 8 and 12 missing (stratum 2), patients with only month 12 missing (stratum 3), and patients with no *NMB* missing (stratum 4). Alternative strata that are used in studies include reason for discontinuation of therapy, and patients with and without relapse of their medical condition within some timeframe. Weights are based on the number of

individuals within each stratum, and population parameter estimates are the weighted average of the estimates from the strata (Fairclough, 2002).

One main disadvantage of pattern-mixture models is the many potential patterns of missing data. For example, if strata are based on time point of assessment, there can be 2^k possible patterns in a study with k assessments over time (i.e., if intermittent missing are included). Also, when the number of assessments is high, it may be impossible to obtain estimates of the parameters within each stratum, or obtaining estimates may require additional assumptions or restrictions to be specified. Further, the choice of patterns (number of nonmissing assessments or reason for discontinuation of therapy) for stratifying the population is arbitrary and the model results can depend on the pattern that is chosen.

Selection models offer another approach for dealing with MNAR data. The term "selection model" originated from a classification of models with a univariate response (as opposed to a joint response such as time-to-dropout and NMB), where the probability of being selected into a sample depended upon the value of the response (Heckman, 1976). The factorization of the selection model, that originated with Heckman (1976) and was further developed by Little and Rubin (1987), can be specified as

$$f(Y, M \mid X) = f(M \mid Y, X)\, f(Y \mid X) \qquad (2.5)$$

The first factor in Equation 2.5, $f(M \mid Y, X)$, models the nonresponse mechanism as a function of the observed and missing response values and covariates, and the second factor, $f(Y \mid X)$, is a complete data model for the within-subject regressions (Little, 1995). The selection approach models the hypothetical complete data along with the nonresponse mechanism conditional on the hypothetical complete data. Each

individual's response is described in the selection model by a linear function of time, with random variation among individuals in the intercept and linear rate of change (slope). The model incorporates the time of discontinuation by allowing a function of the time to discontinuation to be correlated with the random effects of the longitudinal model for the response (Fairclough, 2002).

One criticism of selection models is that the validity of the nonresponse mechanism component of the model is untestable because the model includes the information regarding the missing values (Y_{mis}) as an explanatory variable. Further, the primary parameter estimates that describe change in response are sensitive to misspecification of the nonresponse model (Fairclough, 2002). Estimating these models has been computationally challenging in the past, however, SAS software is now available in PROC NLMIXED that fits a mixed-effects model by maximizing an approximation likelihood integrated over the random effects (Wolfinger, 1997).

Schluchter (1992) proposed the trivariate normal model as a type of selection model that is based on a log-normal survival model. He also reviewed other proposed approaches for analyzing MNAR data in longitudinal studies, including generalized least squares, and weighted and unweighted averages of ordinary least squares approaches that are valid when missing data are MCAR or MAR. He did not apply his proposed method to an actual dataset or simulation studies. The trivariate normal model by Schluchter used the EM algorithm to cope with the difficulty of estimating the hypothetical complete data when the missing data are MNAR. The model was based on a linear random-effects model that assumed the measurements for patient *i* follow a linear regression in time, and that the true intercept (β_{i0}) and slope (β_{i1}) come from a bivariate normal distribution.

Schluchter extended the linear random effects model by assuming that the true intercept, slope, and log of the survival time (T_i) follow a trivariate normal distribution. The unobserved random effects, β_{i0} and β_{i1}, were considered part of the 'complete data' in Schluchter's form of the EM-algorithm. The algorithm obtained maximum likelihood estimates of all model parameters by computing conditional expected values of the complete data sufficient statistics (the Expectation-step), and computing updated estimates of the parameters (the Maximization step). The algorithm cycles between the two steps until the parameters converge. This model allowed for unbalanced data due to staggered patient entry into a study, missed visits, and loss to follow-up. Also, the estimation procedure made use of all data, including patients with only one measurement. Further, likelihood ratio tests can be constructed to test for MNAR (i.e., testing that the covariance between the log of the time-to-dropout and intercept and/or slope = 0). A limitation of the EM algorithm is that it can require large datasets in order to obtain stable estimates and avoid problems with convergence.

Little and Wang (1996) compared results from pattern-mixture models under different assumptions about the nonresponse mechanism in the analysis of data from a clinical trial of three alternative doses (5 mg, 10 mg, and 20 mg) of haloperidol for the treatment of schizophrenia. Results from the pattern-mixture models were also compared to results from a complete case analysis and a probit selection model. The clinical trial involved 65 patients newly admitted to the hospital for schizophrenia. Efficacy was measured by the Brief Psychiatric Rating Scale Schizophrenia (BPRSS) factor, assessed at baseline, week 1, and week 4. The analysis focused on the difference in mean BPRSS, between baseline and week 4. Twenty-nine (45%) patients dropped out of the study

before week 4 for a variety of reasons, including drug side effects. Further, the proportions of dropouts varied across dosage groups (33%, 41%, and 63% missing in the 5, 10, and 20 mg groups, respectively), suggesting that missingness was related to dose. The effect of MNAR on results was assessed by computing pattern-mixture model estimates under different assumptions about the nonresponse mechanism. This was accomplished by adding an extra parameter to a MAR maximum likelihood model with the purpose of modeling the extent to which missingness depended on the missing variable. Missingness was assumed to depend upon treatment group and four different linear combinations of BPRSS scores at baseline, week 1 and week 4. Assumptions ranged from ignorable missing (i.e., MAR), where missingness was assumed to be weakly dependent on the missing values at week 4, to an extreme departure from ignorable missing (MNAR), where missingness was assumed to be strongly dependent on the missing values at week 4.

Results showed that estimates from the complete case analysis deviated noticeably from the estimates from the other methods, with mean differences being larger among the 5 and 10 mg treatment groups, and smaller for the 20 mg treatment group, compared to estimates from the pattern-mixture and probit selection models. Across the pattern-mixture models, the size of treatment effect did not vary widely across the four different nonresponse mechanism assumptions. The differential in estimated treatment effect by size of dose was slightly increased as the assumption of MNAR increased. Standard errors of the estimates also increased as the assumption of MNAR increased. Treatment effect estimates varied the most across the modeling approaches for the high dose treatment group, which was probably due to the higher proportion of missing cases

in this group. The probit selection model had similar results to the pattern-mixture model under the assumption of MAR.

The pattern-mixture approach proposed by Little and Wang was based on the assumption that the nonresponse mechanism depended on the observed and missing data for the response variable, *Y,* in an additive manner, which may not be true. The authors concluded that a limitation of the pattern-mixture model is that nothing is actually known about the conditional distribution of the missing responses, given the observed responses and covariates for nonrespondents. Therefore, predictions of the missing data could take any form, and that form may not be the one chosen for the analysis. (This is similar to the concern expressed by Fairclough (2002) regarding how the primary parameter estimates that describe change in response are sensitive to misspecification of the nonresponse model.) It should be noted that the structure of the multivariate regression pattern-mixture models evaluated by Little and Wang are not appropriate for repeated measures data where the means are modeled as a function of within-subject covariates (such as time). The approach is appropriate, however, for analysis of differences of means between time points.

Fairclough et al. (1998) compared a pattern-mixture and a selection model (a joint mixed-effects and time to disease progression model) in the analysis of longitudinal HRQOL outcomes. Their evaluation of methods also included a complete case analysis and two mixed-effects models (one model included covariates that were associated with the probability of missing data, and the other model did not). Except for the complete case model, the models used close to 100 percent of the patient data. The different

models were compared on the basis of the sensitivity of longitudinal estimates of HRQOL and hypothesis tests of the various underlying missing data assumptions.

Data from two clinical trials of cancer therapy were analyzed. Both trials had at least 30 percent of the planned HRQOL assessment missing. The first trial was an 18-month, 4-arm study of adjuvant therapy involving 1,212 post-menopausal patients with node-positive breast cancer. Fifteen percent of the patients experienced disease progression with an overall average of 31 percent of patients with missing data. The second trial was a 6-month, 3-arm study involving 576 patients with advanced nonsmall-cell lung cancer. Thirty-five percent mortality was observed and with an overall average of 39 percent of patients with missing data.

The complete case analysis of the first trial included only 33 percent of the patients, whereas the other 4 methods included 95 percent of the patients (i.e., all patients who had at least one assessment in the first 18 months of treatment). The event for the joint mixed-effects model was the time to disease progression within 18 months and the strata for the pattern-mixture model were defined by disease progression. As in the previously described study by Little and Wang (1996), complete case estimates of treatment effect were higher for all treatment arms when compared to results from the other four modeling approaches. Estimates from the models that used all available data were almost identical for all treatment arms, except for the control arm (Tamoxifen only), where the pattern-mixture model deviated from the other models and estimated higher mean HRQOL scores at the end of the 18 month study than the complete case analysis. An unexpected result among the models that used all available data was that the standard errors for the estimates were smallest for the joint mixed-effects model and largest for the

pattern-mixture model. The authors concluded that the additional information on time to disease progression in the joint model might have led to more precise estimates. Whereas in the mixture model, there was less information about the patients who progressed early, leading to less certainty about estimates that are based on the later observations. Therefore, although the mixture model estimates may have appeared to be less precise, they may actually better reflect the uncertainty of the estimates.

Fairclough's analysis of the second trial included only 24 percent of the patients for the complete case analysis and 94 percent of patients for the other 4 methods. The event for the joint mixed-effects model was the time to death. Strata for the pattern-mixture model were defined as the number of courses of therapy completed. As in the first trial, the estimates of HRQOL from the complete case analysis were higher for all three of the treatment arms, relative to the other four modeling approaches. One of the two mixed-effects models included two patient characteristics as covariates for the nonresponse mechanism: a measure of patient health status at baseline and survival status at six months. The estimated rate of decline in HRQOL with this model was greater than the estimate from the mixed-effects model without covariates, and was very similar to the estimated rate of decline from the joint mixed-effects model.

Across the two analyses by Fairclough et al., results were more variable when there was a higher proportion of missing data. The authors concluded that this variability reflects increasing sensitivity of the estimates of the response variable to the choice of analytic model used. Also, the joint mixed-effects may not have been as appropriate for the first trial as it was for the second because only 15 percent of patients experienced the event of disease progression and many of the patients in the first trial were likely to be

cured with therapy. To find the best model for a particular analysis, the authors recommended using different methods of analysis of real data from clinical trials, and using simulations under ideal conditions where the true missing data mechanism is known.

Ribaudo et al. (2000) applied a random effects selection model to the problem of analyzing joint HRQOL response and log of the survival time in a post-hoc analysis of data from a clinical trial of treatment for patients with colorectal hepatic metastases. A nonignorable nonresponse mechanism was suspected because survival differed between the treatment groups and HRQOL response (based on the physical sub-scale scores from the Rotterdam Symptom Checklist) was worse both at baseline and in change over time for the patients with the shortest survival. One hundred patients were involved in the study (51 received an experimental treatment, and 49 received conventional treatment). HRQOL data were available for only 86 patients, and only 43 of these patients had more than 60 percent of the planned HRQOL assessments. Assessments were taken monthly for up to 15 months. Published results of the primary analysis (a quality-adjusted survival time endpoint using TwiST-based analyses) showed evidence of an advantage from the experimental treatment, therefore, the researchers wanted to test if "normal" HRQOL could be sustained longer with the experimental treatment compared to the conventional treatment.

The post-hoc selection model was based on Schlucter's trivariate normal model described previously. Without patient-level covariates, the model is represented as

$$y_{ij} = f_1(\alpha_1 + \beta_1 t_{ij} + \delta_1 t_{ij} trt_i + u_i + v_i t_{ij} + e_{ij}) z_{ij}^{(1)} + f_2(\alpha_2 + \delta_2 trt_i + s_i) z_{ij}^{(2)} \qquad (2.6)$$

The HRQOL component of the model is an identity link function (f_1), which means that f_1 is a linear function of the dependent variable, HRQOL, with fixed parameters for the intercept, α_1, and the slope, β_1. The identity link function is modeled alongside an exponential link function (f_2), which represents time-to-event model for estimating the mean log of the time-to-dropout, α_2. The observed HRQOL and survival time data for patient i can be described as a vector, $\underline{y}_i = (\underline{y}_i^{(1)}, y_i^{(2)})$, where $\underline{y}_i^{(1)}$ represents the m_i HRQOL responses ($y_{i1},\ldots,y_{imi}$), observed for patient i at times $t_{i1},\ldots, t_{imi}$, and $y_i^{(2)}$ (the m_i + 1st element of $\underline{y}_i$) is the patient's corresponding survival time. The dummy variables, $z_{ij}^{(1)}$ and $z_{ij}^{(2)}$, are indicators to distinguish the two model components for the response values. The indicator variable $z_{ij}^{(1)} = 1$ for $j = 1, \ldots, m_i$ indicates when the model is estimating the HRQOL responses for each time point, 0 otherwise; and $z_{ij}^{(2)} = 1$ for $j = m_i + 1$ indicates when the model is estimating the survival time, 0 otherwise. Between-subject random residual components are represented by u_i, v_i, and s_i for the HRQOL intercept and slope and log of the survival time, respectively. The within-subject residuals are represented by the ((m_i + 1) x 1) vector, $\underline{e}_i = (e_{i1},\ldots, e_{imi}, 0)$ where the first m_i elements correspond to the m_i HRQOL responses, and the last element is 0 because there is no variance in subject survival time. Linear and piece-wise linear models that assumed linear rates of change in HRQOL response over time were estimated, using the EM-algorithm to obtain parameter estimates given the missing data. Three different covariance structures were compared. The first assumed no correlation between HRQOL and survival ($\sigma_{us} = \sigma_{vs} = 0$), the second assumed correlation between

survival and HRQOL intercept only ($\sigma_{vs} = 0$), and the third allowed correlation between survival and both HRQOL intercept and slope. The parameter estimates from the model were compared to estimates from a model based on complete survival information from full patient follow-up that became available at the completion of the study.

Results from the linear model under the first covariance assumption of independence between HRQOL and survival substantiated the results from the primary analysis with an estimate of a steeper rate of decline for the control arm compared to the experimental arm. The piece-wise linear model under the same assumption, estimated an initial deterioration in HRQOL, with a steeper decline in the experimental arm initially. Parameter estimates were not affected very much when the model was estimated with the assumptions of correlations between survival and HRQOL intercept and slope. The piecewise linear model parameter estimates were in close agreement to the estimates from the full patient follow-up data, indicating that the piece-wise random effects selection model produced good parameter estimates

Another study by Fairclough et al. (2003) compared results from a mixed-effects model and a joint mixed-effects log of the time-to-dropout model, in post hoc analyses of clinical trial data with nonrandom dropout. The double-blind trial involved 375 cancer patients with anemia who were randomized to receive either epoetin alfa (N=251) or placebo (N=124). Response variables included four HRQOL measures specific to cancer, one measure specific to anemia, and two general health-related HRQOL measures. Data were collected at baseline and at three follow-up assessments, the timing of which varied according to each patient's chemotherapy cycle. A unique characteristic

of this trial for the post hoc analysis was that neither the length of treatment nor the timing of assessments could be prospectively predetermined.

Previously reported primary findings from the trial were based on between treatment group differences in changes from baseline to last assessment. Results indicated a significant benefit of increased HRQOL for patients treated with epoetin alfa on all cancer and anemia measures, and trended in favor of epoetin alfa on general measures. However, approximately 42 percent of enrolled patients withdrew from the study early and lower HRQOL scores were reported for patients who discontinued early. Further, correlations ranging from 0.37 to 0.77 between individual rates of change and time to early termination of therapy or death supported the hypothesis that censored HRQOL was associated with HRQOL after the point of dropout, i.e., a nonrandom dropout process. The objective of the study, therefore, was to investigate the robustness of the conclusions from the previously reported results using two alternative modeling approaches that assumed missing data were MAR or MNAR.

The longitudinal models for the sensitivity analyses were based on mixed-effects growth-curve models, defined as $Y_I = X_i\beta + Z_i d_I + e_i$, where Y_I was the vector of HRQOL responses on the ith patient, and X_i and Z_i were design matrices of known covariates corresponding to fixed and random effects, β and d_I, respectively. The possibility of a nonlinear change (i.e., slope) in HRQOL over time was handled by piecewise linear regression with the assumption that the rate of change in the response variable was approximately linear within short time intervals. The model allowed the rate of change in HRQOL scores to change at 4 and 16 weeks from baseline. Piecewise linear regression models included an indicator term for treatment (TX), a continuous variable for weeks

from baseline (WEEK), and two additional covariates to model the change in slope at weeks 4 and 16 (WEEK4 and WEEK16). Additional covariates were defined as WEEK04 = max(0,WEEK – 4) and WEEK16 = max(0, WEEK – 16). Eight possible covariance structures were considered for the mixed-effects model for all seven HRQOL response variables. Treatment group differences in the mean change in HRQOL from baseline to 16 weeks were the outcomes of interest.

Analyses included a mixed-effects (ME) model (assumes a MAR nonresponse mechanism) and a joint mixed-effects and log of the time-to-dropout model (joint ME) (assumes a MNAR nonresponse mechanism). The second model was an extension of the first, where HRQOL was modeled jointly with the log of the time-to-dropout. The joint modeling was accomplished with the assumption that the random effects, d_I, were correlated with the time of censoring T_i (i.e., $\sigma_{dt} \neq 0$). For example, if individuals with HRQOL that declined more rapidly over time dropped out earlier, the random effects associated with the slope of HRQOL would be positively correlated with the time-to-dropout. With the joint ME model, one or both of the following conditions must be met in order to estimate the variance of the random effects and the covariance between the random effects and time: (1) a random-effects covariance structure should be a reasonable approximation of the covariance structure, and (2) there should be variation in the random effects (intercept and slope) across patients. Fairclough et al. recommend that the variances of the random effects be checked first by estimating the ME model. Then estimates from the ME model are used as initial estimates of β, D, and $\sigma_I^2 = Var[\, e_i]$ in the joint ME model.

Generally, both models supported the original conclusions from the previously reported results. Results from the MAR (ME) and MNAR (joint ME) models were similar for all measures of HRQOL, however, within treatment group estimates of changes were smaller for the MNAR model. There were some practical issues with the joint ME model, such as the random component for the modification of the rate of change after 16 weeks was difficult to estimate because data became sparser as time progressed, and the estimating algorithm for the SF-36 PCS model failed to converge due to minimal variation in the rate of change in the SF-36 PCS. The authors recommended including treatment-specific covariance parameters to allow the correlations between random effects and time-to-event to vary by treatment, should this occur in a study.

Many of the published studies reviewed in this chapter suggest that joint selection models can provide good estimates of treatment effect on HRQOL when MNAR data are present. However, most of these studies did not compare results from the different estimation approaches to true parameters. Comparisons between pattern-mixture and joint selection models indicate that the joint models may give more precise estimates because they include the additional information about survival time. However, pattern-mixture model estimates may more accurately reflect the uncertainty in the estimates, especially those that are based on later observations where more data are censored. The strengths and weaknesses of the different modeling approaches should be considered when interpreting estimates treatment effect in the presence of MNAR missing data.

The current study attempts to build upon the previously published work by applying a joint ME model to estimating cost-effectiveness with NMB_λ as the dependent variable. A simulation study was used to evaluate and compare estimates of $INMB_\lambda$ from

a joint ME model, a repeated measures ME model, and an ANCOVA model. Model estimates were compared to a true parameter for $INMB_{\lambda}$ that was derived from the simulated data. ANCOVA was selected because this approach is commonly used for analyzing longitudinal clinical trial data but does not account for the effects of MAR or MNAR data. A repeated measures ME model was chosen because it is also commonly used but does not account for MNAR data. The three models are described in detail in Chapter 3.

CHAPTER 3. METHODS

The objectives of the study were to evaluate and compare estimates of incremental net monetary benefit ($INMB_\lambda$) from ANCOVA, ME, and joint ME models, using data with simulated MAR and MNAR nonresponse mechanisms. The dependent variable in the models was a total one-year NMB_λ, and the parameter of interest was the treatment group effect on NMB_λ ($INMB_\lambda$). $INMB_\lambda$ is defined in Chapter 2 as a function of costs, utilities, and willingness to pay (λ). An ANCOVA model was selected for comparison because ANCOVA is commonly used in clinical trial analyses. A mixed-effects model was selected because these models can account for the impact of missing at random (MAR) data, but cannot account for nonignorable missing at random (MNAR) data. Last, a joint ME model was selected because these models can account for both MAR and MNAR nonresponse mechanisms. Joint ME models have been shown to provide good estimates of HRQOL in clinical trials with MAR and MNAR missing data, however, these models have not been reported in studies of incremental net monetary benefit. It should be noted that the joint ME model can account for MNAR nonresponse mechanisms when these are related to individual trajectories as measured by random effects. The joint ME model, however, may not necessarily account for other MNAR mechanisms (Fairclough, personal communication, May 2008).

The hypothesis was that the joint ME model would produce the best estimate of $INMB_\lambda$ compared to estimates from ME and ANCOVA models. Estimates from the three models were evaluated and compared to each other and to the "true" $INMB_\lambda$,

calculated from the simulated complete dataset before nonresponse mechanisms were applied.

This chapter describes the analysis methods, including variables, models, and data simulation procedures. The measures of cost, effectiveness, and the λ constants that represent levels of willingness to pay, are described in sections 3.1-3.3. Section 3.4 provides an overview of the dependent variable and timeframes for deriving the estimated NMB_λ. Section 3.5 provides the specifications of each model. The rationale for basing the data simulation on the ROSE Study outpatient subgroup is provided in Section 3.6. Procedures for creating the simulated data are described in Section 3.7. Last, the analyses are specified in Section 3.8.

3.1 Cost Measure: Direct Medical Costs

Costs were simulated from the original ROSE Study outpatient subgroup. (The rationale for selecting this subgroup as the basis for the simulation is provided in Section 3.6.) This section describes costs from the ROSE Study as they pertain to the current analysis.

ROSE Study costs consisted of direct medical costs per patient. Costs were measured by multiplying each unit of health care service used times the cost per unit. Estimates of the unit costs for each type of service were derived from secondary sources (see Chapter 2, section 2.1 for details). Direct medical costs per patient at each of the study time points were calculated as the sum of all health care costs over the prior four-month time period.

The ROSE Study did not collect resource use data for the four-month time period prior to randomization. Therefore, baseline costs (representing the cost of care over the

four months prior to randomization) were imputed for the sake of calculating a baseline NMB_λ. Details on the imputation of baseline costs and the simulation of follow-up costs are provided in the section on simulation procedures.

In the ROSE Study and the current analysis, annual health care costs were not discounted to reflect the value of health care costs at the start of the study because the study timeframe was only 12 months. For the current analysis, all of the original ROSE Study costs were adjusted for inflation using the 2005 Medical Component of the Consumer Price Index.

3.2 Effectiveness Measure: Quality-adjusted Life Years

As described in Chapter 2, SF-36 scores were collected in the ROSE Study for each patient at each study time point. For the current analysis, SF-36 values were converted to utility scores using the mapping function developed by Brazier et al. (2002). The resulting utility values were then used in the simulation procedure, and the simulated utilities were converted to QALYs.

The SF-36 in the ROSE Study was assessed at baseline and every four months up to month 12, using the one-month recall version of the questionnaire. This meant that patients were asked to respond to the questions while considering their health status over the last month. For the purpose of calculating QALYs in the current analysis, an assumption was made that the SF-36 scores (and hence the utility scores) at each time point reflected the entire previous four-month period. This assumption allowed the QALYs to align with the cost measures over each of the same time intervals. The utility scores at each time point were multiplied by 0.33 to generate a QALY based upon one-

third of a year. The response variable, $NMB_{\lambda it}$, for patient *i* at each time point *t* was then calculated from the resulting QALYs and costs.

3.3 Willingness to Pay: Values of λ

The value (λ) that payers are willing to pay for a new therapy is usually unknown. Therefore, Stinnett & Mullahy (1998) recommended conducting analyses at different levels of λ and reporting the estimated $INMB_{\lambda}$ as a function of λ. In this study, λ = $50,000 was selected because it is widely referenced in the literature (Earle et al, 2000; Jonsson, 2004; Eichler et al, 2004), and the National Institute for Clinical Excellence in England uses λ = £30,000 (approximately $58,380 US Dollars) in their health technology assessments. Higher and lower levels for this analysis were chosen arbitrarily as λ = $100,000 and λ = $25,000. The level of λ = $0 was also included because it allowed for an analysis of negative costs as an additional interpretation of willingness to pay equal to zero, and for graphing cost-effectiveness acceptability curves described later in this chapter.

3.4 Dependent Variable and Timeframes for Estimation

The dependent variable in the models was the total annual $NMB_{\lambda i}$ for patient *i* at λ = \$0, \$25,000, \$50,000, and \$100,000. The total annual $NMB_{\lambda i}$, which will be denoted as $NMB^*_{\lambda i}$, is the sum of each patient's NMB_{λ} values across the time points, month 4, 8, and 12. Because of basic dissimilarities in the models that were selected for this analysis, the predicted $\hat{NMB}_{\lambda}^{*}$ was derived one way for the ANCOVA model and somewhat differently for the ME models. For example, in the ANCOVA model the observed $NMB_{\lambda it}$ within patient across time points *t* = 4, 8, and 12 were first summed to create the $NMB^*_{\lambda i}$. Then $NMB^*_{\lambda i}$ was used as the dependent variable in the model for estimating parameters and a predicted $\hat{NMB}_{\lambda}^{*}$ (Equation 3.1).

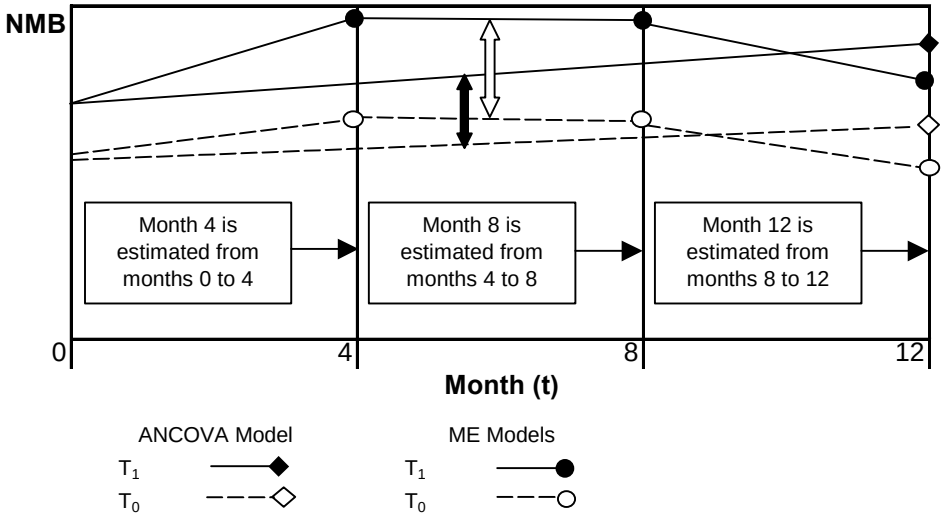
$$\sum_{t=4,8,12} NMB_{\lambda it} = NMB^*_{\lambda i} = \beta X_i + \varepsilon_i \tag{3.1}$$

In the ME models, the observed $NMB_{\lambda it}$ within patient at each time point were used as dependent variables (Equation 3.2), and the estimator $\hat{NMB}_{\lambda}^{*}$ was then calculated as the sum of the estimated parameters at months 4, 8, and 12. The detailed specifications of the models, which are provided in the next section, explain further how this was implemented with the use of "knot" variables.

$$NMB^*_{\lambda it} = \sum_{t=0,4,8,12} X_{it}\beta + Z_{it}d_i + \varepsilon_{it} \tag{3.2}$$

To help illustrate the differences in the predicted $\hat{NMB}_{\lambda}^{*}$, a graphical depiction of hypothetical model results from the ANCOVA and ME models is shown in Figure 3.4-1. The ANCOVA model provides the estimated $\hat{NMB}_{\lambda}^{*}$ based on the sum of the observed $NMB_{\lambda i}$ across time points (diamonds). The ME models provide estimates of $NMB_{\lambda i}$ at each time point (circles) which are summed to obtain the estimated $\hat{NMB}_{\lambda}^{*}$. The solid lines represent estimated regression lines for T_1; the dashed lines represent the same for T_0. The text provided in the boxes explain how the time intervals between months 0 and 4, months 4 and 8, and months 8 and 12 include the data for estimating the $NMB_{\lambda i}$ at each time point in the ME models. The vertical arrows point out the differences between the areas under the curves for the two treatment groups (the areas extend across the entire study, not just where the arrows are shown). The differences represent the $INMB_{\lambda}$ or treatment effect. The black and white vertical arrows indicate the $INMB_{\lambda}$ for the ANCOVA and ME models, respectively.

Figure 3.4-1 Hypothetical model results from the ANCOVA and ME models



3.5 Model Specifications

This section provides descriptions of the models used in the analysis. Table 3.5-1 presents definitions of the terms included in the three models. The fixed effects terms included in the models were patient age, previous hospitalizations, baseline *NMB*, treatment, time, and treatment-time interaction. These covariates were selected because they comprised a parsimonious set of factors expected to be associated with the outcome, *NMB*. The covariates were centered (i.e., rescaled) to facilitate interpretation of the *NMB* mean intercepts. Centering of covariates was accomplished by subtracting the covariate mean value from each patient's age (i.e. age – 40), previous hospitalizations (previous hospitalizations – 0.5), and baseline NMB_λ (NMB_λ - mean NMB_λ). The interpretation of the *NMB* mean intercepts with centered covariates is the expected *NMB* value at time *t* for a 40-year old patient, with average values for the measures of previous hospitalizations and baseline *NMB*. Another advantage of using centered covariates is

that the SAS procedure used to estimate the joint ME model (Proc NLMIXED) converges easier if the model variables are not widely different in scale (Fairclough, personal communication, Feb 2008). The dependent variable was rescaled by dividing by 1,000 to provide results that were easier to read for all three models. Thus, NMB is measured in thousands of dollars and the coefficients on the right-hand side variables show their effect on NMB in thousands of dollars.

Table 3.5-1 Definitions of variables and parameters used in each model

Dependent Variables		**ANCOVA**	**ME**	**Joint ME**
Y_i^N	Overall annual $NMB_{\lambda i}^*$ response for patient *i* in thousands of dollars (superscript N represents NMB)	√		
Y_{it}^N	$NMB_{\lambda it}$, observed at t (months) = 0, 4, 8, 12 for patient *i* in thousands of dollars (superscript N represents NMB)		√	√
Y_i^T	Log time-to-dropout response (continuous variable) for patient *i* (superscript Y represents time to dropout)			√
Indicator Variables				
z^N	NMB_λ response indicator			√
z^T	Log time-to-dropout response indicator			√
$Group_i$	Treatment group indicator for patient *i* (=1 for T_1; =0 for T_0)	√	√	√
Fixed Effects (Covariates)				
$Month_{it}$	Time in months (continuous variable) for patient *i*		√	√
Age_i	Patient age (continuous variable); rescaled by subtracting approximate mean value of 40	√	√	√
$Phosp_i$	Previous hospitalizations in the 2 years before randomization for patient *i* (=0 for 1 hosp; =1 for >=2 hosp); rescaled by subtracting mean of 0.5	√	√	√
$T_i^{[4]}$	"Knot" term to allow NMB_λ slope to change at month 4. $T_i^{[4]} = \max(0, t_{ij} - 4)$		√	√
$T_i^{[8]}$	"Knot" term to allow NMB_λ slope to change at month 8. $T_i^{[8]} = \max(0, t_{ij} - 8)$		√	√
BL_NMB_i	Baseline NMB_λ for patient *i*; rescaled by subtracting mean baseline NMB_λ	√		
Parameters for Fixed Effects				
β_1	NMB_λ mean intercept	√	√	√
β_2	NMB_λ mean slope (month)		√	√
β_3	Treatment group effect on NMB_λ response	√	√	√
β_4	Patient age effect on NMB_λ response	√	√	√
β_5	Previous hospitalizations effect on NMB_λ response	√	√	√
β_6	Interaction with treatment and time effect on NMB_λ	√	√	√
β_7	Change in NMB_λ slope at month 4	√	√	√
β_8	Interaction between treatment and change in NMB_λ slope at month 4	√	√	√
β_9	Change in NMB_λ slope at month 8	√	√	√
β_{10}	Interaction with treatment and change in NMB_λ slope at month 8	√	√	√

Table 3.5-1 Definitions of variables and parameters *(continued)*

Parameters for Fixed Effects		**ANCOVA**	**ME**	**Joint ME**
β_{11}	Baseline NMB_λ effect on NMB_λ response	√		
τ_1	Log of time-to-dropout mean intercept			√
Variance of Random Effects and Residual Errors				
u_i	Between-patient random effect for $NMB_{\lambda i}$ intercept		√	√
v_i	Between-patient random effect for $NMB_{\lambda i}$ slope		√	√
s_i	Between-patient random effect for log of time-to-dropout			√
ε_{it}	Residual errors for $NMB_{\lambda it}$	√[1]	√[2]	√[2]

√ indicates term is included in the model.

[1] Subject-level residual errors for the annual $NMB^*_{\lambda i}$.

[2] Subject-level residual errors for $NMB_{\lambda it}$ at each time point.

3.5.1 Analysis of Covariance Model

ANCOVA was selected because it is widely used for analyzing clinical trial data, but does not account for the effects of MAR and MNAR data. Equation 3.3 presents the ANCOVA model specifications for this study.

$$Y_i^N = \beta_1 + \beta_3 Group_i + \beta_4 Age_i + \beta_5 PHosp_i + \beta_{11} BL\_NMB_i + \varepsilon_i \qquad (3.3)$$

The terms in the joint ME model are defined in Table 3.5-1 and are indicated with check marks under the column labeled "ANCOVA." The response variable, Y_i^N, represents the overall annual $NMB^*_{\lambda i}$ for patient *i*. Common to all three models are the NMB_λ intercept or population average NMB_λ represented by parameter β_1; treatment group represented by the indicator variable $Group_i$ and treatment effect on NMB_λ represented by parameter β_3; patient age represented by continuous variable Age_i and the effect of age on NMB_λ by parameter β_4*;* number of previous hospitalizations represented by the dichotomous variable $PHosp_i$ and the effect of previous hospitalizations on NMB_λ

by the parameter β_5. Included in the ANCOVA model, but not in the ME and joint ME models is the term for baseline $NMB_{\lambda i}$, represented by *BL_NMB*, and the effect of baseline on the annual $NMB^*_{\lambda i}$, by parameter, β_{11}. *BL_NMB* is rescaled by subtracting mean baseline NMB_{λ}, which allows all remaining parameters to be interpreted as the value expected for a patient with average *NMB*. The ANCOVA model does not include a term for time (*Month*) because the dependent variable in this model was the annual $NMB^*_{\lambda i}$ that was first computed as the sum of the observed $NMB_{\lambda it}$ across the three time points, then modeled (see section 3.4). The ANCOVA model is a simple linear function that does not account for the effect of time-to-dropout, or the potential changes in $NMB_{\lambda i}$ slope over time. The ANCOVA model is a fixed effects model except for the random error, ε_i, which represents the residual error for the annual $NMB^*_{\lambda i}$.

ANCOVA models require that observations with incomplete data either be discarded (when the number of missing observations is small) or be imputed (when the number of missing observations is large). The simulated missing dataset had approximately 33% of patients with response values set to missing by month 12, therefore, the ANCOVA analysis used the imputation method of last observed value carried forward (LOCF). LOCF was selected because it is a commonly used approach for handling monotone missing data.

SAS Proc REG was used to estimate the ANCOVA model. (See Appendix II.A for ANCOVA model SAS code.)

3.5.2 Repeated Measures Mixed-Effects Model

A repeated measures mixed-effects model (ME) was selected because it is commonly used in longitudinal clinical trials and can provide unbiased estimates when the dataset includes MAR data. The ME model, however, cannot account for the effects of MNAR data. Mixed-effects models allow repeated measurements on the same patient to be correlated (Littel et al, 1996) and do not require that all observations be complete (as in the ANCOVA model). The ME model used in this analysis was piece-wise linear (explained later). The foundation of the piece-wise linear ME model is shown in Equation 3.4.

$$Y_{it}^{N} = \beta_1 + \beta_2 Month_{it} + \beta_3 Group_i + \beta_4 Age_i + \beta_5 PHosp_i + \beta_6 Group_i * Month_{it} + u_i + v_i Month_{it} + \varepsilon_{it} \quad (3.4)$$

The terms in the ME model are defined in Table 3.5-1 and are indicated with check marks under the column labeled "ME." The $NMB_{\lambda it}$ response for the i^{th} patient is represented by Y_{it}^{N} (the reason for using this notation will become apparent in the discussion of the joint ME). The response data for each patient can be thought of as a vector with four elements, each representing the values of $NMB_{\lambda it}$ observed at times t = 0, 4, 8, and 12 months. Patients who do not drop out of the study are considered censored. The fixed effects (covariates) are the same as in the ANCOVA model, with the additional fixed effect for time and interactions involving time. Time is measured in months from the start of the study for each patient and is represented by the continuous variable $Month_{it}$ and the NMB_{λ} linear rate of change (i.e., slope) by the parameter β_2. The interaction between treatment group and time is represented by the variable $Group_i$*$Month_{it}$, and interaction effect by parameter β_6. Fixed effects parameters β_1 and

β_2 represent the population average regression coefficients for NMB_λ intercept and NMB_λ slope, respectively.

The remaining terms in the model represent between-patient random effects for NMB_λ intercept and NMB_λ slope, represented by u_i and v_i, respectively. The random effects coefficients are patient-specific and measure the deviation of the *i*th individual parameters from the corresponding population averages. The between-patient effect is considered to be random because inference is to be made to the entire population of chronically ill individuals with schizophrenia who could have received one of the two treatment options. The random effects are assumed to have normal distributions, with means equal to 0 and variance-covariance matrix Ω.

$$\Omega = \begin{bmatrix} \sigma^2_u & \sigma_{uv} \\ \sigma_{vu} & \sigma^2_v \end{bmatrix}$$

The diagonal elements of Ω represent the variability between patients that is unexplained by the model. The off-diagonal elements are covariances that represent the relationships between these random effects; σ_{uv} represents the measure of the association between the NMB_λ intercept and the rate of change in NMB_λ. These random effects are incorporated into the fixed effects estimates by estimating the fixed effects conditional on the random effects. In other words, the fixed effect treatment group parameter is the treatment fixed effect averaged over the subject-level random effects. The random effects covariance structure that was specified in the ME model allowed the random effects on the NMB_λ intercept and the rate of change over time (i.e., slope) to be

correlated (Fairclough, personal correspondence, May 3, 2008). In SAS Proc MIXED, this covariance structure is referred to as unstructured.

The last random effect term is the residual error, ε_i that captures the variation of the NMB_λ within each patient. The residual error can be thought of as a vector with four elements that correspond to the four $NMB_{i\lambda}$ values observed at times t = 0, 4, 8, and 12 months. The $NMB_{\lambda i}$ residual errors are assumed to have a covariance structure where the errors are independent and normally distributed with means 0 and homogeneous variance σ_e^2.

The ME model described thus far is linear over the one-year study period. A more flexible model is a piecewise-linear model that allows the slope of the estimated line to change at the time points for months 4 and 8 (Fairclough, 2003). The NMB_λ in such a model is treated as a linear function, however, it is modeled over three shorter time intervals as was illustrated in Figure 3.1-1. A piecewise-linear model was chosen for the ME and ME joint models because it should provide a better fit to the data and be easier to interpret than a model with higher order terms to account for departures from linearity.

The ME model in Equation 3.4 is converted to a piecewise-linear model by adding two "knot" terms and two interaction terms that involve the knot terms. These terms are referred to as "knots" because they allow the slope to change at discrete points in time. The "knot" for patient *i* at month 4 is defined as $T_i^{[4]} = \max(0, Month - 4)$, which is equal to 0 until month 4 and then is equal to the value of *Month - 4* from month 4 to 12. Similarly, the "knot" for patient *i* at month 8 is defined as $T_i^{[8]} = \max(0, Month - 8)$, which is equal to 0 until month 8 and then is equal to the value

of *Month – 8* from month 8 to 12 (Fairclough et al, 2003; Fairclough et al, 2004). The terms, $T_i^{[4]} * Group_i$ and $T_i^{[8]} * Group_i$, represent the interactions between treatment and the change in slope indicators. The slope of the estimated line from month 0 to 4 is accounted for in the model by the term $\beta_2 * Month_i$. The piecewise-linear ME model is presented in Equation 3.5.

$$\begin{aligned} Y_{it}^N = {} & \beta_1 + \beta_2 Month_{it} + \beta_3 Group_i + \beta_4 Age_i + \beta_5 PHosp_i \\ & + \beta_6 Group_i * Month_{it} + u_i + v_i Month_{it} + \varepsilon_{it} \\ & + \beta_7 T_i^{[4]} + \beta_8 T_i^{[4]} * Group_i + \beta_9 T_i^{[8]} + \beta_{10} T_i^{[8]} * Group_i \end{aligned} \tag{3.5}$$

SAS Proc MIXED was used to estimate the ME model (Littell et al, 1996). (See Appendix II.B for ME model SAS code.)

3.5.3 Joint Mixed-Effects Log of Time-to-dropout Model

The last modeling approach was a joint mixed-effects log of time-to-dropout (joint ME) model, which is an extension of the mixed-effects model. The joint ME was selected because the impact of MNAR missing data on the estimate of treatment effect can be accounted for by simultaneously modeling NMB_λ response and log time-to-dropout in the same model. Specifically, the non-ignorable missing data are accounted for by allowing the time of dropout to be correlated with the between-subject random effects on NMB_λ intercept and slope. Additional random effects could have been included, however, the two random effects for the intercept and slope are usually enough to obtain a good approximation of the covariance structure. The joint ME model allows the changes in the response variable to be a function of the dropout time and the time of dropout to be a function of the initial response value at baseline and the rate of change overtime (Fairclough, 2002).

The piecewise-linear joint ME model is presented in Equation 3.6. This model is identical to the piecewise-linear ME model, except it includes an additional exponential link function for log of time-to-dropout.

$$
\begin{aligned}
Y_{it}^{N} \text{ or } Y_i^{T} = f_1(&\beta_1 + \beta_2 Month_{it} + \beta_3 Group_i + \beta_4 Age_i + \beta_5 PHosp_i \\
&+ \beta_6 Group_i * Month_{it} + u_i + v_i Month_{it} + \varepsilon_{it} \\
&+ \beta_7 T_i^{[4]} + \beta_8 T_i^{[4]} * Group_i + \beta_9 T_i^{[8]} + \beta_{10} T_i^{[8]} * Group_i) z^N \\
&+ f_2(\tau_1 + s_i) z^T
\end{aligned}
\tag{3.6}
$$

All of the terms in the joint ME model are defined in Table 3.5-1 and are indicated with check marks under the column labeled "Joint ME." The majority of the terms of the joint ME model are defined as in the ME model, with a few differences that are noted here. The $NMB_{\lambda it}$ response for the i^{th} patient is represented by Y_{it}^{N} (where the superscript, N, represents NMB) and log time-to-dropout is represented by Y_i^{T} (where the superscript, T, represents time-to-dropout). The response data for each patient can be thought of as a vector with five elements, with the first four elements representing the values of $NMB_{\lambda i}$ observed at times t = 0, 4, 8, and 12 months, and the last element of the vector representing the value for log of the time-to-dropout. Patients who do not drop out of the study are considered censored.

The first function in Equation 3.6, f_1, is an identity link function for the NMB_{λ} component of the model. Indicator variable $z^N = 1$ when the NMB_{λ} response component is modeled, otherwise $z^N = 0$. The second function, f_2, is the exponential link function for log of the time-to-dropout. Indicator variable $z^T = 1$ when the log of the time-to-dropout is modeled, otherwise $z^T = 0$. The fixed effects are the same as in the

ME model, with the addition of the fixed effect for log of the time-to-dropout in f_2, where the mean log of time-to-dropout is represented by the parameter τ_1. The decision to take the log of the time-to-dropout was based on two considerations: (1) the distribution of the dropout times (which were skewed towards later time points) and (2) the relationships between the time-to-dropout and the RE. The relationships are more important than the distributional aspect for taking a log transformation because the earlier time periods have the stronger relationships, and a log transformation maintains that relationship better by weighting the earlier dropouts more. A log transformation resulted in positive predicted values and approximately normally distributed residuals. Fixed effects parameters $\beta_1, \beta_2,$ and τ_1 represent the population average regression coefficients for NMB_λ intercept, NMB_λ slope, and log of time-to-dropout, respectively. As with the ME model, the fixed effects have no variance because all of the variance is captured in the random effects and residual errors.

Similar to the ME model, the terms u_i and v_i, represent between-patient random effects for NMB_λ intercept and slope, and the additional term s_i represents the residual error for log of time–to-dropout. Again, the random effects coefficients are patient-specific and measure the deviation of the *i*th individual from the corresponding population averages. The random effects and residual error are assumed to have normal distributions, with means equal to 0 and variance-covariance matrix Ω'.

$$\Omega' = \begin{bmatrix} \sigma^2_u & \sigma_{uv} & \sigma_{us} \\ \sigma_{uv} & \sigma^2_v & \sigma_{vs} \\ \sigma_{us} & \sigma_{vs} & \sigma^2_s \end{bmatrix}$$

The covariance matrices are similar between the ME and joint ME models, except in Ω' there is the additional variance for the residual error of time-to-dropout and the covariances of the residual error for time-to-dropout with the random effects for NMB_{λ} intercept and slope. Covariance σ_{us} represents a measure of association between random variation in NMB_{λ} intercept and log time-to-dropout, and covariance σ_{vs} represents the association between the rate of change in NMB_{λ} and log time-to-dropout. If $\sigma_{us} = \sigma_{vs} = 0$, this would imply that each patient's time-to-dropout is independent of the true slope and intercept. In other words, the nonresponse mechanism would not be MNAR under that particular model (Schluchter, 1992). A null hypothesis of independence between time-to-dropout and the random effects can be tested, but only under that model. If the null hypothesis cannot be rejected , this does not mean that the non-response mechanism is MAR, but rather that under that model, the covariance is not statistically significantly different from zero. Because MNAR comprises an infinite number of different mechanism, there is no one definitive test for MNAR. The covariance structure that was specified in the joint ME model allowed the random effects on the NMB_{λ} intercept and slope to be correlated with time-to-dropout (Fairclough, personal correspondence, May 2008). Similar to the ME model, these random effects are incorporated into the fixed effects estimates by estimating the fixed effects, conditional on the random effects.

The last random effect term in f_1 is the residual error ε_{it}. Similar to the ME model, the residual error captures the variation of the $NMB_{\lambda it}$ within each patient. It can be thought of as a vector with four elements that correspond to the four $NMB_{\lambda it}$ values observed at times $t = 0$, 4, 8, and 12 months. The $NMB_{\lambda it}$ residual errors are assumed to

be independent and normally distributed with means 0 and variance σ_e^2. The joint ME model in Equation 3.6 is a piecewise-linear model with the four "knot" terms included in the identity link function. These terms are defined exactly as in the ME model. Refer to Table 3.5-1 for definitions of all model terms.

SAS Proc NLMIXED was used to estimate the joint ME model. Proc NLMIXED uses numerical integration to maximize the approximation of the likelihood integrated over the random effects (Wolfinger, 1997). Estimates of fixed and random effects parameters from the ME model were used as initial estimates for the joint ME model. (See Appendix II.C for joint ME model SAS code.)

All models were estimated at λ = \$0, \$25,000, \$50,000, and \$100,000.

3.6 Subgroup of the ROSE Study for Data Simulation

The observed missing data pattern from a clinical trial may suggest one or more nonresponse mechanisms. Ribaudo et al (2000), Fairclough (2002), and Fairclough et al (2003) proposed that the missingness patterns found in their studies of patients with different cancers suggested MAR and possibly MNAR data. The patterns showed that individuals who dropped out earlier had lower baseline response scores and lower response scores just prior to dropout, compared to individuals who remained in the studies longer. Patients with cancer would be expected to have different reasons for dropout and probably different patterns of dropout compared to patients with schizophrenia. For example, dropout due to death would probably be more common with cancer patients, and dropout due to side effects and noncompliance would probably be more common with schizophrenia patients. In the current study, it was believed there

would also be a dropout pattern among the patients with schizophrenia in the ROSE Study, and that the dropout pattern should be reflected in the simulated data. The missingness patterns in the ROSE Study data, however, were unknown and required exploration. This section is devoted to a thorough examination of the missingness patterns in the ROSE Study.

In health economic evaluations, patients' health care costs might be proxies for health status because costs for sicker patients would be expected to be higher. Studies have shown health care costs are higher among patients with greater severity of illness, complex health conditions, and multiple comorbidities (Hlatky et al., 2004; Marciniak et al., 2005). Hence, it was believed that ROSE Study schizophrenia patients with higher costs early in the study would also have lower health status and would be more likely to drop out earlier. These same patients would also have lower *NMB* early in the study (because *NMB* is a function of cost (*C*) and health status (*E*), i.e., $NMB_i = \lambda E_i - C_i$).

Missingness patterns were checked using the graphical approach presented in Chapter 2, Figure 2.5-1 (Fairclough, 2002). Patterns of missingness were examined for total costs, utilities, and NMB_{50000}. ROSE Study patients were grouped into four cohorts according to time-to-dropout (i.e., dropout at months 0, 4, 8, and 12, corresponding to cohorts 1, 2, 3, and 4). The expectation was that cohorts 1 and 2 would have the lowest utilities and highest costs (reflecting they were sickest), as well as the lowest NMB_{50000}. Patterns were inspected for all patients (N=675) and for the subgroups of patients who were randomized in the hospital (N=442) and patients who were randomized in the outpatient setting (N=233). These subgroups were examined because they were expected to be different. In particular, cost outcomes were expected to be higher for patients

randomized as inpatients, at least initially. Moreover, psychiatric patients who were randomized in the hospital may exhibit different patterns of dropout compared to other patients because hospitalized patients should be under careful supervision.

The numbers of patient dropouts at months 0, 4, and 8, and study completers at month 12 are provided in Table 3.6-1. Among the 675 patients who were randomized in the ROSE Study, 42 completed only the month 0 assessment and had nonmissing utility data, 499 patients completed all assessments and had nonmissing utility data, and 550 completed all assessments and had nonmissing cost data. Similar results are presented for the two subgroups of patients. The numbers of patients in cohorts 1, 2, and 3 are small (ranging from 6 to 42). Approximately 80% (186/233) of the subgroup of patients who were randomized as outpatients had not dropped out and had nonmissing data for analysis at the end of the study.

Table 3.6-1 Number of ROSE Study patients by time-to-dropout (months 0, 4, and 8) or study completion (month 12)

	Time-to-dropout N with nonmissing utilities / N with nonmissing costs			
	Month 0* Cohort 1	Month 4 Cohort 2	Month 8 Cohort 3	Month 12 Cohort 4
All patients (N=675)	42/NA	27/30	34/37	499/550
Patients randomized in hospital (N=442)	36/NA	17/19	21/22	313/350
Patients randomized as outpatients (N=233)	6/NA	10/11	13/15	186/200

* Month 0 costs are NA because cost data were not collected at baseline.
Note: Ns in the table represent numbers of patients who dropped out at each time point and had nonmissing utility or cost data.

Figures 3.6-1 A, B, and C present results for health status (utilities) by patient group. The figures illustrate how missingness on this variable does not follow a clear

pattern. Cohorts who dropped out earliest tended have the highest and lowest utility scores. Cohort 2 had relatively high health status at baseline, then worsened by month 4. Patients who remained in the study longer tended to improve (cohorts 3 and 4). Patients with lower health status at month 0 either were the first to drop out (cohort 1), or remained in study the longest (cohorts 3 and 4). Health status did not vary greatly. However, at month 0 the extreme values occurred in the subgroup of patients who were randomized as outpatients, with cohort 2 having the highest mean values and cohorts 1 and 3 having the lowest. This variance was probably due to the extremely small number of patients in these cohorts (Ns ranged from 6 to 15). Another possible explanation is this subgroup may have included a range of patient types, such as higher functioning patients who did not require hospitalization, and patients who required hospitalization but were not hospitalized for reasons such as no available hospital bed or patient refusal.

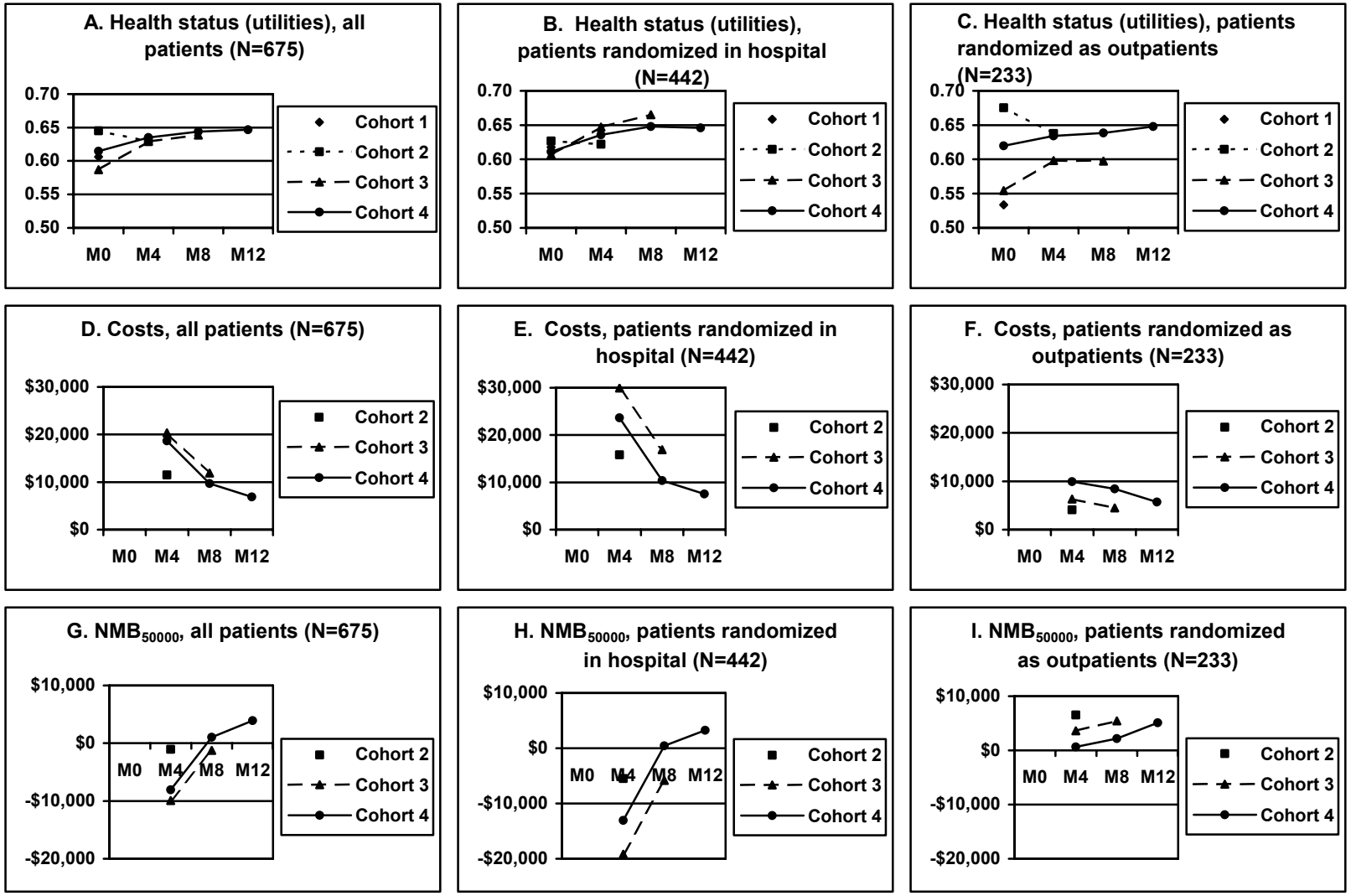
ROSE Study costs by patient group are presented in Figures 3.6-1 D, E, and F. Recall that month 0 costs were not collected in the ROSE Study. Therefore, costs are summarized only for months 4, 8, and 12, corresponding to cohorts 2, 3, and 4. Contrary to what was expected, the patients with the lowest costs early in the study were the first to drop out. The figures also illustrate how mean costs for patients who remained in the study longer tended to decrease overtime (cohorts 3 and 4). Consistent with expectations, patients who were randomized as outpatients had lower costs compared to patients who were randomized in the hospital (month 4 mean costs ranged from $4,084 to $9,931 per patient randomized in the outpatient setting, compared to $15,834 to $29,956 per patient randomized in the hospital).

Last, Figures 3.6-1 G, H, and I present results for mean NMB_{50000} by patient group. (since missingness patterns for *NMB* were similar for all levels of λ, graphs are provided only for NMB_{50000}.) Similar to costs, *NMB*s are summarized for only months 4, 8, and 12, corresponding to cohorts 2, 3, and 4. The figures illustrate how NMB_{50000} for patients who remained in the study longer tended to increase overtime (cohorts 3 and 4), however, patients with the highest NMB_{50000} at month 4 were the first to drop out (cohort 2). Patients randomized as outpatients had higher NMB_{50000} than patients randomized as inpatients (month 4 mean NMB_{50000} ranged from \$637 to \$6,547 per patient randomized in the outpatient setting, compared to negative \$19,173 to \$3,248 per patient randomized in the hospital). Cohorts with the lowest mean costs and the highest mean health status also had the highest mean NMB_{50000} values. There was a sequential pattern to missingness among patients randomized as outpatients. For example, at month 4 cohort 2 had the highest NMB_{50000}, followed by cohort 3, then cohort 4. By month 12, the mean NMB_{50000} (\$5,090) for cohort 4 had increased to a value nearly equal to the mean NMB_{50000} for cohort 2 at month 4 (\$6,547). Contrary to expectations, patients with the lowest NMB_{50000} values early in the study were not the first to drop out.

The observed missingness patterns in the ROSE Study data was opposite of what was expected. Patients with low NMB_{50000} values early in the study tended to remain in the study longer. Overtime, the mean NMB_{50000} values for patients who remained in the study increased and matched or surpassed the mean NMB_{50000} values for patients who dropped out early. Among patients who were randomized as outpatients, individuals who dropped out earlier had higher NMB_{50000} values early in the study and their NMB_{50000} values were higher before time of drop out. Although this pattern was the reverse of

what was expected, it suggests that missingness may be dependent on previously observed data, and that the nonresponse mechanism could be MAR. It is also possible that missingness depended on what occurred after patients were last observed (an MNAR nonresponse mechanism). The purpose of the above examination was to explore the unknown missingness patterns for the schizophrenia patients in the ROSE Study. Missingness patterns for schizophrenia patients were expected to differ from those for the cancer patients observed in the studies by Ribaudo and Fairclough. Further, missingness patterns for NMB_{λ} would be expected to differ from patterns based on health status measures. The examination revealed a unique pattern that may be reflective of the complexity of schizophrenia and its treatment, such as patients having psychotic and paranoid symptoms, severe social dysfunction, and high levels of medication noncompliance. For the purpose of the current study, the ordered pattern of missingness that was observed among patients who were randomized in the outpatient setting was thought to reflect a pattern that could be suited for selection model analysis. Moreover, schizophrenia treatment patterns since the mid 1990s have shifted from care being provided largely in the inpatient setting to the outpatient setting (Zeber et al., 2006). Therefore, the patterns of missingness and the relationships among variables for this subgroup of patients may be more representative of schizophrenia patients today. For these reasons, this study used a simulated dataset that was based on the distributional properties of the subgroup of patients in the ROSE Study who were randomized in the outpatient setting.

Figure 3.6-1 ROSE Study missing data patterns, by outcomes, subgroups, and cohorts



3.7 Creating the Simulated Dataset

An overview of the simulation procedure is provided in this section, followed by details in sections 3.7.1 and 3.7.2. The simulation procedure for the current study was based on a regression approach to produce a simulated complete dataset with realistic relationships between variables and across time. The procedure used a mixed-effects model to simulate NMB_{λ} values that were predicted from the covariance structure of patient characteristics, cost, and utilities over time from the ROSE Study outpatient subgroup. In addition to creating a realistic simulated dataset, a regression approach allowed a specific treatment effect to be simulated directly into the *NMB* response variable. As a result, the treatment group difference was a known parameter for assessing the performance of the models. Further, a regression approach allowed diagnostics of the data to be examined throughout the process. A concern with using a ME model for the simulation procedure is that the ME model for estimating the *INMB* may perform better as a result of this simulation. The ME model that generated the data looked at similar covariates, but interacted all of these and jointly modeled costs and utilities, whereas the analysis ME model had *NMB* as the dependent variable. An alternative model for the data simulation would have been a repeated measures model. However, with a repeated measures model it would have been more difficult to maintain the correlations between the costs and utilities, which was thought to be more important at the time.

Nonresponse mechanisms were also simulated. The base case analysis used a combination of simulated MAR or MNAR missing and complete cases. A combination of complete and missing cases was used because this is what would typically be found in

a clinical trial database. Approximately equal proportions of patients were simulated to be either complete, MAR, or MNAR (i.e., 1/3, 1/3, and 1/3) in the base case. The effects of different proportions of data types on the estimates of $\hat{INMB}_{\lambda}$ were examined with sensitivity analyses. MAR and MNAR data were simulated because these are the nonresponse mechanisms that are most likely to occur in long-term clinical trials and they pose analytical challenges. The MCAR nonresponse mechanism was not included in the simulation because simple analytical methods, such as ANCOVA models, are usually adequate for inferences from MCAR data.

The MAR and MNAR data were generated with two nonresponse algorithms based on a threshold NMB_{λ} criterion, i.e., NMBλ responses or subsequent responses were simulated to be missing if they exceeded a threshold value. The threshold was a value that would result in at least the same proportion of missing cases as was observed in the ROSE Study. A threshold criterion is a direct interpretation of Rubin and Little's definition of MNAR nonresponse, which stated that the MNAR nonresponse mechanism occurs when the missingness is dependent on the missing responses, i.e., $\Pr(M_i \mid \boldsymbol{y}_i, \boldsymbol{X}_i) = \Pr(\mathbf{y}_{mis})$. Other approaches were possible, such as trajectories of the response values or change scores, as in the study by Oostenbrink et al. (2005). (In February 2008, the author discussed the threshold approach used in this study with Dr. Fairclough. She voiced concerns based on work-in-progress by another doctoral student. The work suggested threshold-based simulated data may not have the necessary variability for joint ME models to converge. However, Dr. Fairclough agreed that the threshold approach was worthwhile trying for this study.)

The first phase of the simulation was to generate a complete dataset of 600 patients with NMB_λ values at all time points. The second phase of the simulation involved creating a subset of incomplete observations on the NMB_λ response variable. Details on the two phases of the simulation process are described in the following sections.

3.7.1 Phase 1: Creating the Simulated Complete Dataset

The simulated complete dataset was generated through a process of constructing cost and utility values from the components of a mixed-effects model's β parameter estimates, covariance parameter estimates, and residual errors, using the ROSE Study data (outpatient subgroup, N=233) as inputs. The approach resulted in a dataset that reflected the relationships between variables and time points found in the ROSE Study outpatient subgroup, and it allowed a specified treatment effect to be built into the response data. The process began with identifying the best predictors of log of costs and utilities in two separate mixed-effects models. Log of costs, instead of costs, was used in the data simulation because the transformed variable was approximately normally distributed, whereas cost was not. Log of costs produced parameter estimates and simulated costs with good fit to the original data.

The potential predictor variables in the separate mixed-effects models included patient age, previous hospitalization, time (month), and the two-way interactions between these variables. Significant predictors were based on Type 3 sums of squares tests of the fixed effects with p values <0.15. For log of costs, the significant predictors were previous hospitalizations (p=0.04) and month (p<0.01). The reduced model for log of costs with only these two independent variables revealed that the variance in the log of

costs increased with time (Var = 1.45, 1.61, and 2.09 for months 4, 8, and 12). Further, the variance parameter estimates for the random subject variations in the intercepts and slopes for log of costs were significantly different from zero (intercept p=0.03, slope p=0.02), meaning there was significant variability between patients in their starting values and their changes over time in log of costs in the ROSE Study outpatient subgroup. For utilities, the significant predictors were age (p=0.06), month (p=0.06), and the interaction between month and previous hospitalizations (p=0.12). The reduced model for utilities with these independent variables revealed the variance parameter estimates for the random variations in the intercepts were significantly different from zero (p<0.01), however, the random variations in the slopes for utilities were not (slope p=0.10). The interpretation is there was significant variability between patients in their starting values for utilities and little variability between patients in the rate of change in utility over time. This is noted here because small variance in the rate of change in a dependent variable could potentially lead to convergence problems for the joint ME model. However, because *NMB* (not utilities) is the dependent variable in the final models, the small variance in utilities was not an issue for this analysis.

The resulting best predictors of log of cost and utilities were then combined into one mixed-effects model to jointly estimate parameters for the fixed effects of age, previous hospitalizations, month, the interaction between previous hospitalizations and month, and the random effects of the covariance between intercept and slope for costs and utilities, and the residual errors for costs and utilities. The general form of the joint cost and utility mixed-effects model is presented in Equation 3.5.

$$Y_{it}^{C} or Y_{it}^{U} = (X_{it}\beta + Z_{it}d_i + e_{it})z^{C} + (X_{it}\beta + Z_{it}d_i + e_{it})z^{U} \qquad (3.5)$$

$$Var\begin{bmatrix} d_{1i} \\ d_{2i} \end{bmatrix} = \begin{bmatrix} D_{11} & D_{12} \\ D_{21} & D_{22} \end{bmatrix} \tag{3.6}$$

$$Var[e_{it}] = \sigma_r^2 I \tag{3.7}$$

Simulated costs and utilities for patient *i* at time *t* are represented by Y_{it}^{C} and Y_{it}^{U}, respectively. Indicator variable $z^C = 1$ when costs were modeled, otherwise $z^C = 0$. Likewise, indicator variable $z^U = 1$ when utilities were modeled, otherwise $z^U = 0$. The component, $X_{it}\beta$, represents the fixed effects and parameters for the average costs or utilities, and the covariate effects for month, patient age, and previous hospitalizations. The component, $Z_{it}d_i$, represents the random variation in the intercepts (d_{1i}) for costs and utilities, and the random variation in the rate of change overtime, i.e., the slopes (d_{2i}) for costs and utilities. The final component, e_{it}, represents the residual errors for costs and utilities from the joint cost and utility model.

The beta estimate results from the joint log of cost and utility model are presented in Equations 3.8 and 3.9.

$$Y_{it}^{C} = 2.032 + 0.330 * PHosp_i - 0.097 * Month_{it} + u_i^{C} + v_i^{C} Month_{it} + e_{it}^{C} \tag{3.8}$$

$$Y_{it}^{U} = 6.177 - 0.017 * Age_i + 0.022 * Month_{it} - 0.023 * Month_{it} * PHosp_i + u_i^{U} + v_i^{U} Month_{it} + e_{it}^{U} \tag{3.9}$$

The joint model generated correlated data for the random effects for the intercept and slope of log of costs (u_i^{C} and v_i^{C}) and residual errors for log of costs (e_{it}^{C}), and the random effects for the intercept and slope of utilities (u_i^{U} and v_i^{U}) and residual errors for

utilities (e_{it}^{U}). The correlation between the residual errors for log of costs and utilities was small enough to ignore (r = 0.05) in the data simulation, i.e., in a subsequent step of the simulation it was unnecessary to jointly sample the cost and utility residuals to account for this correlation. The joint model produced output data sets that included the fixed effects parameter estimates and the variance/covariance of the estimates, the variance/covariance estimates of the random effects, and the residuals errors, all of which were used in the following steps to compute each simulated patient's cost and utility values. (See Appendix II.D for SAS code that generated the joint log of cost and utility model.)

The X_i's (Equation 3.5) for 600 patients were generated by sampling with replacement from the ROSE Study variables for age and previous hospitalization, which allowed the simulated age and previous hospitalization values to have the same distributions as age and previous hospitalization in the original study. The random effects for cost and utilities intercepts and slopes, Z_i's, were randomly generated standard normal variables. The $\hat{d}_i$'s were covariance estimates for the random effects, obtained from the joint cost and utility model using the Cholesky decomposition of the covariance matrix represented in Equation 3.6 (Fairclough, personal correspondence, Feb 2008), and the residual errors were obtained by random sampling with replacement from the residual errors of the joint log of costs and utilities model.

At this point, all necessary components were available to generate cost and utility values for each patient at each time point as shown in Equation 3.8 and 3.9. The cost values per patient were the sums of the cost components, which were retransformed back to costs by exponentiating the sums. Likewise, the utility values per patient were the

sums of the utility components. Recall that resource use data were not collected in the ROSE Study for the four-months before randomization. Therefore, baseline costs (month 0) were imputed in this step by "backwards extrapolation." That is, month 0 costs were estimated by setting Month = 0 in the estimated Equation 3.8 above. The simulated month 0 costs were intended to represent the cost of care over the four months before randomization and were used to calculate a baseline NMB_λ for each patient.

Treatment group differences were also simulated. This was done by adding \$900 to the cost values and 0.10 to the utility values at each time point after baseline for patients in the experimental group, T_1. These time point increments made annual costs for T_1 \$2,700 higher and health status better by 0.10 QALYs, compared to T_0. The rationale for simulating higher costs and utilities for the experimental arm is that new treatments typically cost more than standard treatments, and it is generally expected that new treatments will improve patients' health status compared to the standard treatments. The cost and utility increments were chosen to make T_1 approximately cost-effective at the λ = \$50,000 level. The resulting ICER is approximately \$27,000, which would not be favorable for T_1 at λ = \$25,000, but would be favorable at λ = \$50,000 and at λ = \$100,000. The "true" *INMB* values at the different levels of λ are discussed further in the next section.

The final step of Phase 1 involved combining the simulated costs and utilities with lambda values of \$0, \$25,000, \$50,000, and \$100,000 to create the simulated NMB_λ values. The final simulated complete dataset is analogous to data from a hypothetical study where all patients complete every assessment and have nonmissing costs and

utilities, hence nonmissing NMB_λ values, at each time point. (See Appendix II.E for SAS code to generate the final simulated complete dataset.)

3.7.2 Phase 2: Creating the Simulated Missing Dataset by Imposing Nonresponse Mechanisms

Phase 2 of the simulation procedure involved turning a subset of the simulated complete dataset into data with missing response values. NMB_λ responses were simulated to be missing at months 4, 8, or 12 according to MAR and MNAR nonresponse mechanisms using a threshold criterion for NMB_λ. The final simulated dataset was a combination of complete and incomplete (MAR and MNAR) observations.

The threshold value for NMB_λ was determined as follows. First, NMB_λ values at each level of λ were calculated for each patient at each time point. Because λ = \$50,000 is a referenced value in the current literature, the distribution of the NMB_{50000} at month 8 for group T_0 was examined (month 8 was arbitrarily selected). NMB_{50000} = \$8,915.69 was the threshold value that would result in at least the same proportion of missing data (across both treatment groups) as was observed in the ROSE Study. NMB_{50000} values greater than the threshold were set to missing if they met the MAR or MNAR criteria described in the following sections. After the MAR and MNAR criteria were applied to all data for $NMB_{50000,}$ the same missing data pattern was applied to the *NMB* values at the other levels of λ, i.e., if a patient was simulated to drop out at month 4 for $NMB_{50000,}$ then that same patient was simulated to dropout at month 4 for NMB_0, $NMB_{25000,}$ and NMB_{100000}. The reasoning behind using the same missingness pattern for all λ was that a missingness pattern in a dataset is observed and inherent in the data, whereas λ is not.

Before turning a subset of the simulated complete dataset into data with missing response values, one third of the simulated complete dataset (N=200) across treatment groups was randomly chosen to remain as complete observations. The other 400 observations were equally and randomly distributed to either MAR (N=200) or MNAR (N=200) simulation algorithms for generating incomplete observations. A mix of complete cases, MAR, and MNAR data was selected for the base case because it was thought that real datasets will include a mix of these data types.

MAR Algorithm. Data that are MAR can be predicted from the observed response data. The algorithm to generate monotone MAR data compared NMB_{50000} values to the threshold value of NMB_{50000} = \$8,915.69 for each of the randomly selected 200 patients. If the response value at a given time point was greater than the threshold value, then the NMB_{50000} at <u>all subsequent time points</u> for a patient were set to missing.

Step 1. Baseline NMB_{50000} values were evaluated for all 200 patients. If a patient's baseline NMB_{50000} was greater than the threshold value, then NMB_{λ} values for Months 4, 8, and 12 were set to missing for that patient. Patients whose baseline NMB_{50000} values did not meet the threshold criterion were evaluated in Step 2.

Step 2. Month 4 NMB_{50000} values were evaluated. If a patient's month 4 NMB_{50000} was greater than the threshold value, then all NMB_{λ} values for Months 8 and 12 were set to missing for that patient. Patients whose month 4 NMB_{50000} values did not meet the threshold criterion were evaluated in Step 3.

Step 3. Month 8 NMB_{50000} values were evaluated. If a patient's month 8 NMB_{50000} was greater than the threshold value, then all NMB_{λ} values for Month 12 were set to missing for that patient.

MNAR Algorithm. Data that are MNAR are not entirely predictable from the observed response data. Instead, the probability of missingness depends on events that occurred after the last observed response. Because the simulation process began with a complete dataset, monotone MNAR data could be simulated by evaluating "observed" NMB_{λ} values at each time point, then setting those and all subsequent values to missing if they failed to meet the threshold criterion. The algorithm to generate monotone MNAR data compared NMB_{50000} values to the threshold value of NMB_{50000} = \$8,915.69 for each of the second set of 200 randomly selected patients. If the response value at a given time point was greater than the threshold value, then the NMB_{50000} <u>at that time point and all subsequent time points</u> for a patient were set to missing.

Step 1. Month 4 NMB_{50000} values were evaluated for all 200 patients. If a patient's NMB_{50000} was greater than the threshold value, then NMB_{λ} values for Months 4, 8, and 12 were set to missing for that patient. Patients whose month 4 NMB_{50000} values did not meet the threshold criterion were evaluated in Step 2.

Step 2. Month 8 NMB_{50000} values were evaluated. If a patient's NMB_{50000} was greater than the threshold value, then NMB_{λ} values for Months 8 and 12 were set to missing for that patient. Patients whose month 8 NMB_{50000} values did not meet the threshold criterion were evaluated in Step 3.

Step 3. Month 12 NMB_{50000} values were evaluated. If a patient's NMB_{50000} was greater than the threshold value, then NMB_{λ} values for Months 12 were set to missing for that patient.

The final simulated missing dataset was formed by concatenating the 200 complete observations with the 400 observations that were processed through the MAR and MNAR algorithms. Some of the latter 400 observations were complete observations because it was possible for a patient to have response values not exceeding the threshold value at all time points. The simulated missing data resulted in a greater proportion of missing observations for T_1 versus T_0, based on the simulated higher costs and higher utilities for T_1. This pattern of missingness (i.e., patients with higher *NMB* values dropping out earlier) was based on the observed pattern found among the ROSE Study subgroup of outpatients. (See Appendix II.F for SAS code of the MAR and MNAR algorithms for the base case, sensitivity analyses, and post hoc analysis.)

3.8 The True Incremental Net Monetary Benefit

The true $INMB_{\lambda}$ was based on the cost and utility increments that produced a cost-effective result for T_1 versus T_0 at λ = \$50,000. The annual cost increment for T_1 was computed as \$900 multiplied by 3 time points for an annual incremental cost of \$2,700. The effectiveness measure, QALYs, (represented by E) is equal to utilities multiplied by time in the health state. Utilities were incremented for T_1 by 0.10 at each time point. Since the time intervals between time points represented 1/3 of a year, the annual QALY increment for T_1 was equal to (0.10/3 + 0.10/3 + 0.10/3) = 0.10 QALYs.

The true $INMB_{\lambda}$ is derived from these two incremental values such that $\overline{E}_1 = \overline{E}_0 + 0.10$, and $\overline{C}_1 = \overline{C}_0 + \$2{,}700$, and true $INMB_{\lambda} = 0.10\lambda - 2700$ for T_1- T_0.

Values for the algebraically-derived true $INMB_\lambda$ at different levels of λ are shown in Table 3.8-1. Evaluated at λ=0, $INMB_0$ can be interpreted as the negative of the treatment group cost difference. The true $INMB_\lambda$ increases as λ increases, i.e., the net monetary benefit of T_1 relative to T_0 goes up as willingness to pay increases.

Table 3.8-1 Algebraically-derived true $INMB_\lambda$ at different levels of λ

λ	True $INMB_\lambda$ for T_1- T_0
\$0	-\$2,700
\$25,000	-\$200
\$50,000	\$2,300
\$100,000	\$7,300

The treatment group differences in NMB_λ from the complete simulated dataset should be approximately equal to the above values. The complete data $INMB_\lambda$ was used in many of the analyses because its variance could be computed directly from the simulated complete data.

3.9 Analyses

The analyses that were conducted are described in this section. Results from the analyses are reported in Chapter 4.

3.9.1 Descriptive Analyses

Descriptive statistics were generated to evaluate the simulation results for the base case. Statistics were generated from the (1) ROSE Study outpatient dataset, (2) simulated complete dataset, (3) simulated missing dataset, and (4) simulated missing dataset with LOCF imputation, as indicated.

- Descriptive statistics were generated for costs, utilities, patient age, and previous hospitalizations, by treatment group and time point. Descriptive statistics include

number and percent of patients remaining in the study at each time point, means, standard deviations (SD), medians, minimums, and maximums for costs, utilities, age, and previous hospitalizations (all datasets).

- Spearman rank correlations between costs, utilities, patient age, and previous hospitalizations (all datasets) were calculated.
- Descriptive statistics were generated for NMB_{λ} (datasets 2, 3, and 4).
- The Kolmogorov-Smirnov test was provided to check the assumption of normally distributed NMB_{λ} (dataset 3). Histograms of NMB_{50000} across all time points were compared to normal curves for visual inspection of the assumption of normally distributed *NMB* (datasets 2 and 3).
- Graph of NMB_{50000} by time point, before and after MAR and MNAR nonresponse mechanisms were applied to the simulated complete data (datasets 2 and 3) was generated.
- Graphs of NMB_{λ} response values by time-to-dropout to examine the pattern of missingness in the simulated data (data sets 2 and 3) were generated.
- Complete data *INMB* values derived from the complete simulated dataset (dataset 2) were compared to the algebraically-derived true $INMB_{\lambda}$ values.
- ICERs from the simulated missing data (with and without LOCF imputation) were compared to the complete data ICER to assess the impact of missingness and LOCF imputation on a traditional cost-effectiveness analysis (datasets 2,3, and 4). ICERs were generated for descriptive purposes, therefore, standard errors were not estimated with bootstrapping or Taylor series approximation.

3.9.2 Model Diagnostics

The following diagnostics were generated for each model in the base case analysis.

- The Kolmogorov-Smirnov test was provided to check the assumption of normally distributed errors (all models) and visual inspection of the residual errors compared to a normal curve.

3.9.3 Evaluating and Comparing the Models

The primary focus of the evaluation and comparison of the models was on how well each model estimated the incremental net monetary benefit across different levels of λ. According to the algebraically-derived true and the complete data $INMB_\lambda$, treatment group T_1 should not be cost-effective compared to T_0 until λ =\$50,000. The following analyses were conducted to compare model results in the base case.

- Model parameters, standard errors, and p-values were estimated.
- Variances of the random effects for NMB_λ intercept and slope, residual errors for log time-to-dropout and NMB_λ, and correlations between the log of time-to-dropout and the NMB_λ intercept and slope for the joint ME model were estimated.
- Total annual $\hat{NMB}_\lambda$ and $\hat{INMB}_\lambda$ for each model were summarized. Each model's ability to estimate treatment cost-effectiveness across the different levels of λ was assessed by the statistical significance of $\hat{INMB}_\lambda$. The estimated $\hat{INMB}_\lambda$ were descriptively and visually compared to the complete data $INMB_\lambda$. (The complete

data $INMB_\lambda$ was calculated as least squares mean differences from a generalized linear model that included only treatment group.)

- Bias of the $\hat{INMB}_\lambda$, defined as the absolute difference between the estimated and complete data $INMB_\lambda$, was summarized and displayed graphically. The estimate with smallest bias was desired.
- Precision of the $\hat{INMB}_\lambda$ was determined with a ratio of the $\hat{INMB}_\lambda$ variances from each model to the variance of the complete data $INMB_\lambda$. A variance ratio close to 1.0 was desired.
- Cost-effectiveness acceptability curves (CEACs) were generated to assess the probability of the cost-effectiveness of T_1 relative to T_0 across a range of λ values from \$0 to \$100,000, by increments of \$5000. CEACs, first introduced by Van Hout et al. (1994), show the proportion of the joint density of incremental costs and incremental effectiveness for which T_1 is cost-effective at each value of λ (Fenwick et al., 2004). One minus that proportion (the acceptability estimate) corresponds to the minimum significance level in the *NMB* regression models at which the null hypothesis of T_1 not being cost-effective can be rejected (Zethraeus et al., 2003). The probabilities in the CEACs were generated as 1 minus the one-sided p-values from the tests of significant difference between treatment groups. The CEACs for the ME and joint ME models (both using the simulated missing data) were taken from the p-values associated with the ESTIMATE statements for the test of the significance of the difference in total *NMB*. Similarly, the CEAC for the ANCOVA model (using the simulated missing data with LOCF imputation) was taken from the p-values associated with the test of the

significance of the difference in total *NMB*. The CEACs for the models were plotted on a single graph and compared by visual inspection to the complete data CEAC. The complete data CEAC was generated by first computing a patient-level total *NMB* across all available time points, then using independent sample t-tests to generate p-values.

3.9.4 Sensitivity Analyses

Different proportions of MAR or MNAR missing data may affect the precision of $INMB_\lambda$ estimates. Two sensitivity analyses were conducted to examine the potential impact. Sensitivity Analysis 1 used simulated data from a simulation procedure that involved putting all 600 simulated complete observations through the MAR nonresponse algorithm (Chapter 3.7). The result was a simulated missing dataset with a smaller proportion of complete observations than in the base case, and all missing cases MAR. Sensitivity analysis 2 was similar to sensitivity analysis 1, except the simulation procedure involved putting the 600 simulated complete observations through the MNAR nonresponse algorithm (Chapter 3.7). The result was a simulated missing data with an even smaller proportion of complete observations compared to the base case, and all missing cases MNAR.

The sensitivity analyses were limited to results for λ = \$100,000, because treatment group T_1 should undoubtedly be cost-effective compared to T_0 at this level of λ, according to the algebraically-derived true and complete data $INMB_\lambda$. The following analyses were done using the sensitivity analysis simulated missing data sets. Base case results were presented along with sensitivity analysis results for comparison.

- Means (SDs) for NMB_{100000}, by treatment group and time point were generated.
- Graphs were provided for visual inspection of the NMB_{100000} distribution across all time points compared to a normal curve.
- Total annual $\hat{NMB}_{100000}$ and $\hat{INMB}_{100000}$ for each model were summarized. Each model's ability to estimate treatment cost-effectiveness was assessed by the statistical significance of $\hat{INMB}_{100000}$. $\hat{INMB}_{100000}$ were descriptively and visually compared to the complete data $INMB_{100000}$.
- Bias of the $\hat{INMB}_{100000}$ was summarized and displayed graphically.
- Precision of the $\hat{INMB}_{100000}$ was determined with a ratio of the $\hat{INMB}_{\lambda}$ variances from each model to the variance of the complete data $INMB_{\lambda}$.

All analyses were performed with SAS version 9.1 (SAS Institute, Inc) and Microsoft Excel 2000.

CHAPTER 4. RESULTS

Results of the simulation procedure and the base case analyses are presented in sections 4.1-4.3. The base case analyses were conducted using the simulated missing dataset comprising 200 complete case observations and some proportion of the remaining 400 observations (the proportion depended on the level of the criteria for being set to missing) being simulated to be missing according to MAR and MNAR nonresponse mechanisms. LOCF imputation of the missing observations was used in the ANCOVA modeling, while no imputation of the missing observations was used in the ME and joint ME models. Two sensitivity analyses were conducted to assess the impact of different proportions of MAR or MNAR missing data on the estimates of INMBλ. Sensitivity analysis results are presented in section 4.4.

4.1 Descriptive Analyses

Descriptive statistics for number of patients remaining in the study, costs, utilities, patient age, and previous hospitalizations, by treatment group and time point are presented in Table 4.1-1. Results begin with descriptive statistics from the ROSE Study outpatient dataset, the source data for the simulated dataset. Table 4.1-1A shows the number of patients in treatment groups, T_0 and T_1, were 118 and 114, respectively at month 0. By month 12 the numbers had decreased to 97 (82%) and 103 (90%). Costs were not measured at month 0 in the original study. Mean costs decreased for both treatment groups from month 4 (T_0: \$8,680; T_1: \$10,163) to month 12 (T_0: \$5,640; T_1: \$5,771). Mean utilities increased from month 0 (T_0: 0.61; T_1: 0.63) to month 12 (T_0: 0.64; T_1: 0.65). Mean patient age ranged from 37.51 to 38.84 across treatment groups.

For the dichotomous variable, Phosp, 49 percent of T_0 and 46 percent of T_1 had two or more hospitalizations in the two years prior to randomization.

Table 4.1-1B presents the descriptive statistics for the simulated complete dataset that resulted from Phase I of the simulation procedure. The simulated complete dataset had complete data for all 600 patients at every time point. The number of patients in each treatment group was 300. Mean costs decreased for both treatment groups from the imputed costs at month 0 (T_0: \$15,988; T_1: \$15,989), to month 4 (T_0: \$9,259; T_1: \$10,158), and month 12 (T_0: \$5,663; T_1: \$6,563), similar to the ROSE Study month 4 and 12 costs. Mean utilities increased from month 0 (T_0: 0.62; T_1: 0.62) to month 12 (T_0: 0.65; T_1: 0.75), somewhat higher than the month 12 values in the ROSE Study. Mean patient ages and previous hospitalizations were similar to the ROSE Study means. Patient age and previous hospitalization are baseline patient characteristics and are therefore the same in each of the simulated datasets.

Table 4.1-1C presents the descriptive statistics for the simulated missing dataset that resulted from Phase II of the simulation procedure. Recall that the base case analysis used a mixture of simulated complete cases (N~=200) and missing cases that were either MAR (N~=200) or MNAR (N~ =200) (because a clinical trial would typically include a mixture of complete and missing data, with patients dropping out for a variety of reasons). At month 0, each treatment group had 300 patients. By month 12, the simulated MAR and MNAR nonresponse mechanisms resulted in "dropping" 82 patients in T_0 and 115 patients in T_1 from the study, leaving 218 (73%) and 185 (62%) for T_0 and T_1, respectively. The proportions of dropouts were somewhat larger than the ROSE Study outpatient subgroup proportions noted earlier. Month 0 costs and utilities were

equivalent to the values from the simulated complete dataset. At month 12, mean costs were lower (T_0: $6,711; T_1: $8,660) and mean utilities were higher (T_0: 0.63; T_1: 0.73). Comparing to the simulated complete data, the effect of the simulated MAR and MNAR nonresponse mechanisms on costs and utilities was to increase the unadjusted mean costs at all time points and decrease the unadjusted mean utilities after month 0. The observed differences in the means between the simulated complete and simulated missing datasets seem reasonable give that 27% to 38% of the patients were simulated to drop out by month 12.

Table 4.1-1D presents the descriptive statistics for the simulated missing dataset with LOCF imputation. The number of patients in each treatment group was 300 at every time point. Month 0 costs and utilities were equivalent to the values from the simulated complete dataset. Mean costs with LOCF by month 12 were higher compared to the simulated complete data, but not as high as the simulated missing data (T_0: $6,100; T_1: $7,623). Mean utilities with LOCF at month 12 were lower than the simulated complete data and similar to the simulated missing data (T_0: 0.64; T_1: 0.73).

Table 4.1-1 Number of patients remaining in study and descriptive statistics for costs, utilities, patient age, and previous hospitalizations
A. ROSE Study outpatient dataset

Treatment group T_0				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
N (%)	118 (100%)	115 (97%)	108 (92%)	97 (82 %)
Costs ($)				
Mean (SD)	--	8,680 (12,318)	7,177 (10,335)	5,640 (8,254)
Median	--	3,624	3,270	2,040
Minimum	--	0	0	0
Maximum	--	79,465	58,581	52,128
Utilities				
Mean (SD)	0.61 (0.10)	0.62 (0.10)	0.64 (0.10)	0.64 (0.10)
Median	0.60	0.60	0.63	0.65
Minimum	0.40	0.43	0.46	0.43
Maximum	0.83	0.87	0.92	0.94
Age, mean (SD)	37.51 (9.40)			
Prev hosp, mean (SD)	0.49 (0.50)			
Treatment group T_1				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
N (%)	114 (100%)	111 (97%)	107 (94%)	103 (90%)
Costs ($)				
Mean (SD)	--	10,163 (11,760)	9,189 (13,380)	5,771 (9,287)
Median	--	5,963	3,414	2,736
Minimum	--	613	0	0
Maximum	--	82,220	78,586	73,274
Utilities				
Mean (SD)	0.63 (0.10)	0.65 (0.10)	0.64 (0.11)	0.65 (0.11)
Median	0.62	0.65	0.64	0.63
Minimum	0.42	0.43	0.35	0.41
Maximum	0.88	0.94	0.88	0.94
Age, mean (SD)	38.84 (8.69)			
Prev hosp, mean (SD)	0.46 (0.50)			

(See Appendix II.G. ROSE Descriptive Stats for SAS code.)

Table 4.1-1 Number of patients remaining in study and descriptive statistics for costs, utilities, patient age, and previous hospitalizations,
B. Simulated complete dataset

Treatment group T_0				
	Time Point			
	Month 0	**Month 4**	Month 8	**Month 12**
N (%)	**300 (100%)**	300 (100%)	300 (100%)	**300 (100%)**
Costs ($)				
Mean (SD)	15,988 (27,734)	9,258 (13,120)	7,277 (11,223)	5,663 (10,308)
Median	8,066	5,166	3,786	2,294
Minimum	249	409	78	65
Maximum	272,859	115,320	111,679	78,867
Utilities				
Mean (SD)	**0.62 (0.09)**	0.63 (0.09)	0.64 (0.10)	0.65 (0.10)
Median	0.62	0.63	0.64	0.65
Minimum	0.31	0.32	0.40	0.37
Maximum	0.88	0.91	0.94	0.91
Age, mean (SD)	37.55(9.38)			
Prev hosp, mean (SD)	0.45 (0.50)			
Treatment group T_1				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
N (%)	300 (100%)	300 (100%)	300 (100%)	300 (100%)
Costs ($)				
Mean (SD)	15,988 (18,556)	10,158 (13,973)	8,180 (12,708)	6,563 (9,581)
Median	8,689	6,114	4,300	3,117
Minimum	1,738	1,409	532	837
Maximum	118,227	165,610	109,068	65,304
Utilities				
Mean (SD)	0.62 (0.09)	0.73 (0.09)	0.74 (0.10)	0.75 (0.10)
Median	0.62	0.74	0.74	0.75
Minimum	0.37	0.49	0.50	0.43
Maximum	0.94	0.96	1.0	1.0
Age, mean (SD)	**37.87 (8.37)**			
Prev hosp, mean (SD)	0.49 (0.50)			

(See Appendix II.G. Univariate for SAS code.)

Table 4.1-1 Number of patients remaining in study and descriptive statistics for costs, utilities, patient age, and previous hospitalizations,
C. Simulated missing dataset, [a] base case

Treatment group T_0				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
N (%)	300 (100%)	278 (93%)	252 (84%)	218 (73%)
Costs ($)				
Mean (SD)	15,988 (27,734)	9,827 (13,449)	8,198 (11,996)	6,711 (11,127)
Median	8,066	5,582	4,477	3,063
Minimum	249	475	78	110
Maximum	272,859	115,320	111,679	78,867
Utilities				
Mean (SD)	**0.62 (0.09)**	0.63 (0.09)	0.62 (0.09)	0.63 (0.10)
Median	0.62	0.63	0.63	0.63
Minimum	0.31	**0.32**	0.40	0.37
Maximum	0.88	0.85	0.89	0.91

Treatment group T_1				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
N (%)	300 (100%)	273 (91%)	225 (75%)	185 (62%)
Costs ($)				
Mean (SD)	15,988 (18,556)	**10,836 (14,444)**	9,799 (14,151)	8,660 (11,447)
Median	8,689	6,704	5,341	4,157
Minimum	1,738	1,409	900	903
Maximum	118,227	165,610	109,068	65,304
Utilities				
Mean (SD)	0.62 (0.09)	0.73 (0.89)	0.73 (0.09)	0.73 (0.10)
Median	0.62	0.73	0.72	0.73
Minimum	0.37	0.49	0.50	0.43
Maximum	0.94	0.92	1.00	**1.00**

[a] The simulated missing data for the base case analysis was a mixture of simulated complete cases and missing cases that were either MAR or MNAR. (See Appendix II.G. Missing for SAS code.)

Table 4.1-1 Number of patients remaining in the study and descriptive statistics for costs, utilities, patient age, and previous hospitalizations,
D. Simulated missing dataset with LOCF imputation,[a] base case

Treatment group T_0				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
N (%)	300 (100%)	300 (100%)	300 (100%)	300 (100%)
Costs ($)				
Mean (SD)	15,988 (27,734)	9,473 (13,127)	7,705 (11,284)	6,100 (9,912)
Median	8,066	5,313	4,145	2,756
Minimum	249	249	78	110
Maximum	272,859	115,320	111,679	78,867
Utilities				
Mean (SD)	**0.62 (0.09)**	0.63 (0.09)	0.64 (0.09)	0.64 (0.09)
Median	0.62	0.63	0.63	0.65
Minimum	0.31	0.32	0.40	0.37
Maximum	0.88	0.85	0.89	0.91

Treatment group T_1				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
N (%)	**300 (100%)**	300 (100%)	300 (100%)	300 (100%)
Costs ($)				
Mean (SD)	15,988 (18,556)	10,646 (13,969)	9,101 (12,691)	7,623 (9,673)
Median	8,689	6,572	4,970	4,160
Minimum	1,738	1,409	900	903
Maximum	118,227	165,610	109,068	65,304
Utilities				
Mean (SD)	**0.62 (0.09)**	0.72 (0.09)	0.73 (0.09)	0.73 (0.09)
Median	0.62	0.73	0.73	0.74
Minimum	0.37	0.47	0.47	0.43
Maximum	0.94	0.92	1.00	1.00

[a] The simulated missing data for the base case analysis was a mixture of simulated complete cases and missing cases that were either MAR or MNAR. The ANCOVA model used the simulated missing data with LOCF imputation. (See Appendix II.G. Univariate LOCF for SAS code.)

Table 4.1-2 presents the Spearman rank correlations between costs, utilities, patient age, and previous hospitalizations for the ROSE Study outpatient data and the three simulated datasets, by time point. A comparison of the correlations across the ROSE Study and simulated complete dataset shows how the simulation process approximately maintained the original relationships between variables. All correlations between the variables were weak and the signs of the correlations from ROSE Study to simulated data were maintained, except for month 4 correlations between costs and utilities and costs and age, month 8 correlations between costs and age, and month 12 correlations between costs and age. There was greater statistical significance among the simulated correlations than the ROSE Study correlations, which was probably due to the larger sample size. (The month 0 correlations from the simulated missing and simulated missing with LOCF imputation datasets are not shown because these correlations are equal to the correlations from the simulated complete dataset.)

Table 4.1-2 Spearman rank correlations for costs, utilities and covariates, treatment groups combined

A. ROSE Study outpatient dataset

Month 0, N=232	Utilities	Age	Prev hosp
Costs	--	--	--
Utilities	--	-0.09	-0.01
Age	--	--	-0.11
Month 4, N=226	Utilities	Age	Prev hosp
Costs	-0.00	-0.04	0.17**
Utilities	--	-0.16*	-0.02
Month 8, N=215	Utilities	Age	Prev hosp
Costs	-0.09	-0.02	0.14*
Utilities	--	-0.14*	-0.06
Month 12, N=200	Utilities	Age	Prev hosp
Costs	-0.03	0.05	0.09
Utilities	--	-0.17*	-0.11

B. Simulated complete dataset

Month 0, N=600	Utilities	Age	Prev hosp
Costs	0.00	-0.04	0.08
Utilities	--	-0.13**	-0.02
Age	--	--	-0.09*
Month 4, N=600	Utilities	Age	Prev hosp
Costs	0.13**	0.03	0.14**
Utilities	--	-0.09*	-0.03
Month 8, N=600	Utilities	Age	Prev hosp
Costs	-0.01	0.01	0.16**
Utilities	--	-0.09*	-0.07
Month 12, N=600	Utilities	Age	Prev hosp
Costs	-0.03	-0.06	0.20**
Utilities	--	-0.05	-0.16**

* $p<0.05$; **$p<0.01$

Table 4.1-2 Spearman rank correlations for costs, utilities and covariates *(continued)*

C. Simulated missing dataset, [a] base case

Month 4, N=551	Utilities	Age	Prev hosp
Costs	0.18**	0.01	0.12**
Utilities	--	-0.09*	-0.02
Age	--	--	-0.09*
Month 8, N=477	Utilities	Age	Prev hosp
Costs	0.13**	-0.04	0.13**
Utilities	--	-0.07	-0.06
Month 12, N=403	Utilities	Age	Prev hosp
Costs	0.06	-0.08	0.15**
Utilities	--		

D. Simulated missing dataset with LOCF imputation, [b] base case

Month 4, N=600	Utilities	Age	Prev hosp
Costs	0.17**	0.01	0.13**
Utilities	--	-0.09*	-0.04
Age	--	--	-0.09*
Month 8, N=600	Utilities	Age	Prev hosp
Costs	0.11**	-0.03	0.11**
Utilities	--	-0.07	-0.06
Month 12, N=600	Utilities	Age	Prev hosp
Costs	0.07	-0.07	0.14**
Utilities	--	-0.04	-0.11**

* $p<0.05$; **$p<0.01$

[a] The simulated missing data for the base case analysis was a mixture of simulated complete cases and missing cases that were either MAR or MNAR.

[b] The ANCOVA model used the simulated missing data with LOCF imputation. (See Appendix II.G. ROSE Descriptive Stats, Univariate, Missing, and Univariate LOCF for SAS code.)

Table 4.1-3 presents descriptive statistics for NMB_λ for the three simulated datasets, by treatment group and by time point. Results for the simulated complete dataset are presented in Table 4.1-3A. Mean NMB_λ values increase as λ increases, as they should. Mean NMB_λ values also steadily increased overtime, but increases were greater for T_1 as intended by the simulation. For example, at month 12, NMB_{50000} = \$5,119 for T_0 and NMB_{50000} = \$5,885 for T_1.

Results for the simulated missing dataset are presented in Table 4.1-3B. Mean NMB_λ values at month 0 for both T_0 and T_1 were equal to the values in the simulated complete dataset. Compared to the simulated complete data, the effect of the simulated nonresponse mechanisms was to decrease the unadjusted mean NMB_λ at all time points after month 0. This result is consistent with the previously reported higher costs and lower utilities after simulation of the nonresponse mechanisms.

Last, the results for the simulated missing dataset with LOCF imputation are presented in Table 4.1-3C. Again, mean NMB_λ values at month 0 for both T_0 and T_1 were equal to the values in the simulated complete dataset, and mean NMB_λ increased overtime, with greater increases for T_1. LOCF imputation resulted in higher unadjusted mean NMB_λs than those from the simulated missing dataset without LOCF imputation.

Table 4.1-3 Descriptive statistics for NMB_λ

A. Simulated complete dataset

Treatment group T_0				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
N (%)	300 (100%)	300 (100%)	300 (100%)	300 (100%)
NMB_0 ($)				
Mean (SD)	-15,988 (27,734)	-9,258 (13,120)	-7,280 (11,223)	-5,663 (10,308)
Median	-8,066	-5,166	-3,786	-2,294
Minimum	-272,859	-115,320	-111,679	-78,867
Maximum	-249	-409	-78	-65
NMB_{25000} ($)				
Mean (SD)	-10,827 (27,737)	-3,979 (13,094)	-1,933 (11,256)	-272 (10,361)
Median	-3,240	135	1,215	2,950
Minimum	-268,077	-109,646	-106,389	-73,090
Maximum	5,717	5,842	6,386	7,180
NMB_{50000} ($)				
Mean (SD)	**-5,667 (27,762)**	1,299 (13,109)	3,414 (11,344)	5,119 (10,483)
Median	2,198	5,173	6,403	7,890
Minimum	-263,295	-103,971	-101,099	-67,313
Maximum	13,012	12,333	14,254	14,472
NMB_{100000} ($)				
Mean (SD)	4,655 (27,878)	11,856 (13,263)	14,107 (11,680)	15,900 (10,920)
Median	11,894	15,417	16,778	18,173
Minimum	-253,730	-92,622	-90,519	-55,758
Maximum	27,601	27,574	29,991	29,056

(See Appendix II.G. Univariate for SAS code.)

Table 4.1-3 Descriptive statistics for NMB_λ
A. Simulated complete dataset *(continued)*

Treatment group T_1				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
N (%)	300 (100%)	300 (100%)	300 (100%)	300 (100%)
NMB_0 ($)				
Mean (SD)	-15,988 (18,556)	-10,158 (13,973)	-8,180 (12,708)	-6,563 (9,581)
Median	-8,689	-6,114	-4,300	-3,117
Minimum	-118,227	-165,610	-109,068	-65,304
Maximum	-1,738	-1,409	-532	-837
NMB_{25000} ($)				
Mean (SD)	-10,827 (18,571)	-4,046 (13,928)	-2,000 (12,754)	-339 (9,717)
Median	-3,543	-86	1,989	3,132
Minimum	-113,289	-158,340	-102,881	-59,614
Maximum	4,415	6,150	7,726	7,321
NMB_{50000} ($)				
Mean (SD)	-5,667 (18,615	2,065 (1,3925)	4,180 (12,848)	5,885 (9,916)
Median	1,717	5,719	7,838	9,206
Minimum	-108,351	-151,069	-96,694	-53,925
Maximum	10,929	14,111	16,285	16,006
NMB_{100000} ($)				
Mean (SD)	4,655 (18,793)	14,288 (14,041)	16,540 (13,177)	18,333 (10,487)
Median	11,517	17,574	19,633	21,140
Minimum	-98,474	-137	-84,322	-42,546
Maximum	23,956	30,033	33,402	33,375

(See Appendix II.G. Univariate for SAS code.)

Table 4.1-3 Descriptive statistics for NMB_λ
B. Simulated missing dataset, [a] base case

Treatment group T_0				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
N (%)	300 (100%)	278 (93%)	252 (84%)	218 (73%)
NMB_0 ($)				
Mean (SD)	-15,988 (27,734)	-9,827 (13,449)	-8,198 (11,996)	-6,711 (11,127)
Median	-8,066	-5,582	-4,477	-3,063
Minimum	-272,859	-115,320	-111,679	-78,867
Maximum	-249	-475	-78	-110
NMB_{25000} ($)				
Mean (SD)	-10,828 (27,737)	-4,575 (13,405)	-2,960 (11,968)	-1,479 (11,125)
Median	-3,240	**-479**	621	2,247
Minimum	-268	-109,646	-106,389	-73,090
Maximum	5,717	5,842	6,270	6,330
NMB_{50000} ($)				
Mean (SD)	-5,667 (27,762)	676 (13,402)	2,277 (11,989)	3,753 (11,180)
Median	2,198	4,657	5,488	7,241
Minimum	-263,295	-103,971	-101,099	-67,313
Maximum	13,012	12,158	12,878	13,646
NMB_{100000} ($)				
Mean (SD)	4,654 (27,878)	11,178 (13,515)	12,752 (12,171)	14,216 (11,455)
Median	11,894	14,687	15,526	17,133
Minimum	-253,730	-92,622	-90,519	-55,758
Maximum	27,601	24,791	26,095	28,502

[a] The simulated missing data for the base case analysis was a mixture of simulated complete and MAR and MNAR missing cases.
(See Appendix II.G. Missing for SAS code.)

Table 4.1-3 Descriptive statistics for NMB_λ
B. Simulated missing dataset,[a] base case *(continued)*

Treatment group T_1				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
N	300 (100%)	273 (91%)	225 (75%)	185 (62%)
NMB_0 ($)				
Mean (SD)	-15,988 (18,556)	-10,836 (14,444)	-9,799 (14,151)	-8,660 (11,447)
Median	-8,689	-6,704	-5,341	-4,157
Minimum	-118,227	-165,610	-109,068	-65,304
Maximum	-1,738	-1,409	-900	-903
NMB_{25000} ($)				
Mean (SD)	-10,827 (18,51)	-4,778 (14,367)	-3,743 (14,134)	-2,596 (11,530)
Median	-3,543	-865	656	1,709
Minimum	-113,289	-158,340	-102,881	-59,614
Maximum	4,415	5,690	6,557	7,134
NMB_{50000} ($)				
Mean (SD)	-5,667 (18,615)	1,280 (14,329)	2,313 (14,157)	3,469 (11,668)
Median	1,717	5,092	6,403	7,289
Minimum	-108,351	-151,069	-96,694	-53,925
Maximum	10,929	13,124	14,493	15,435
NMB_{100000} ($)				
Mean (SD)	4,655 (18,793)	13,396 (14,369)	14,425 (14,320)	15,599 (12,095)
Median	11,517	16,318	18,326	18,868
Minimum	-98,474	-136,527	-84,321	-42,546
Maximum	23,956	27,991	30,799	32,038

[a] The simulated missing data for the base case analysis was a mixture of simulated complete and MAR and MNAR missing cases.
(See Appendix II.G. Missing for SAS code.)

Table 4.1-3 Descriptive statistics for NMB_λ
C. Simulated missing dataset with LOCF imputation,[a] base case

Treatment group T_0				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
N	300 (100%)	300 (100%)	300 (100%)	300 (100%)
NMB_0 ($)				
Mean (SD)	-15,988 (27,734)	-9,473 (13,127)	-7,705 (11,284)	-6,100 (9,912)
Median	-8,066			
Minimum	-272,859	-115,320	-111,679	-78,867
Maximum	-249	-249	-78	-110
NMB_{25000} ($)				
Mean (SD)	-10,828 (27,737)	-4,189 (13,094)	-2,397 (11,266)	-750 (9,916)
Median	-3,240			
Minimum	-268	-109,646	-106,389	-73,090
Maximum	5,717	5,842	6,270	6,330
NMB_{50000} ($)				
Mean (SD)	-5,667 (27,762)	1,095 (13,102)	2,911 (11,298)	4,600 (9,979)
Median	2,198			
Minimum	-263,295	-103,971	-101,099	-67,313
Maximum	13,012	12,158	12,878	13,646
NMB_{100000} ($)				
Mean (SD)	4,654 (27,878)	11,662 (13,239)	13,528 (11,511)	15,301 (10,281)
Median	11,894			
Minimum	-253,730	-92,622	-90,519	-55,758
Maximum	27,601	25,272	26,095	28,502

[a] The simulated missing data for the base case analysis was a mixture of simulated complete and MAR and MNAR missing cases. The ANCOVA model used the simulated missing data with LOCF imputation. (See Appendix II.G. LOCF for SAS code.)

Table 4.1-3 Descriptive statistics for NMB_λ
C. Simulated missing dataset with LOCF imputation, [a] base case *(continued)*

Treatment group T_1				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
N	300 (100%)	300 (100%)	300 (100%)	300 (100%)
NMB_0 ($)				
Mean (SD)	-15,988 (18,556)	-10,646 (13,969)	-9,101 (12,691)	-7,762 (9,673)
Median	-8,689			
Minimum	-118,227	-165,610	-109,068	-65,304
Maximum	-1,738	-1,409	-900	-903
NMB_{25000} ($)				
Mean (SD)	-10,827 (18,51)	-4,644 (13,892)	-3,057 (12,696)	-1,548 (9,779)
Median	-3,543			
Minimum	-113,289	-158,340	-102,881	-59,614
Maximum	4,415	5,690	6,557	7,134
NMB_{50000} ($)				
Mean (SD)	-5,667 (18,615)	1,358 (13,858)	2,987 (12,749)	4,527 (9,948)
Median	1,717			
Minimum	-108,351	-151,069	-96,694	-53,925
Maximum	10,929	13,124	14,493	15,435
NMB_{100000} ($)				
Mean (SD)	4,655 (18,793)	13,362 (13,920)	15,076 (12,995)	16,677 (10,463)
Median	11,517			
Minimum	-98,474	-136,527	-84,321	-42,546
Maximum	23,956	27,991	30,799	32,038

[a] The simulated missing data for the base case analysis was a mixture of simulated complete and MAR and MNAR missing cases. The ANCOVA model used the simulated missing data with LOCF imputation. (See Appendix II.G. LOCF for SAS code.)

A check of the assumption of normally distributed *NMB* values in the simulated complete and simulated missing data was done using the Kolmogorov-Smirnov test. The null hypothesis of *NMB* values being normally distributed was rejected for all λs and at all time points (all $p<.01$, not shown). Because the Kolmogorov-Smirnov test is conservative, the distribution of NMB_{50000} values from the simulated complete data across all time points was compared to a normal curve in Figure 4.1-1. Visual inspection indicates that NMB_{50000} in the complete data is not normally distributed. A similar nonnormal distribution was found for NMB^{*}_{50000i}, the annual *NMB* used in the ANCOVA model as the dependent variable (not shown).

Figure 4.1-1 Check of the assumption of normally distributed NMB_{50000} values across all time points, complete data

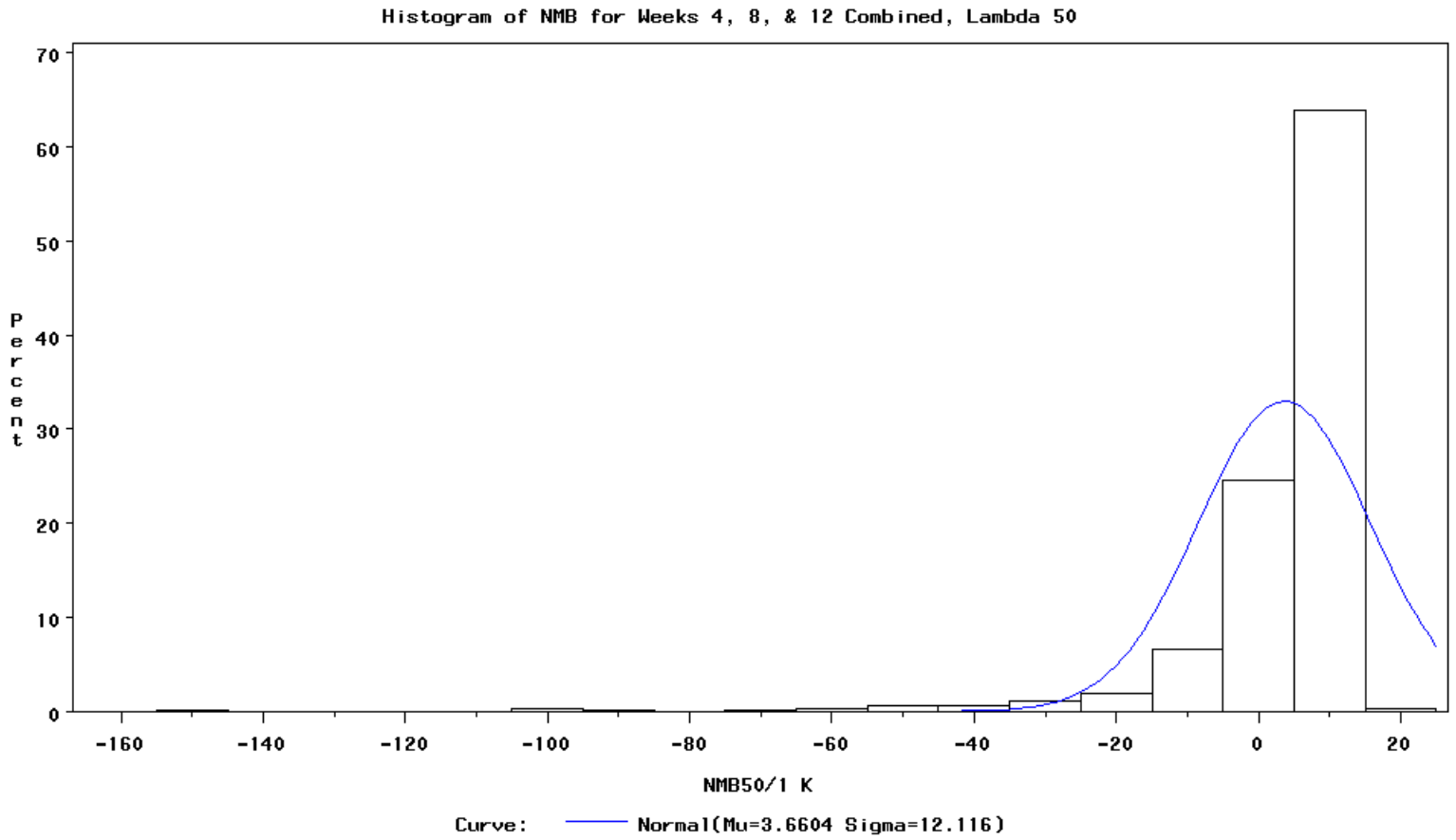
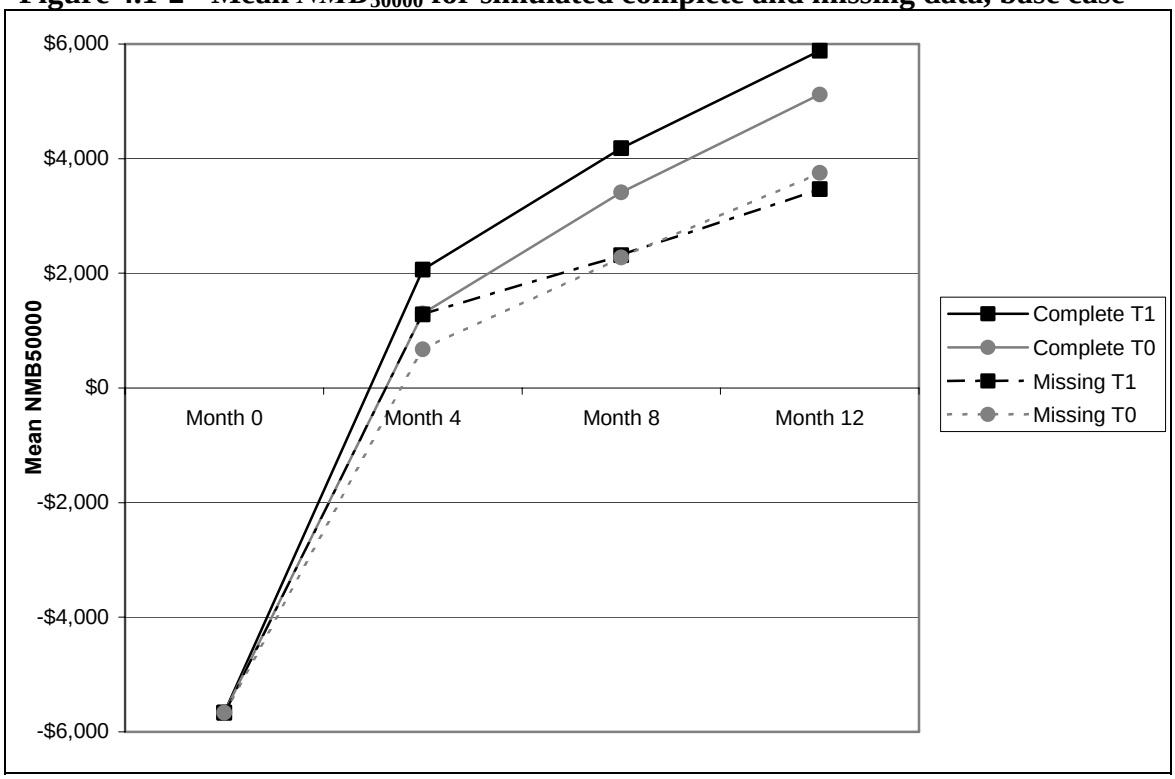


Figure 4.1-2 summarizes the simulation results on mean NMB_{50000} by time point, before and after the MAR and MNAR nonresponse mechanisms were applied to the complete simulated data. The solid lines represent the simulated complete data and dotted lines the simulated missing data. At month 0 the means from the two simulated datasets are equal because missing values were simulated only for months 4, 8, and 12 based on the assumption that all patients were present at baseline (month 0). The figure shows how the complete data NMB_{50000} values are higher than the values estimated from the simulated missing data at nearly all time points for each treatment group. The one exception was at month 4 where the mean response for T_0 from the simulated complete data is equal to the mean response for T_1 from the simulated missing data. Treatment group differences are apparent in the simulated complete data from month 4 to end of study. In the simulated missing data, however, there is little difference between the treatment groups except at month 4. The graph illustrates how MAR and MNAR missing data can have the affect of lowering unadjusted mean response values, obscuring treatment differences, and thereby making accurate estimation of treatment effect difficult. The opposite could also occur, where treatment differences may be overstated depending on the pattern and mechanism of missingness.

Figure 4.1-2 Mean NMB_{50000} for simulated complete and missing data, base case

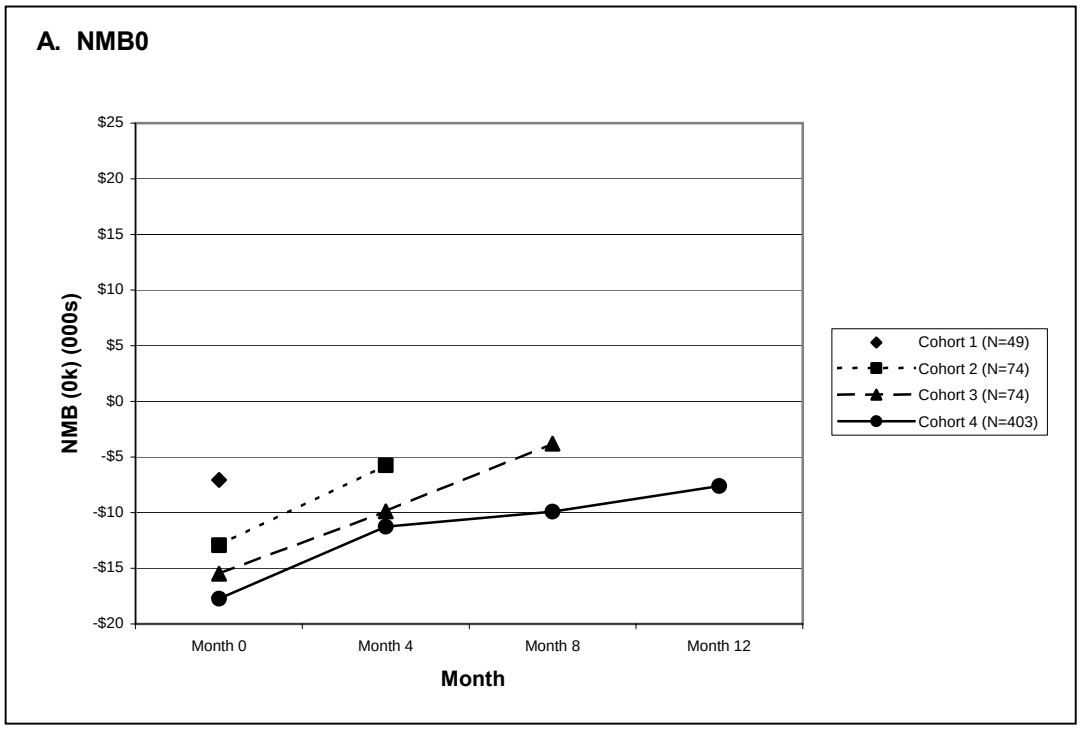


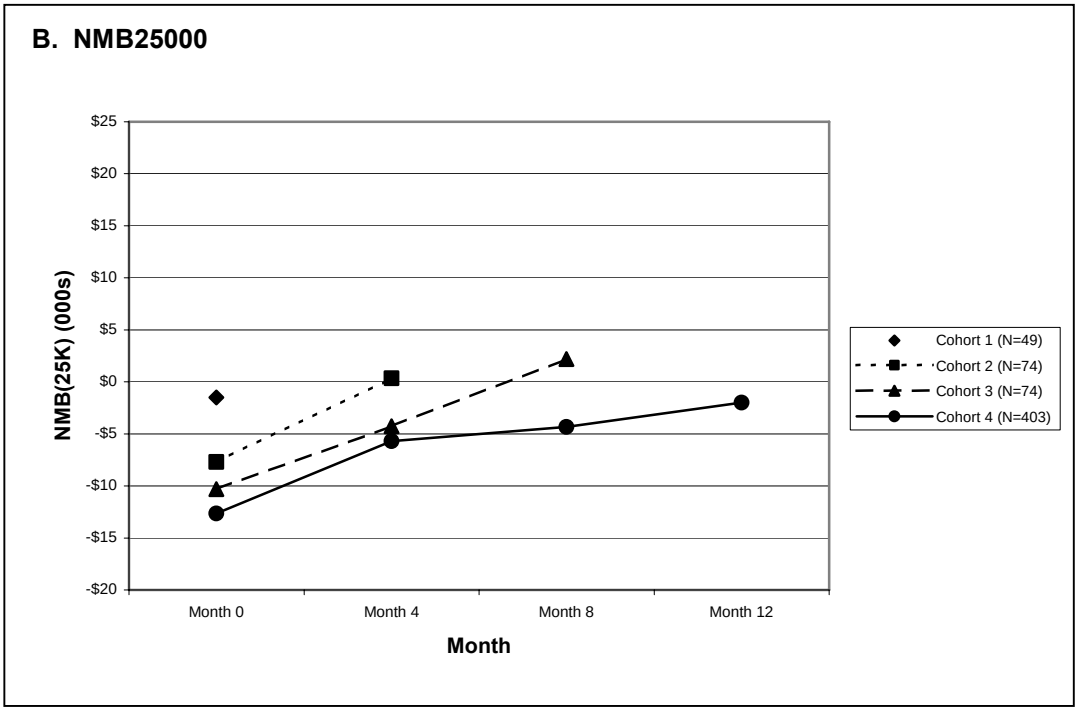
(See Appendix II.G. Univariate and Missing for SAS code.)

Figure 4.1-3 presents the missingness patterns in the simulated missing dataset with both treatment groups combined. Similar to the graphs in Chapter 3 that showed the missingness patterns in the ROSE Study data, patients were grouped into cohorts 1, 2, 3, or 4, according to time of last nonmissing assessment. *NMB*s were graphed by cohort, time point, and level of λ. The missingness pattern that was seen in the ROSE Study (Figure 3.6-1 I) can be seen in these patterns, with an ordered pattern across cohorts (i.e., cohort 1 having the highest *NMB* at baseline, followed by cohorts 2, 3, and 4). There was a slight trend for patients who remained in the study longer to have higher *NMB*s at time of dropout. However, patients who dropped out between months 0 and 4 had only slightly higher mean *NMB* at time of dropout compared to patients who completed the study through month 12. The simulated dropout pattern may suggest a MAR (and

possibly MNAR) nonresponse mechanism because the missingness may be predictable from the observed data in the study, i.e., higher baseline *NMB* values predict early dropout and lower *NMB* values predict later dropout and increasing *NMB* values over time. Thus, the simulation procedure appeared to work successfully to impose at least a MAR missingness patterns on the simulated complete data. Figure 4.1-3 also shows how the dropout pattern is the same across the levels of λ, as intended by the simulation procedure. As expected, mean *NMB* increases as λ increases, with mean *NMB* values ranging from -$12,600 to $20,000.

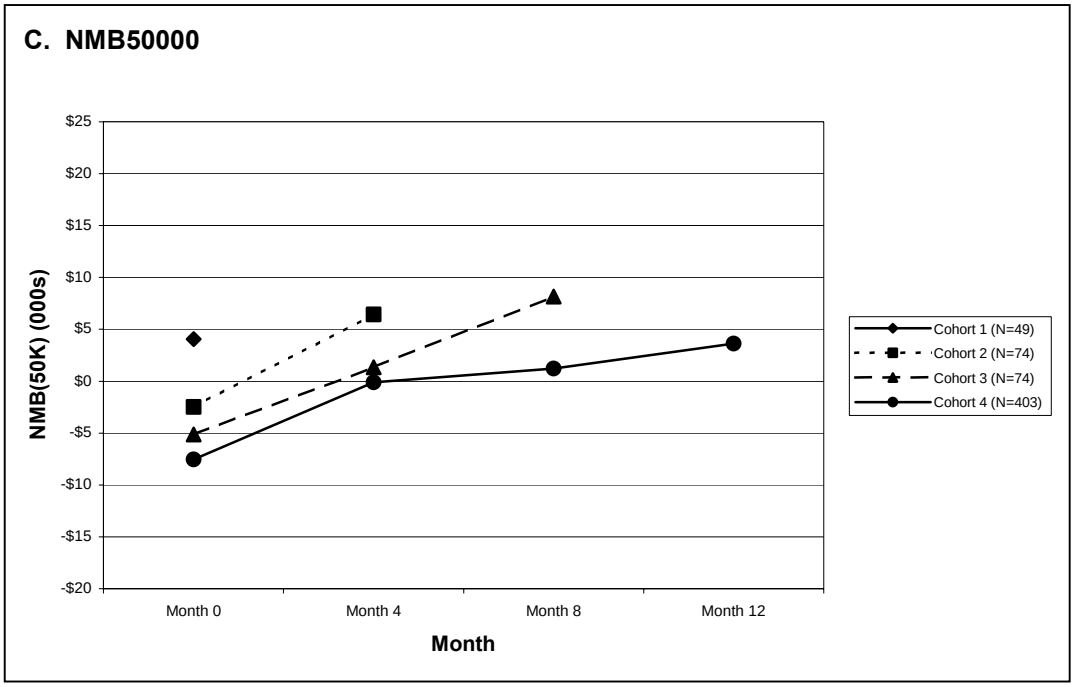
Figure 4.1-3 Missingness patterns for mean *NMB* in the simulated missing dataset, both treatment groups combined, base case

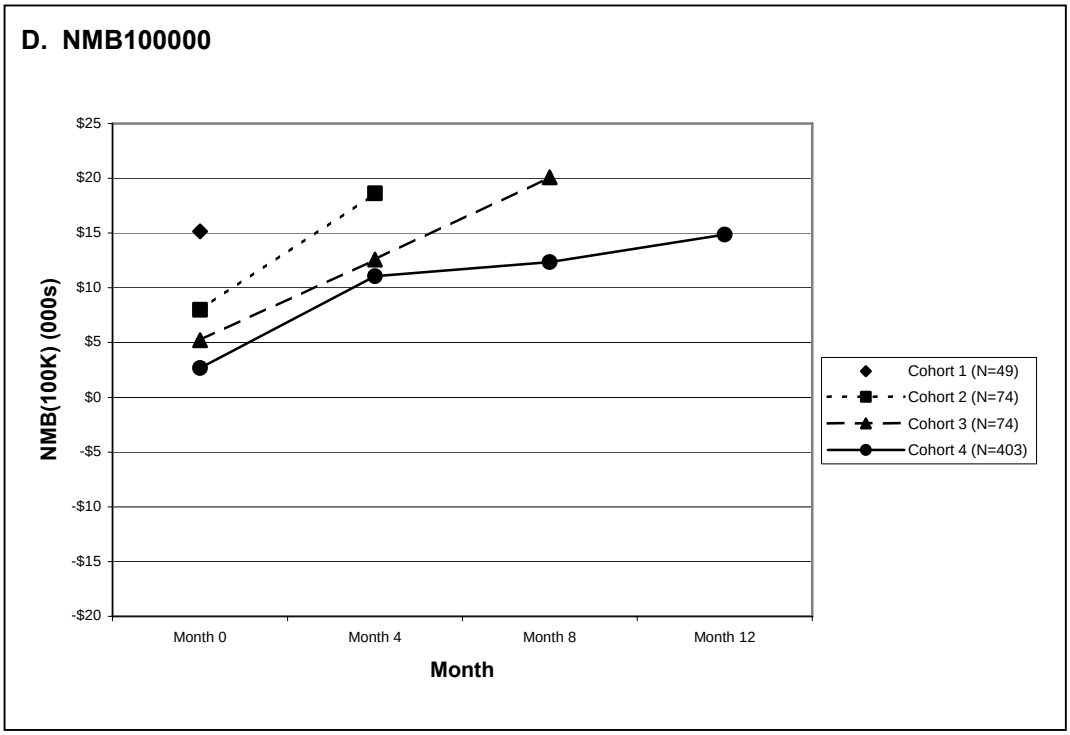




(See Appendix II.H. Cohort_sim for SAS code.)

Figure 4.1-3 Missingness patterns for mean *NMB* in the simulated missing dataset, both treatment groups combined, base case (continued)





(See Appendix II.H. Cohort_sim for SAS code.)

The algebraically-derived, true $INMB_\lambda$ values are presented in Table 4.1-4, with the means (s.e.) computed from the simulated complete dataset. The complete data $INMB_\lambda$ are virtually identical to the algebraically-derived values. The standard errors of the complete data $INMB_\lambda$ are large, but this is expected in a sample size of N=600, and in the *NMB* that is a function of costs that vary widely.

Table 4.1-4 Algebraically-derived true $INMB_\lambda$s and complete data $INMB_\lambda$s from the simulated complete dataset

λ	True $INMB_\lambda$	Complete data $INMB_\lambda$ (se)
$0	**-$2,700**	**-$2,700** (2,292.3)
$25,000	-$200	-$201 (2,292.1)
$50,000	$2,300	$2,299 (2,202.8)
$100,000	$7,300	$7,298 (2,355.6)

(See Appendix II.I. True for SAS code.)

Incremental cost-effectiveness ratios (ICERs) from the simulated complete and the simulated missing data, with and without LOCF imputation, are presented in Table 4.1-5. The complete data ICER was $27,010 per QALY. ICERs from simulated missing data were $45,467 and $45,559 per QALY, with and without LOCF imputation, respectively. These results demonstrate how the cost-effectiveness of T_1 relative to T_0 would be overestimated by approximately $19,000 per QALY in a traditional cost-effectiveness analysis using the simulated missing data. Despite this overestimation of the benefit, at the willingness to pay level of λ = $50000 one could conclude that T_1 is cost-effective compared to T_0.

Table 4.1-5 Cost-effectiveness as determined by incremental cost-effectiveness ratios

A. Simulated complete data

Treatment	Cost	QALY	ΔC	ΔE	ICER
T_1	$24,901	0.74	$2,701	0.10	$27,010/QALY
T_0	$22,200	0.64	--	--	--

B. Simulated missing data, base case

Treatment	Cost	QALY	ΔC	ΔE	ICER
T_1	$29,295	0.73	$4,559	0.10	$45,559/QALY
T_0	$24,736	0.63	--	--	--

C. Simulated missing data with LOCF imputation, base case

Treatment	Cost	QALY	ΔC	ΔE	ICER
T_1	$27,370	0.73	$4,092	0.09	$45,467/QALY
T_0	$23,278	0.64	--	--	--

4.2 Model Diagnostics

A check of the assumption of normally distributed *NMB* residual errors from all models was done using the Kolmogorov-Smirnov test and visual inspection. The null hypothesis of *NMB* values coming from a normal distribution was rejected for all λs and at all time points (all $p<.01$, not shown). The distributions of residual errors for λ = \$0, \$25000, \$50000, and \$100000 from the ANCOVA model are shown in Figures 4.2-1A-D. Visual inspection shows the distribution to be roughly normal for λ = \$0, \$25000, \$50000, but with a higher peak than a normal distribution. Similar distributions were found for the residual errors of the ME and joint ME models (not shown).

Figure 4.2-1A Check of the assumption of normally distributed residual errors from ANCOVA model, NMB_0, base case

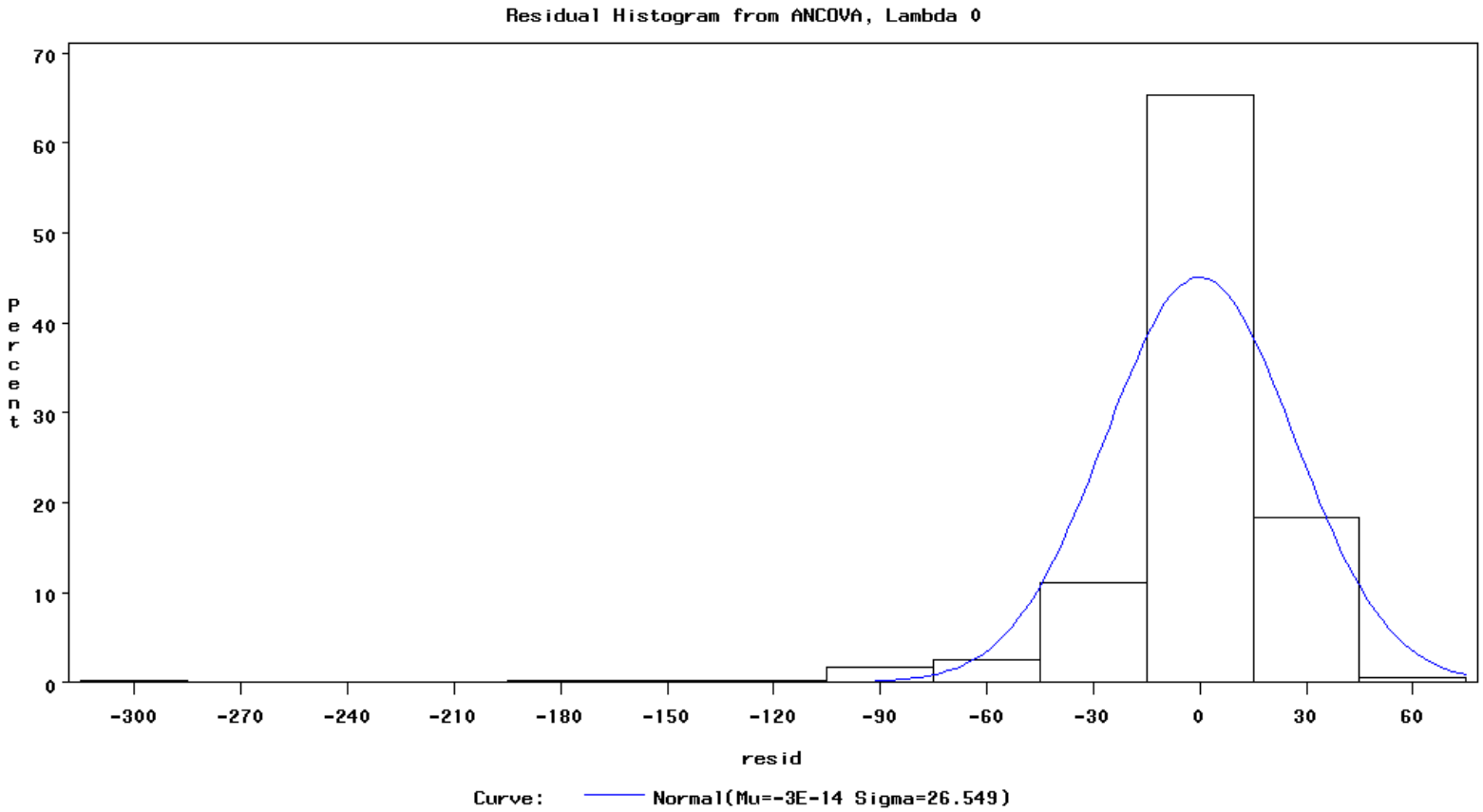


Figure 4.2-1B Check of the assumption of normally distributed residual errors from ANCOVA model, NMB_{25000}, base case

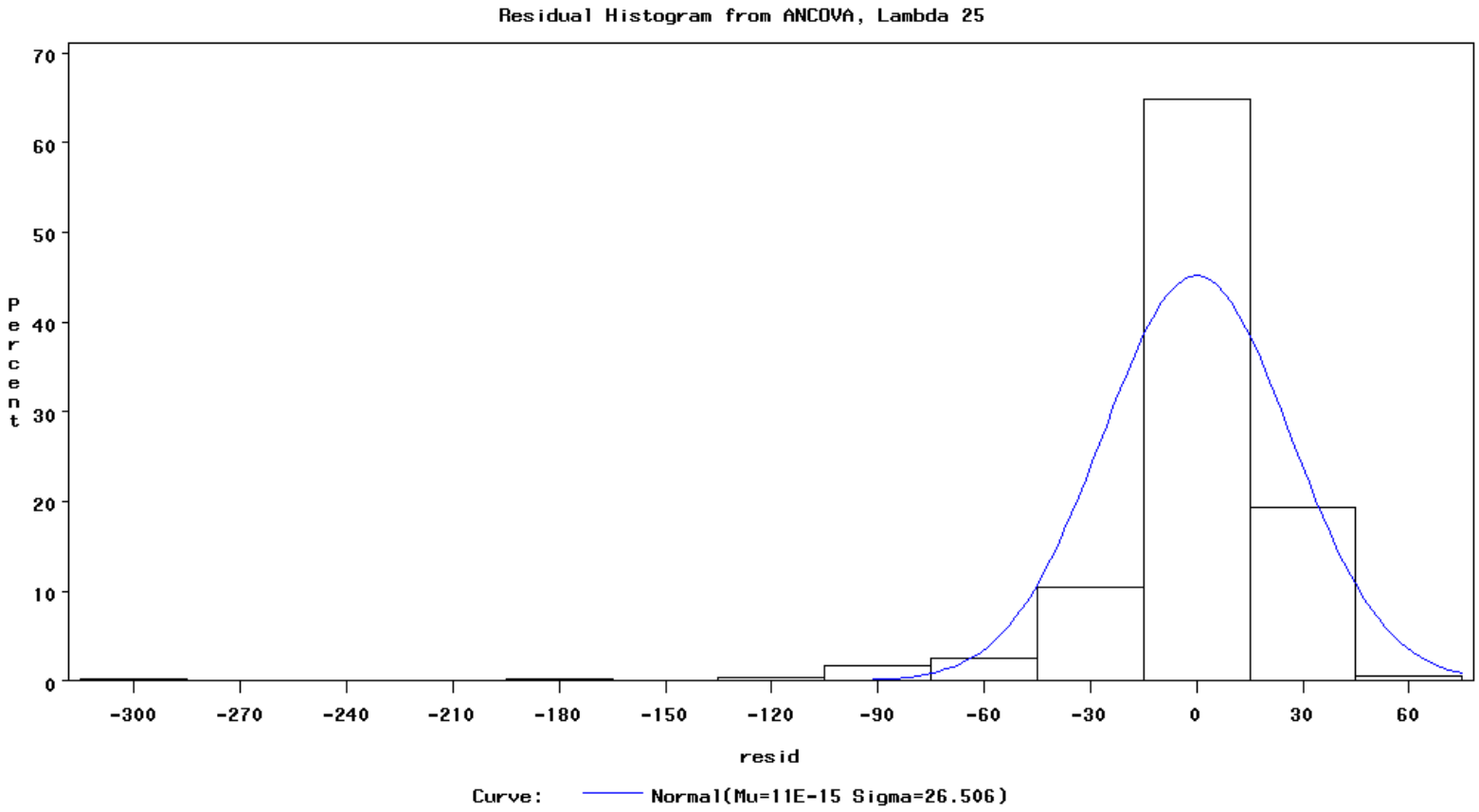


Figure 4.2-1C Check of the assumption of normally distributed residual errors from ANCOVA model, NMB_{50000}, base case

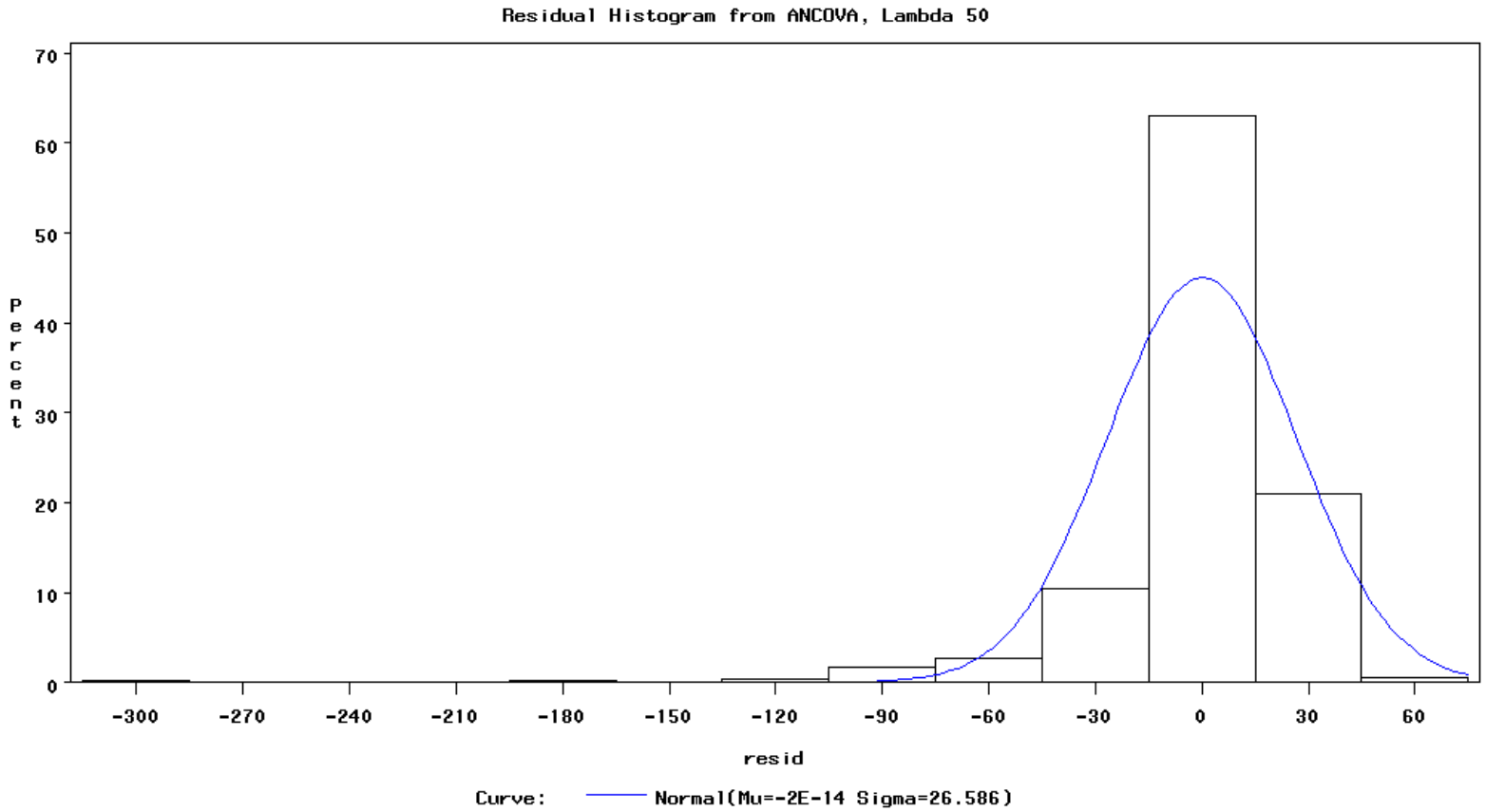
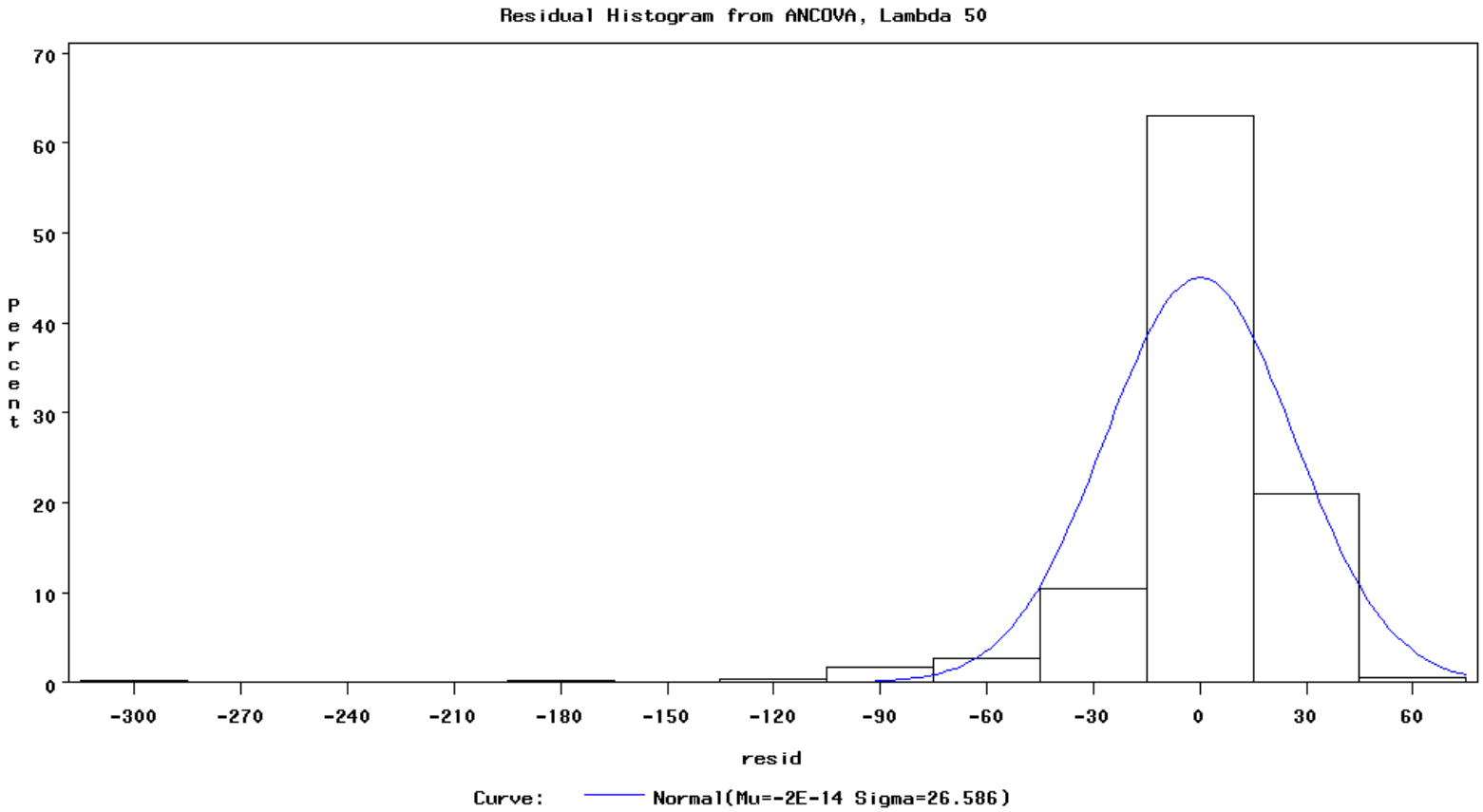


Figure 4.2-1D Check of the assumption of normally distributed residual errors from ANCOVA model, NMB_{100000}, base case



4.3 Evaluating and Comparing the Models

Parameter estimates from the ANCOVA and the ME models are presented and discussed separately because the models differ with regard to their dependent variables and the terms included in each model, as explained in Chapter 3.4 and 3.5. Recall that the *NMB* of a treatment is the difference between the treatment's effect (valued in dollars) and its cost (i.e., $NMB = \lambda E - C$). When λ = \$0, the dependent variable is *NMB* with the willingness to pay being zero for one more unit of effectiveness (i.e., one QALY). Since NMB_0 is simply negative costs, negative parameter estimates imply higher costs.

Parameter estimates from the ANCOVA model with annual $NMB^*_{\lambda i}$ as the dependent variable are presented in Table 4.3-1 by level of λ. For λ = \$0, the treatment group effect was nearly significant ($\hat{\beta}_3$=-3.77, p=0.08), indicating that T_1 was associated with lower annual $NMB^*_{\lambda i}$ (higher annual costs) versus T_0, after adjusting for other variables in the model. As λ increases, the treatment effect on annual $NMB^*_{\lambda i}$ switched from being nearly significant in favor of T_0 to being significant in favor of T_1 (λ =\$100,000, $\hat{\beta}_3$=5.06, p=0.02). The interpretation is that T_1 is not cost-effective until λ = \$100,000. Other significant predictors of annual $NMB^*_{\lambda i}$ were previous hospitalizations (more previous hospitalizations predict lower annual $NMB^*_{\lambda i}$, or higher annual costs when λ = \$0), and baseline *NMB* (higher *NMB* at baseline predicts higher annual $NMB^*_{\lambda i}$, or lower annual costs when λ = \$0). The residual error for $NMB^*_{\lambda i}$ ranged from 707.27 when λ = \$25,000 to 740.20 when λ = \$100,000.

Parameter estimates from the ME and joint ME models with $NMB_{\lambda it}$ as the dependent variable are presented in Table 4.3-2A-D by level of λ. In both models, and for all λ, the treatment group parameter estimate was not significant, however, *INMB* (incremental cost-effectiveness) cannot be determined from this parameter alone because of the interaction terms involving treatment group. The *INMB* must be calculated as the linear combination of these parameters and is presented in a later analysis. The significant predictors of $NMB_{\lambda it}$ were previous hospitalizations (more previous hospitalizations predicted lower $NMB_{\lambda it}$, or higher annual costs when λ = \$0), and *NMB* mean slope and change in *NMB* slope at month 4 ($NMB_{\lambda it}$ is predicted to increase over time, but with a significant decrease or change in slope at month 4), in both models and at all levels of λ.

Variances of the random effects for between-patient NMB_{λ} intercept and slope were significantly different from zero, indicating there was significant variability between patients in their baseline NMB_{λ} and their changes in NMB_{λ} overtime (in both models and at all levels of λ). In the joint model, the residual error for log time-to-dropout was also significantly differently from zero. The correlation between log of time-to-dropout and the random effect of NMB_{λ} slope ranged from 0.34 to 0.39 across the levels of λ (all $p<0.01$), meaning that time-to-dropout was significantly correlated with trajectory of the response. The joint ME model would not converge without an assumption of zero correlation between log of time-to-dropout and the random effect of the *NMB* intercept. This was due to small correlations among the log of time-to-dropout, random intercept and random slope. Convergence, therefore, required an assumption of

zero correlation among one of the pairs. The relationships between the slopes and intercepts are usually strong enough that the joint ME model only needs one of the correlations to be significantly different from zero in order to converge (Fairclough, personal communication, July 8, 2008).

Table 4.3-1 ANCOVA Model parameter estimates from model with annual $NMB^{*}_{\lambda i}$ [a] as dependent variable, base case

		λ = $0		λ = $25,000		λ = $50,000		λ = $100,000	
Fixed Effects		$\hat{\beta}$ **(s.e.)**	**p-value**	$\hat{\beta}$ **(s.e.)**	**p-value**	$\hat{\beta}$ **(s.e.)**	**p-value**	$\hat{\beta}$ **(s.e.)**	**p-value**
β_1	NMB mean intercept[a]	-23.54 (1.57)	<0.01	-7.66 (1.57)	<0.01	8.21 (1.58)	<0.01	39.96 (1.61)	<0.01
β_3	Treatment group (reference group is T_0)	-3.77 (2.18)	0.08	-1.56 (2.17)	0.47	0.64 (2.18)	0.77	5.06 (2.22)	0.02
β_4	Patient age[a]	0.05 (0.12)	0.67	0.04 (0.12)	0.77	0.02 (0.12)	0.88	-0.02 (0.13)	0.90
β_5	Previous hospitalizations[a]	-7.27 (2.19)	<0.01	-7.74 (2.19)	<0.01	-8.21 (2.20)	<0.01	-9.14 (2.24)	<0.01
β_{11}	Baseline *NMB*[a]	0.39 (0.05)	<0.01	0.37 (0.05)	<0.01	0.36 (0.05)	<0.01	0.34 (0.05)	<0.01
Variances of Residual Errors									
ε	Residual error for NMB_{λ} $(\hat{\sigma}^2)$[b]	709.69		707.27		711.55		740.20	

[a] Dependent variable, $NMB^{*}_{\lambda i}$ rescaled as $NMB^{*}_{\lambda i}$/1000; patient age rescaled as age – 40; previous hospitalization rescaled as Phosp - 0.5, and baseline $NMB_{\lambda i}$ rescaled as baseline $NMB_{\lambda i}$ – mean $NMB_{\lambda i}$.

[b] Represents subject-level residual errors for annual $NMB^{*}_{\lambda i}$.

(See Appendix II.A. Uni LOCF Mean BL for SAS code.)

Table 4.3-2A ME and joint ME model parameter estimates from models with $NMB_{\lambda it}$ as dependent variable, λ=$0, base case

		ME		Joint ME	
Fixed Effects		$\hat{\beta}$ **(s.e.)**	**p-value**	$\hat{\beta}$ **(s.e.)**	**p-value**
β_1	NMB mean intercept[a]	-16.06 (1.20)	<0.01	-15.49 (1.20)	<0.01
β_2	NMB mean slope (month)	1.64 (0.26)	<0.01	1.62 (0.26)	<0.01
β_3	Treatment group (reference group is T_0)	0.13 (1.68)	0.94	-0.96 (1.67)	0.57
β_4	Patient age[a]	0.03 (0.05)	0.50	0.04 (0.05)	0.36
β_5	Previous hospitalizations[a]	-2.91 (0.86)	<0.01	-2.52 (0.85)	<0.01
β_6	Interaction: Group X Month	-0.27 (0.37)	0.46	-0.16 (0.37)	0.67
β_7	Change in *NMB* slope, month 4	-1.24 (0.43)	<0.01	-1.32 (0.43)	<0.01
β_8	Interaction: Group X change in *NMB* slope, month 4	0.16 (0.62)	0.80	0.14 (0.62)	0.82
β_9	Change in *NMB* slope, month 8	-0.08 (0.46)	0.87	-0.14 (0.46)	0.77
β_{10}	Interaction: Group X change in *NMB* slope, month 8	0.07 (0.67)	0.92	0.03 (0.67)	0.96
τ_1	Log time-to-dropout mean intercept	--	--	3.31	0.11
Variances of Random Effects, Residual Errors		$\hat{\sigma}^2$ **(s.e.)**	**p-value**	$\hat{\sigma}^2$ **(s.e.)**	**p-value**
u	Between-patient NMB_λ intercept	288.19 (22.83)	<0.01	289.04 (22.84)	<0.01
v	Between-patient NMB_λ slope	2.55 (0.28)	<0.01	2.52 (0.28)	<0.01
s	Residual error for log time-to-dropout	--	--	2.93 (0.35)	<0.01
ε	Residual error for NMB_λ [b]	137.27 (6.19)	<0.01	137.40 (6.18)	<0.01
Correlations with Log of Time-to-dropout		$\hat{\rho}$ **(s.e.)**	**p-value**	$\hat{\rho}$ **(s.e.)**	**p-value**
NMB_λ intercept		--	--	0.00[c]	--
NMB_λ slope		--	--	0.34 (0.85)	<0.01

[a] Dependent variable, $NMB_{\lambda i}$, rescaled as $NMB_{\lambda i}$ / 1000; patient age rescaled as age – 40; previous hospitalization rescaled as Phosp - 0.5.

[b] Represents subject-level residual errors for $NMB_{\lambda it}$ at each time point.

[c] Model would not converge without assuming zero correlation.

(See Appendix II.B. Mar_miss for ME model and Appendix II.C Joint_miss for joint ME SAS code.)

Table 4.3-2B ME and joint ME model parameter estimates from models with $NMB_{\lambda it}$ as dependent variable, λ=$25k base case

Fixed Effects		ME		Joint ME	
		$\hat{\beta}$ (s.e.)	p-value	$\hat{\beta}$ (s.e.)	p-value
β_1	NMB mean intercept[a]	-10.93 (1.20)	<0.01	-10.33 (1.20)	<0.01
β_2	NMB mean slope (month)	1.67 (0.26)	<0.01	1.65 (0.26)	<0.01
β_3	Treatment group (reference group is T_0)	0.14 (1.69)	0.94	-1.01 (1.67)	0.55
β_4	Patient age[a]	0.03 (0.05)	0.61	0.04 (0.05)	0.44
β_5	Previous hospitalizations[a]	-3.07 (0.86)	<0.01	-2.67 (0.85)	<0.01
β_6	Interaction: Group X Month	-0.07 (0.37)	0.85	0.05 (0.37)	0.90
β_7	Change in *NMB* slope, month 4	-1.28 (0.43)	<0.01	-1.36 (0.44)	<0.01
β_8	Interaction: Group X change in *NMB* slope, month 4	-0.04 (0.62)	0.95	-0.06 (0.62)	0.93
β_9	Change in *NMB* slope, month 8	-0.07 (0.46)	0.87	-0.14 (0.46)	0.76
β_{10}	Interaction: Group X change in *NMB* slope, month 8	0.07 (0.67)	0.92	0.032(0.67)	0.96
τ_1	Log time-to-dropout mean intercept	--	--	3.31	0.11
Variances of Random Effects, Residual Errors		$\hat{\sigma}^2$ (s.e.)	p-value	$\hat{\sigma}^2$ (s.e.)	p-value
u	Between-patient NMB_λ intercept	287.96 (22.84)	<0.01	289.11 (22.88)	<0.01
v	Between-patient NMB_λ slope	2.60 (0.28)	<0.01	2.56 (0.28)	<0.01
s	Residual error for log time-to-dropout	--	--	2.94 (0.35)	<0.01
ε	Residual error for NMB_λ [b]	137.61 (6.21)	<0.01	137.76 (6.20)	<0.01
Correlations with Log of Time-to-dropout		$\hat{\rho}$ (s.e.)	p-value	$\hat{\rho}$ (s.e.)	p-value
NMB_λ intercept		--	--	0.00[c]	--
NMB_λ slope		--	--	0.36 (0.08)	<0.01

[a] Dependent variable, $NMB_{\lambda i}$, rescaled as $NMB_{\lambda i}$ / 1000; patient age rescaled as age – 40; previous hospitalization rescaled as Phosp - 0.5.

[b] Represents subject-level residual errors for $NMB_{\lambda it}$ at each time point.

[c] Model would not converge without assuming zero correlation.

(See Appendix II.B. Mar_miss for ME model and Appendix II.C Joint_miss for joint ME SAS code.)

Table 4.3-2C ME and joint ME model parameter estimates from models with $NMB_{\lambda it}$ as dependent variable, λ=$50k base case

		ME		Joint ME	
Fixed Effects		$\hat{\beta}$ **(s.e.)**	**p-value**	$\hat{\beta}$ **(s.e.)**	**p-value**
β_1	NMB mean intercept[a]	-5.80 (1.20)	<0.01	-5.16 (1.20)	<0.01
β_2	NMB mean slope (month)	1.70 (0.26)	<0.01	1.68 (0.26)	<0.01
β_3	Treatment group (reference group is T_0)	0.15 (1.69)	0.93	-1.04 (1.67)	0.53
β_4	Patient age[a]	0.02 (0.05)	0.72	0.03 (0.05)	0.54
β_5	Previous hospitalizations[a]	-3.23 (0.85)	<0.01	-2.81 (0.84)	<0.01
β_6	Interaction: Group X Month	0.13 (0.37)	0.73	0.25 (0.37)	0.50
β_7	Change in *NMB* slope, month 4	-1.31 (0.44)	<0.01	-1.40 (0.44)	<0.01
β_8	Interaction: Group X change in *NMB* slope, month 4	-0.23 (0.62)	0.71	-0.24 (0.62)	0.70
β_9	Change in *NMB* slope, month 8	-0.07 (0.46)	0.87	-0.14 (0.46)	0.76
β_{10}	Interaction: Group X change in *NMB* slope, month 8	0.07 (0.67)	0.92	0.02 (0.67)	0.98
τ_1	Log time-to-dropout mean intercept	--	--	3.31	0.11
Variances of Random Effects, Residual Errors		$\hat{\sigma}^2$ **(s.e.)**	**p-value**	$\hat{\sigma}^2$ **(s.e.)**	**p-value**
u	Between-patient NMB_λ intercept	288.36 (22.89)	<0.01	289.87 (22.98)	<0.01
v	Between-patient NMB_λ slope	2.67 (0.29)	<0.01	2.64 (0.29)	<0.01
s	Residual error for log time-to-dropout	--	--	2.94 (0.35)	<0.01
ε	Residual error for NMB_λ[b]	138.56 (6.25)	<0.01	138.72 (6.24)	<0.01
Correlations with Log of Time-to-dropout		$\hat{\rho}$ **(s.e.)**	**p-value**	$\hat{\rho}$ **(s.e.)**	**p-value**
NMB_λ intercept		--	--	0.00[c]	--
NMB_λ slope		--	--	0.37 (0.08)	<0.01

[a] Dependent variable, $NMB_{\lambda i}$, rescaled as $NMB_{\lambda i}$ / 1000; patient age rescaled as age – 40; previous hospitalization rescaled as Phosp - 0.5.

[b] Represents subject-level residual errors for $NMB_{\lambda it}$ at each time point.

[c] Model would not converge without assuming zero correlation.

(See Appendix II.B. Mar_miss for ME model and Appendix II.C Joint_miss for joint ME SAS code.)

Table 4.3-2D ME and joint ME parameter estimates from models with $NMB_{\lambda it}$ as dependent variable, λ=$100k base case

		ME		Joint ME	
Fixed Effects		$\hat{\beta}$ **(s.e.)**	**p-value**	$\hat{\beta}$ **(s.e.)**	**p-value**
β_1	NMB mean intercept[a]	4.47 (1.21)	<0.01	5.15 (1.20)	<0.01
β_2	NMB mean slope (month)	1.75 (0.27)	<0.01	1.73 (0.27)	<0.01
β_3	Treatment group (reference group is T_0)	0.17 (1.70)	0.92	-1.11 (1.68)	0.51
β_4	Patient age[a]	0.00 (0.05)	0.98	0.01 (0.05)	0.77
β_5	Previous hospitalizations[a]	-3.54 (0.86)	<0.01	-3.10 (0.85)	<0.01
β_6	Interaction: Group X Month	0.53 (0.38)	0.16	0.66 (0.38)	0.08
β_7	Change in *NMB* slope, month 4	-1.37 (0.44)	<0.01	-1.47 (0.44)	<0.01
β_8	Interaction: Group X change in *NMB* slope, month 4	-0.62 (0.63)	0.32	-0.64 (0.63)	0.31
β_9	Change in *NMB* slope, month 8	-0.07 (0.47)	0.88	-0.14 (0.47)	0.76
β_{10}	Interaction: Group X change in *NMB* slope, month 8	0.06 (0.68)	0.93	0.01 (0.68)	0.99
τ_1	Log time-to-dropout mean intercept	--	--	3.31	0.11
Variances of Random Effects, Residual Errors		$\hat{\sigma}^2$ **(s.e.)**	**p-value**	$\hat{\sigma}^2$ **(s.e.)**	**p-value**
Between-patient NMB_λ intercept		290.80 (23.23)	<0.01	293.06 (23.35)	<0.01
Between-patient NMB_λ slope		2.80 (0.30)	<0.01	2.78 (0.30)	<0.01
Residual error for log time-to-dropout		--	--	2.94 (0.35)	<0.01
Residual error for NMB_λ[b]		142.21 (6.42)	<0.01	142.41 (6.41)	<0.01
Correlations with Log of Time-to-dropout		$\hat{\rho}$ **(s.e.)**	**p-value**	$\hat{\rho}$ **(s.e.)**	**p-value**
NMB_λ intercept		--	--	0.00[c]	--
NMB_λ slope		--	--	0.39 (0.08)	<0.01

[a] Dependent variable, $NMB_{\lambda i}$, rescaled as $NMB_{\lambda i}$ / 1000; patient age rescaled as age – 40; previous hospitalization rescaled as Phosp - 0.5.

[b] Represents subject-level residual errors for $NMB_{\lambda it}$ at each time point.

[c] Model would not converge without assuming zero correlation.

(See Appendix II.B. Mar_miss for ME model and Appendix II.C Joint_miss for joint ME SAS code.)

Model estimates for total annual NMB_λ and $INMB_\lambda$ are compared to the complete data $INMB_\lambda$ in Table 4.3-3. The $\hat{INMB}_\lambda$ represents the treatment group difference in NMB_λ (i.e., the measure of incremental cost-effectiveness). Recall that in the ANCOVA model, the observed $NMB_{\lambda it}$ within patient across time points t = 4, 8, and 12 were first summed to create the dependent variable, $NMB^*_{\lambda i}$. In the ME models, each of the observed $NMB_{\lambda it}$ within patient at each time point was used as dependent variables and parameters were summed for a predicted $\hat{NMB}^*_{\lambda i}$. Complete data $\hat{INMB}_\lambda$ were calculated from the simulated complete data as least squares mean differences from generalized linear models that included only treatment group.

ANCOVA model results for $\hat{INMB}_\lambda$ are identical to the model parameter estimate results for treatment group (β_3) reported in Table 4.3-1, because the ANCOVA model included no interaction terms with treatment group. As λ increases, the $\hat{INMB}_\lambda$ switches from being nearly significant in favor of T_0 ($\hat{INMB}_0$ = -$3,770.5, p=0.08) to being significant in favor of T_1 ($\hat{INMB}_{100000}$ = $5,055.7, p=0.02). The ME and joint ME results for $\hat{INMB}_\lambda$ account for the additional interaction effects between treatment group and month and changes in *NMB* slope over time. The ME and joint ME results are similar to the ANCOVA results, with $\hat{INMB}_\lambda$ being nearly significant in favor of T_0 when λ = $0 (ME $\hat{INMB}_0$ = -$4,001.1, p=0.13; joint ME $\hat{INMB}_0$ = -$4,901.2, p=0.06) to being significant in favor of T_1 when λ = $100,000 (ME $\hat{INMB}_{100000}$ = $5,953.9, p=0.02; joint ME $\hat{INMB}_0$ = $4,966.4, p=0.05).

Also reported in Table 4.3-3 are the measures of bias for each estimator. Bias was defined as the absolute difference between the estimated $\hat{INMB}_{\lambda}$ and the complete data $INMB_{\lambda}$. When λ = \$0, the estimators with the smallest and largest bias were produced by the ANCOVA model (bias = \$1,070.5) and the joint ME model (bias = \$2,201.2), respectively. When λ = \$25,000, \$50,000, and \$100,000, the ME model estimators had the smallest bias (\$1,312.5, \$1,324.1, and \$1,344.1, respectively), and the joint ME model consistently produced the estimator with the largest bias. Figure 4.3-1 displays the estimators and 95% confidence intervals, by level of λ and for the three models versus the complete data ("true") $INMB_{\lambda}$. The three models generated estimators that were not significantly different from the complete data $INMB_{\lambda}$, as can be seen by the overlapping 95% confidence intervals. When λ = \$100,000, the estimators from the ANCOVA and ME models were in closest agreement to the complete data $INMB_{\lambda}$ where T_1 was cost-effective compared to T_0 (i.e., 95% confidence intervals not including the value zero). Importantly, the joint model did not correctly estimate $INMB_{\lambda}$ at λ = \$100,000 when the cost-effectivenessness of T_1 was known to be significant.

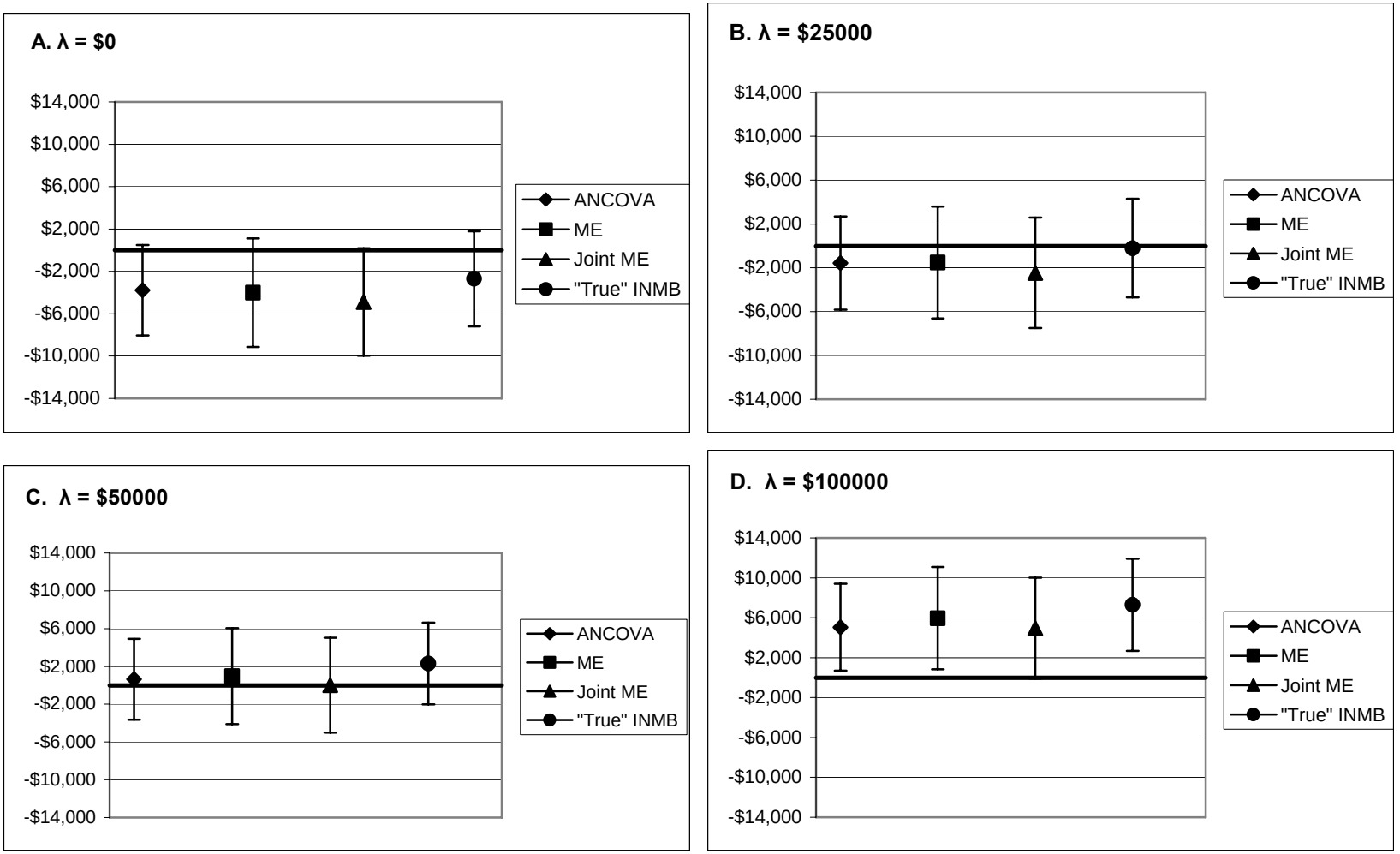
Table 4.3-3 Total annual $\hat{NMB}_\lambda$, $\hat{INMB}_\lambda$, and bias from complete data $INMB_\lambda$, base case

λ		$\hat{NMB}_\lambda$ ($) (s.e.)		$\hat{INMB}_\lambda$ ($) (s.e.)	p value	Bias
		T_1	T_0			
$0	ANCOVA	-27,307.5 (1,560.4)	-23,536.9 (1,573.6)	-3,770.5 (2,177.9)	0.08	1,070.5
	ME	-28,002.6 (1,903.0)	-24,001.5 (1,839.7)	-4,001.1 (2,614.6)	0.13	1,301.1
	Joint ME	-28,797.3 (1,891.0)	-23,896.1 (1,830.6)	-4,901.2 (2,588.9)	0.06	2,201.2
	Complete data [a]	--	--	-2,700.0 (2,292.3)	0.24	--
$25,000	ANCOVA	-9,225.4 (1,557.8)	-7,661.6 (1,571.0	-1,563.8 (2,174.4)	0.47	1,362.8
	ME	-9,844.6 (1,893.7)	-8,331.1 (1,829.0)	-1,513.5 (2,600.0)	0.56	1,312.5
	Joint ME	-10,689.7 (1,880.9)	-8,231.5 (1,819.3)	-2,458.3 (2,572.5)	0.34	2,257.3
	Complete data [a]	--	--	-201.0 (2,292.1)	0.93	--
$50,000	ANCOVA	8,856.4 (1,562.5)	8,213.5 (1,575.7)	642.9 (2,180.9)	0.77	1,656.1
	ME	8,314.5 (1,890.0)	7,339.6 (1,824.7)	974.9 (2,595.1)	0.71	1,324.1
	Joint ME	7,433.7 (1,876.5)	7,419.7 (1,814.3)	13.9 (2,565.0)	1.00	2,285.1
	Complete data [a]	--	--	2,299.0 (2,302.8)	0.32	--
$100,000	ANCOVA	45,019.5 (1,593.7)	39,963.8 (1,607.2)	5,055.7 (2,224.4)	0.02	2,242.3
	ME	44,642.1 (1,904.5)	38,688.2 (1,836.5)	5,953.9 (2,613.7)	0.02	1,344.1
	Joint ME	43,664.5 (1,888.0)	38,698.0 (1,823.8)	4,966.4 (2,577.9)	0.05	2,331.6
	Complete data [a]	--	--	7,298.0 (2,355.6)	<0.01	--

[a] Calculated using the simulated complete data, as least squares mean differences from a generalized linear model that included only treatment group.

(See Appendix II.A. Uni LOCF Mean BL for ANCOVA model, Appendix II.B. Mar_miss for ME model, and Appendix II.C. Joint_miss for SAS code.)

Figure 4.3-1 Total annual $\hat{INMB}\ \lambda$ and complete data $INMB_{\lambda}$, with 95% confidence intervals, base case



The precision results for the model estimates of $\hat{INMB}_{\lambda}$ are presented in Table 4.3-4. Precision was determined with ratios of the variances of $\hat{INMB}_{\lambda}$ from each model, compared to the variance of the complete data $INMB_{\lambda}$. For all levels of λ, the estimators with the best precision were produced by the ANCOVA model, with variance ratios ranging from 0.89 to 0.90. This result indicates that the variances of the ANCOVA estimators were within 10-11% of the complete data $INMB_{\lambda}$ variance. The ME and joint ME models produced estimators with variance ratios ranging from 1.20 to 1.30, depending on λ. Likewise, this result indicates that the ME model estimator variances were within 20-30% of the complete data $INMB_{\lambda}$ variance.

Cost-effectiveness acceptability curves (CEACs) are presented in Figure 4.3-2. These curves assess the probability of the cost-effectiveness of T_1 relative to T_0 across a range of λ values from \$0 to \$100,000, by increments of \$5,000. The probabilities in the CEACs were generated as 1 minus the one-sided p-values from the tests of significant difference between treatment groups. From the graph, the probability of T_1 being cost-effective compared to T_0 when willingness to pay λ = \$50,000 is approximately 83% based on the complete data INMB. (This result can be seen by drawing a vertical line through the curves at λ = \$50,000, then drawing horizontal lines at the intersection points to the y-axis probability values.) The ME model produced a CEAC closest to complete data with a probability of approximately 64%, followed by ANCOVA (60%), and joint ME model (50%).

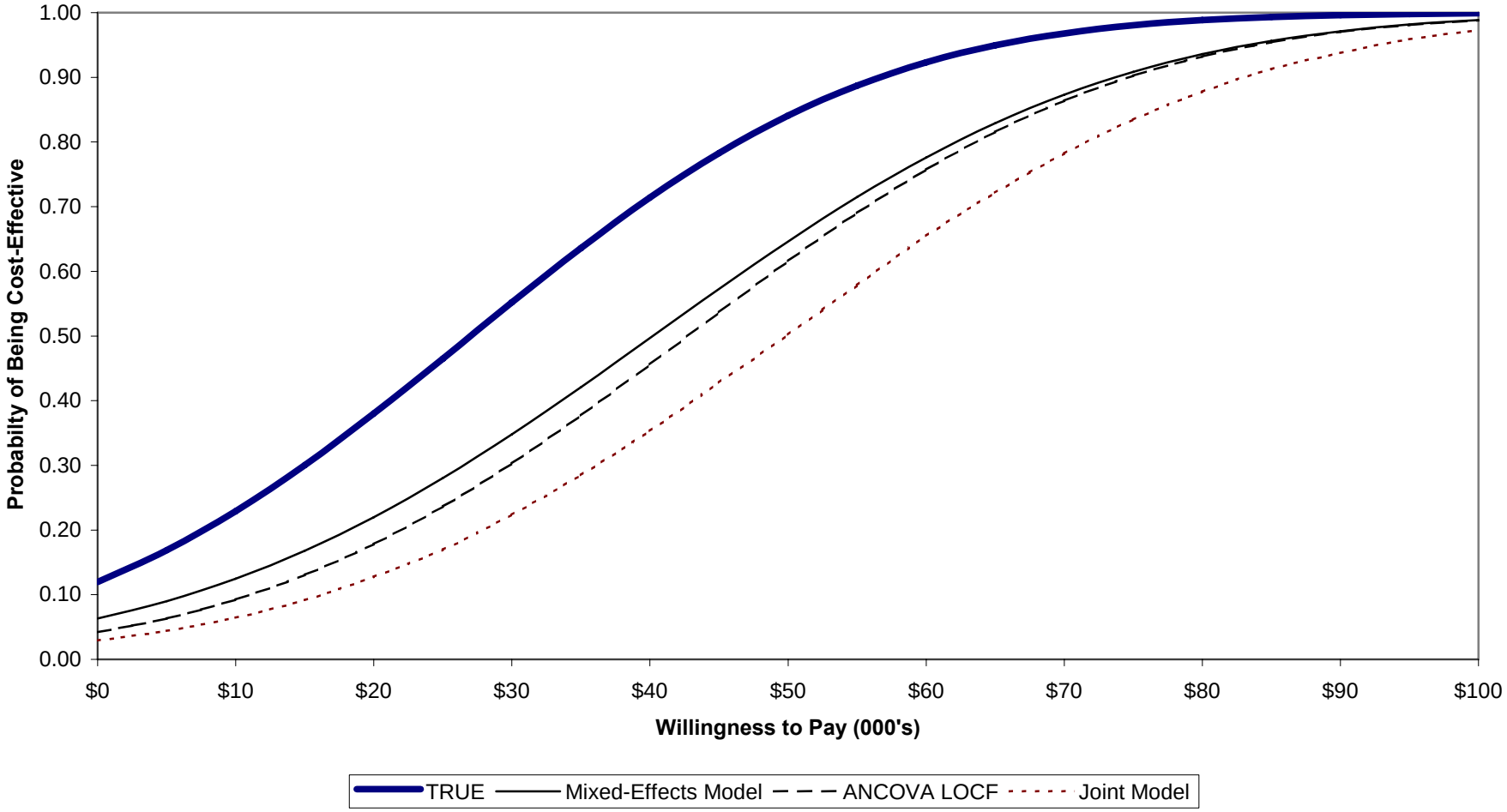
Table 4.3-4 Precision of the estimates of total annual $\hat{INMB}_\lambda$ compared to complete data $INMB_\lambda$, base case

λ	Model	$\hat{INMB}_\lambda$ variance	Variance ratio
\$0	Complete data[a]	3,152.8	--
	ANCOVA	2,846.0	0.90
	ME	4,101.7	1.30
	Joint ME	4,021.4	1.28
\$25,000	Complete data[a]	3,152.2	--
	ANCOVA	2,836.8	0.90
	ME	4,057.3	1.29
	Joint ME	3,970.7	1.26
\$50,000	Complete data[a]	3,181.7	--
	ANCOVA	2,853.8	0.90
	ME	4,040.7	1.27
	Joint ME	3,947.5	1.24
\$100,000	Complete data[a]	3,329.3	--
	ANCOVA	2,968.8	0.89
	ME	4,098.9	1.23
	Joint ME	3,987.3	1.20

[a] Calculated using the simulated complete data, as least squares mean differences from a generalized linear model that included only treatment group.

(See Appendix II.A. Uni LOCF Mean BL for ANCOVA model, Appendix II.B. Mar_miss for ME model, and Appendix II.C. Joint_miss for joint ME model SAS code.)

Figure 4.3-2 Cost effectiveness acceptability curves: Model results compared to complete data, base case



4.4 Sensitivity Analyses

Different proportions of MAR or MNAR missing data may impact the precision of $INMB_\lambda$ estimates. Sensitivity analyses were conducted to examine the potential impact. Sensitivity Analysis 1 used simulated data from a procedure that involved processing all 600 simulated complete observations through the MAR nonresponse algorithm (described in Chapter 3.7). The result was a simulated missing dataset with a larger proportion of dropouts compared to the base case, and all missing cases MAR. Sensitivity analysis 2 was similar to 1, except the procedure involved processing the 600 simulated complete observations through the MNAR nonresponse algorithm (also described in Chapter 3.7), with the result being simulated missing data with an even larger proportion of dropouts than in sensitivity analysis 1, and all missing cases MNAR. The sensitivity analyses were limited to results for λ = \$100,000, where treatment group T_1 should be cost-effective compared to T_0 according to the algebraically-derived true $INMB_\lambda$.

Table 4.4-1 shows the number of patients remaining in the study by treatment group and time point. As expected, the percentages of patients remaining in the study are lower in the sensitivity analysis datasets. For T_0, 64% and 48% of patients remained in the study by month 12 for sensitivity analyses 1 and 2, respectively, while the base case had 73% of T_0 remaining by month 12. Results were similar for T_1, where 53% and 35% of patients remained by month 12 in the sensitivity analysis, compared to 62% in the base case.

Also presented in Table 4.4-1 are the means (SD) for NMB_{100000} by treatment group and time point. Mean NMB_{100000} were similar between sensitivity analysis 1 and

the base case. For example, the mean value at month 4 for T_0 in the sensitivity analysis was \$11,198 versus \$11,178 for the base case, and for T_1 the mean value was \$14,001 versus \$13,396 for the base case. The greater proportions of dropouts in sensitivity analysis 2 resulted in mean NMB_{100000} that varied more from the base case across time points. The mean value at month 4 for T_0 was \$10,170 versus \$11,178 for the base case, and for T_1 was \$11,813 versus \$13,396 for the base case. By month 12, the mean value for T_0 was \$10,849 versus \$14,216 for the base case, and for T_1 was \$9,855 versus \$15,599 for the base case.

The impact of greater proportions of missing observations and the MAR or MNAR nonresponse mechanisms on mean NMB_{100000} can be seen clearly in Figure 4.4.1 where the means from the complete simulated data, base case, and sensitivity analyses are graphed by treatment group. All of means from the simulated missing data are lower than the complete data means after month 4. Sensitivity analysis 1 (dashed lines) has mean NMB_{100000} for both T_1 and T_0 that hovered around the base case mean across time points. By month 12, however, the treatment group difference decreased. Sensitivity analysis 2 (dotted lines), where over 50 percent of patients were simulated to drop out of the study with the MNAR nonresponse mechanism, had much lower means at all time points compared to the base case and sensitivity analysis 1. Further, as more patients drop out over time, the gap between base case and complete data increased. Also, the mean for T_1 trended downwards after month 4 indicating that a false interaction between treatment and time resulted from the increase in dropouts. The graph illustrates how large proportions of missing data and MAR or MNAR nonresponse mechanisms can have a dramatic impact on the crude mean values.

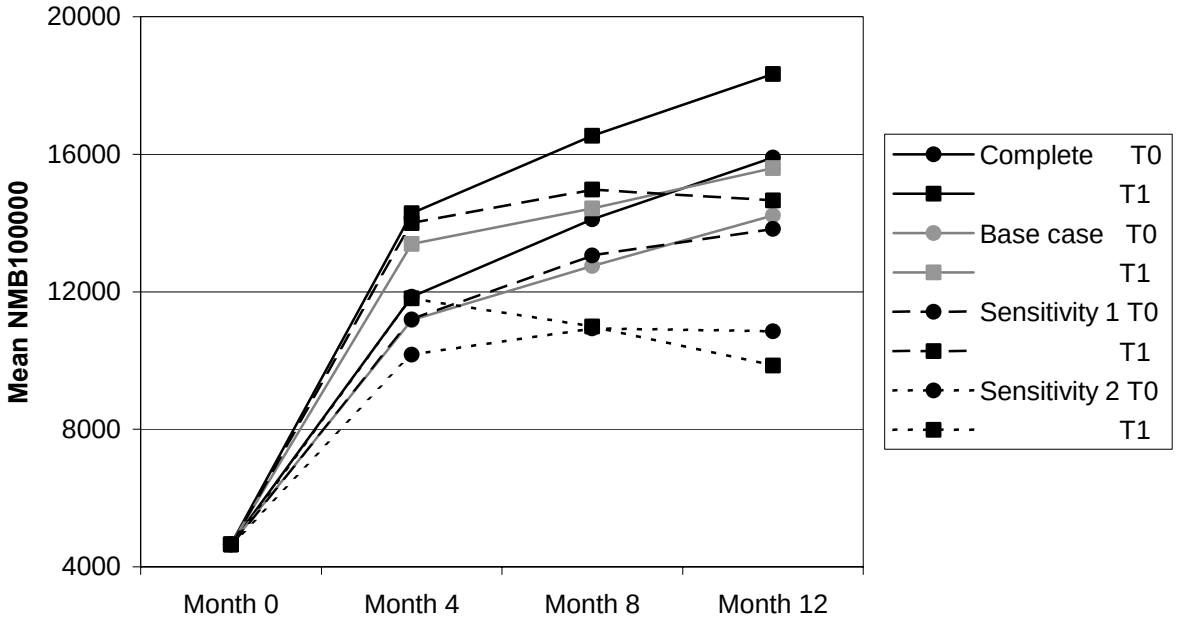
Table 4.4-1 Descriptive statistics for NMB_{100000}: Sensitivity analyses and base case

Treatment group T_0				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
Sensitivity analysis 1[a]				
N (%)	300 (100%)	274 (91%)	241 (80%)	191 (64%)
Mean (SD) ($)	4,654 (27,878)	11,198 (13,662)	13,055 (12,459)	13,831 (12,019)
Sensitivity analysis 2[b]				
N (%)	300 (100%)	256 (85%)	202 (67%)	144 (48%)
Mean (SD) ($)	4,654 (27,878)	10,170 (13,647)	10,936 (12,722)	10,849 (12,612)
Base case[c]				
N (%)	300 (100%)	278 (93%)	252 (84%)	218 (73%)
Mean (SD)	4,654 (27,878)	11,178 (13,515)	12,752 (12,171)	14,216 (11,455)

Treatment group T_1				
	Time Point			
	Month 0	**Month 4**	**Month 8**	**Month 12**
Sensitivity analysis 1[a]				
N (%)	300 (100%)	289 (96%)	232 (77%)	160 (53%)
Mean (SD) ($)	4,655 (18,793)	14,001 (14,186)	14,971 (14,229)	14,662 (12,539)
Sensitivity analysis 2[b]				
N (%)	300 (100%)	237 (79%)	161 (54%)	106 (35%)
Mean (SD) ($)	4,654 (18,793)	11,813 (14,803)	10,986 (15,517)	9,855 (13,122)
Base case[c]				
N (%)	300 (100%)	273 (91%)	225 (75%)	185 (62%)
Mean (SD)	4,655 (18,793)	13,396 (14,369)	14,425 (14,320)	15,599 (12095)

[a] Simulated data include a mixture of MAR missing data and complete observations.
[b] Simulated data include a mixture of MNAR missing data and complete observations.
[c] Simulated data include a mixture MAR and MNAR missing data and complete observations.

Figure 4.4-1 Mean NMB_{100000} for the simulated complete data, base case, and sensitivity analyses 1 and 2



(See Appendix II.G. Univariate and Missing for SAS code.)

The distributions of raw NMB_{100000} values from the two sensitivity analyses were compared to a normal curve as a visual check of the assumption of normally distributed NMB_{100000} values (results not shown). The distributions were similar to the distribution found in the base case, with NMB_{100000} not being normally distributed.

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Model estimates for total annual NMB_{100000} and $INMB_{100000}$ from the sensitivity analyses are compared the estimates based on the complete $INMB_{100000}$ in Table 4.4-2. The ANCOVA and ME models produced significant estimates in sensitivity analysis 1. Sensitivity analysis 2 resulted in the worst estimates, with all models failing to estimate a significant treatment difference and absolute bias of the estimates being the greatest. In sensitivity analysis 1, the ANCOVA and ME models produced better estimates than in the base case, with regard to bias. The ANCOVA model produced the least biased estimates in both sensitivity analyses, and the bias was especially small ($532.5) in sensitivity analysis 1. Across all analyses, the joint model produced the most biased estimates. The above results suggest an issue with the estimation method and/or a possible issue with how the non-response mechanism for MAR and MNAR data were simulated. Results are also illustrated in Figure 4.4-2.

The precision results for the model estimates for the sensitivity analyses are presented in Table 4.4-3. For both sensitivity analyses, the ANCOVA estimates had the best precision with variance ratios ranging from 0.90 to 1.04. The ME and joint ME models produced estimators with variance ratios ranging from 1.30 to 1.91.

Table 4.4-2 Total annual $\hat{NMB}_{100000}$ and $\hat{INMB}_{100000}$, and bias from complete data $INMB_{100000}$: Sensitivity analyses and base case

		$\hat{NMB}_{100000}$ ($) (s.e.)		$\hat{INMB}_{100000}$ ($) (s.e.)	p value	Bias
		T_1	T_0			
Sensitivity analysis 1	ANCOVA	49,847.4 (1,577.5)	43,082.0 (1,582.1)	6,765.5 (2,233.6)	<0.01	532.5
	ME	45,301.9 (1,944.8)	39,164.2 (1,899.9)	6,137.6 (2,687.3)	0.02	1160.4
	Joint ME	45,159.1 (5,666.3)	41,704.8 (7,836.4)	3,454.3 (3,255.6)	0.29	3,843.7
Sensitivity analysis 2	ANCOVA	37,360.3 (1,694.1)	34,919.6 (1,699.1)	2,440.7 (2,398.8)	0.31	4,857.3
	ME	35,061.9 (2,353.4)	33,394.4 (2,131.9)	1,667.4 (3,139.5)	0.60	5,630.6
	Joint ME	34,080.1 (2,332.5)	32,935.8 (2,111.2)	1,144.4 (3,082.6)	0.71	6,153.6
Base case	ANCOVA	45,019.5 (1,593.7)	39,963.8 (1,607.2)	5,055.7 (2,224.4)	0.02	2,242.3
	ME	44,642.1 (1,904.5)	38,688.2 (1,836.5)	5,953.9 (2,613.7)	0.02	1,344.1
	Joint ME	43,664.5 (1,888.0)	38,698.0 (1,823.8)	4,966.4 (2,577.9)	0.05	2,331.6
Complete data [a]				7,298.0 (2,355.6)	<0.01	--

[a] Calculated using the simulated complete data, as least squares mean differences from a generalized linear model that included only treatment group.

(For sensitivity analysis 1 see Appendix II.J. UNI_LOCF MAR for ANCOVA model ; Appendix II.K. MAR_Miss for ME model; Appendix II.L. Joint_miss MAR for joint ME model SAS code. For sensitivity analysis 2 see Appendix II.M. Uni_LOCF MNAR for ANCOVA model; Appendix II.N. Mar_miss MNAR for ME model; Appendix II.O. Joint_miss MNAR for joint ME model SAS code.)

Figure 4.4-2 Total annual $\hat{INMB}_{100000}$ and complete data $INMB_{100000}$, with 95% confidence intervals: Sensitivity analyses and base case

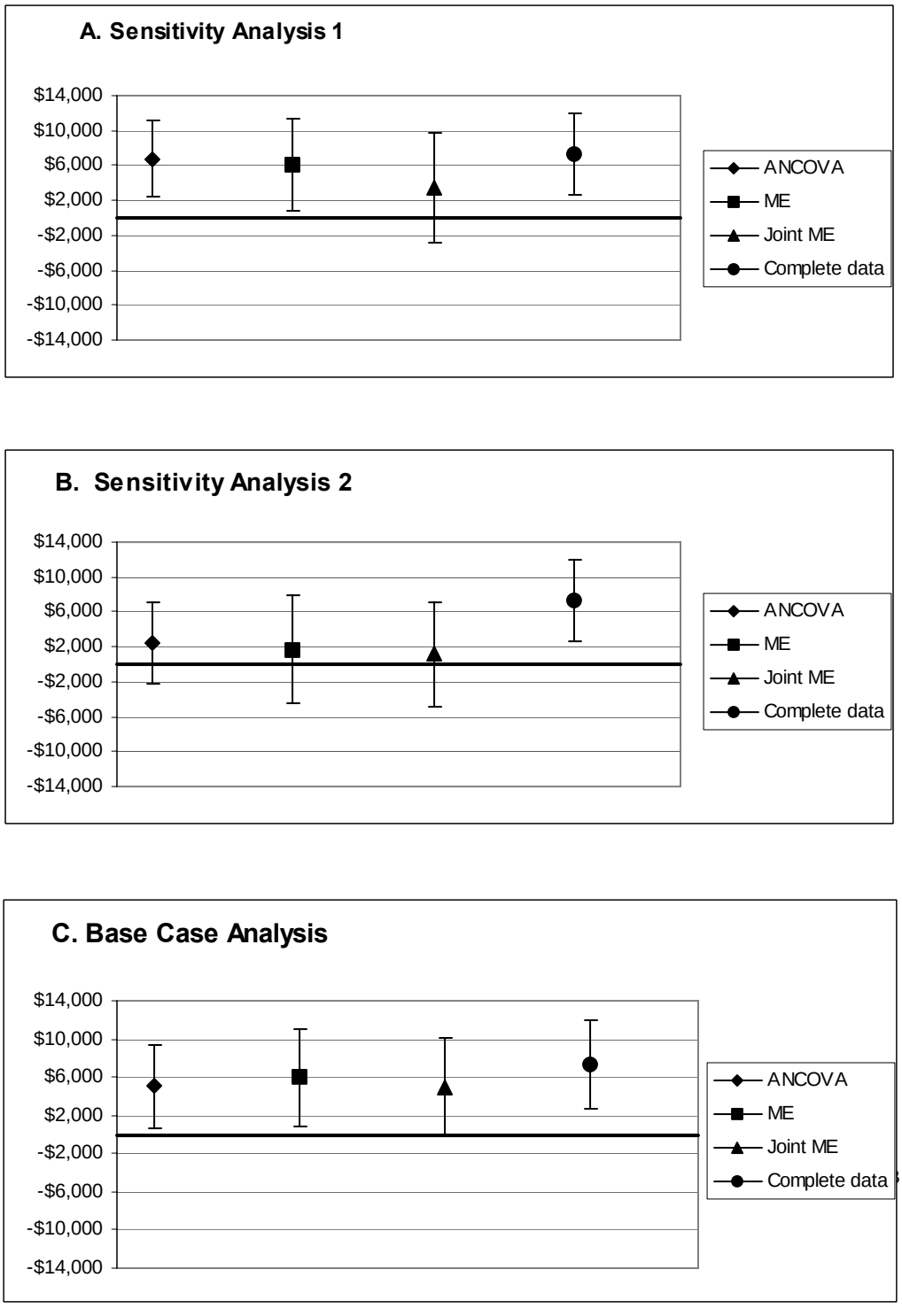

Table 4.4-3 Precision of the estimates of total annual $\hat{INMB}_{100000}$ compared to complete data $INMB_{100000}$: Sensitivity analyses and base case

	Model	$\hat{INMB}_{100000}$ variance	Variance ratio
Sensitivity analysis 1	ANCOVA	2,993.5	0.90
	ME	4,333.0	1.30
	Joint ME	6,359.4	1.91
Sensitivity analysis 2	ANCOVA	3,452.5	1.04
	ME	5,913.9	1.78
	Joint ME	5,701.5	1.71
Base case	ANCOVA	2,968.8	0.89
	ME	4,098.9	1.23
	Joint ME	4,098.9	1.20
Complete data[a]		3,329.3	--

[a] Calculated using the simulated complete data, as least squares mean differences from a generalized linear model that included only treatment group. All observed F are calculated using the base case complete data residual error variance for *NMB*.

(For sensitivity analysis 1 see Appendix II.J. UNI_LOCF MAR for ANCOVA model ; Appendix II.K. MAR_Miss for ME model; Appendix II.L. Joint_Miss MAR for joint ME model SAS code. For sensitivity analysis 2 see Appendix II.M. Uni_LOCF MNAR for ANCOVA model; Appendix II.N. Mar_miss MNAR for ME model; Appendix II.O. Joint_miss MNAR for joint ME model SAS code.)

CHAPTER 5. DISCUSSION

This study compared ANCOVA, ME, and joint ME models using data with simulated MAR and MNAR nonresponse mechanisms. Contrary to expectation, the joint ME model did not produce the best estimates of incremental net monetary benefit (*INMB*). The assumption was that the joint ME model would produce better estimates than ANCOVA and ME models because it incorporated the correlation between time-to-dropout and the random effects of the longitudinal model for *NMB* into a single model. Although all three models successfully estimated significant treatment effect ($INMB_{100000}$), where the experimental treatment was known to be cost-effective versus the standard of care treatment, estimates with the smallest bias (absolute difference) from the known $INMB_{\lambda}$ were produced by the ANCOVA model when λ = \$0 and by the ME model when λ = \$25000, \$50000, and \$100000. Further, estimates with the best precision (variance ratio closest to the value of one) were produced by the ANCOVA model. Results on bias and precision were robust in sensitivity analyses that involved greater proportions of missing data (36% to 65% in the sensitivity analyses, and 27% to 38% in the base case), and only MAR in the first sensitivity analysis, and only MNAR in the second. Last, cost-effectiveness acceptability curves illustrated how the ME model generated the closest approximation to the known probability of cost-effectiveness for \$0 $< \lambda <$ \$80000. For $\lambda >$ \$80000, the ME and ANCOVA models were approximately equivalent and both were closer to the complete data than the joint ME model.

A possible explanation for this unexpected outcome is that the MAR and MNAR simulation procedure did not generate a good approximation for nonignorable missing data. The MAR and MNAR observations were simulated in accordance with Little and Rubin's definitions of these nonresponse mechanisms, which are that MAR missingness is dependent on the observed responses and/or covariates, and MNAR missingness is dependent on unobserved responses. These definitions were implemented for the current study by using a threshold NMB_{λ} criterion. One possible issue with a threshold criterion in conjunction with the data simulation procedure is that variance was built into the imputed baseline NMB, and a threshold criteria for defining nonresponse could result in setting some assessments to missing even if there had not been changes from baseline. Although visual inspection of the mean *NMBs* overtime showed distinctive patterns that resulted from the two nonresponse mechanism algorithms, it cannot be known if the algorithms produced good approximations of MAR and MNAR that would occur in a real dataset.

Numerous alternative implementations to a threshold criterion for the MAR and MNAR nonresponse mechanisms could have been used. For example, Oostenbrink & Al (2005) based MAR missing data on *changes* (rather than a threshold) in costs and effectiveness between time periods, and MNAR missing data on *changes* that occurred after dropout rather than before. Other possible implementations could have combined various changes in *NMB* with various threshold values. Because the time-to-dropout in this study was significantly correlated with the trajectory of the response, an alternative implementation based on change from baseline for the MAR and MNAR nonresponse mechanisms was investigated in a post-hoc analysis. MAR missing involved setting all

observations to missing that occurred subsequent to an NMB_{50000} change from baseline greater than \$2000. MNAR missing was the same as MAR except the observation with the NMB_{50000} change from baseline greater than \$2000 was set to missing, in addition to all subsequent observations. A result from this implementation is there could be no simulated MAR missing at month 4, however, there could be MNAR missing at this time point. Change from baseline of \$2000 was selected because this value maintained approximately the same proportion of missing data as in the base case.

Figure 5.1 shows the missingness pattern resulting from the post-hoc simulation of MAR and MNAR. Although the missingness mechanism was based on change from baseline (i.e., a trajectory), the resulting pattern is not as clear with regard to slope as the pattern that came out of the base case with a threshold criterion. Estimated $INMB_{\lambda}$ from the three models using the post-hoc simulation dataset are presented in Table 5.1. The joint ME model at all levels of λ clearly produced the best estimates of $INMB_{\lambda}$ on the criteria of bias and precision, and the ANCOVA model produced the worst estimates. Figure 5.2 illustrates results from the models with a set of cost-effectiveness acceptability curves. The curves show how the estimates of $INMB_{\lambda}$ from the joint ME most closely predict the true probability of cost-effectiveness along the full range of λ from \$0 to \$100000. The post-hoc analysis results align with what was expected to occur under circumstances of nonignorable missingness.

Figure 5.1 Mean observed NMB_{50000} for cohorts defined by pattern of missing data, post-hoc simulation of MAR and MNAR

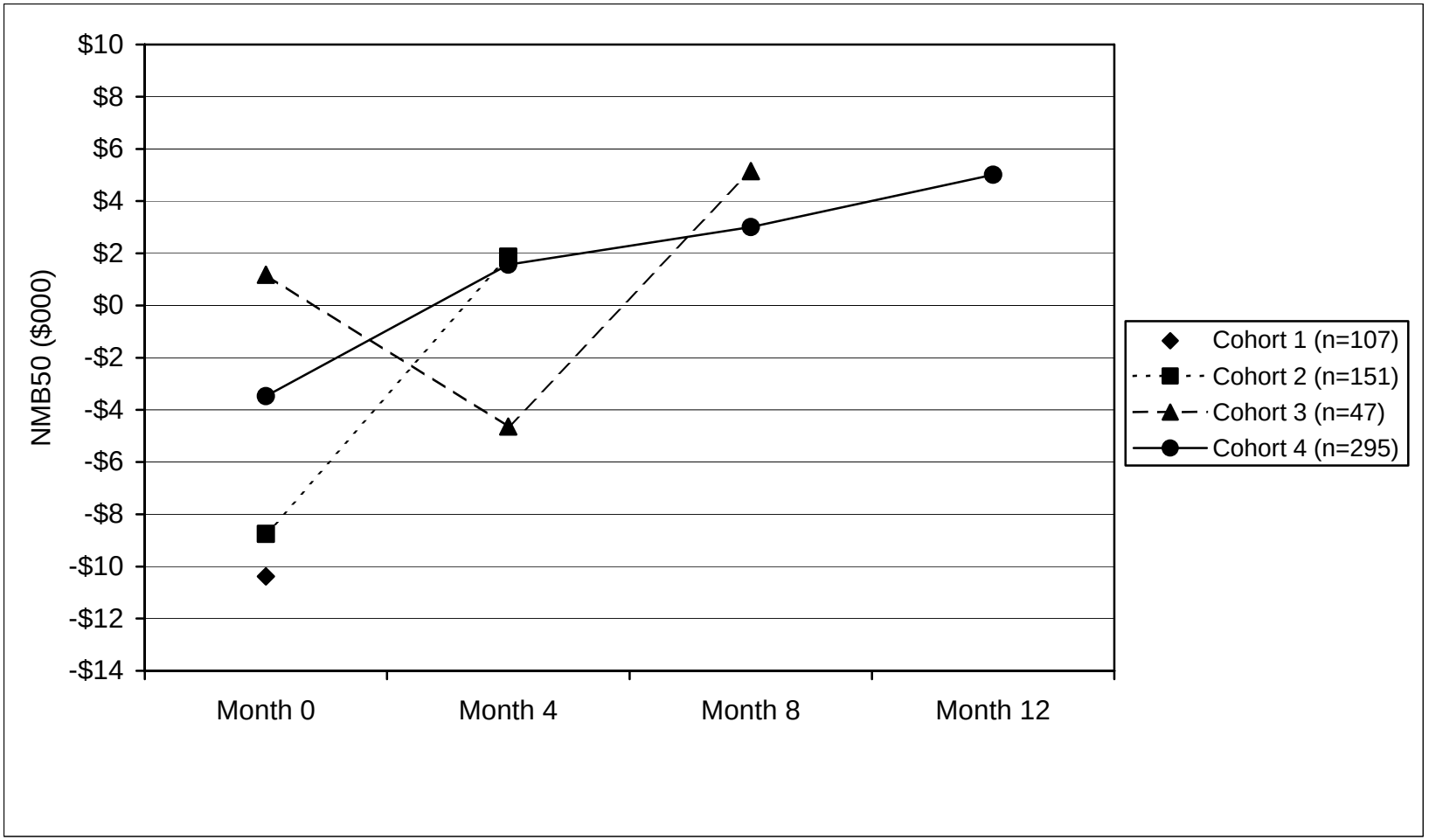

Figure 5.2 Cost-effectiveness Acceptability Curves: Model Results Compared to Complete Data, Post-hoc Analysis

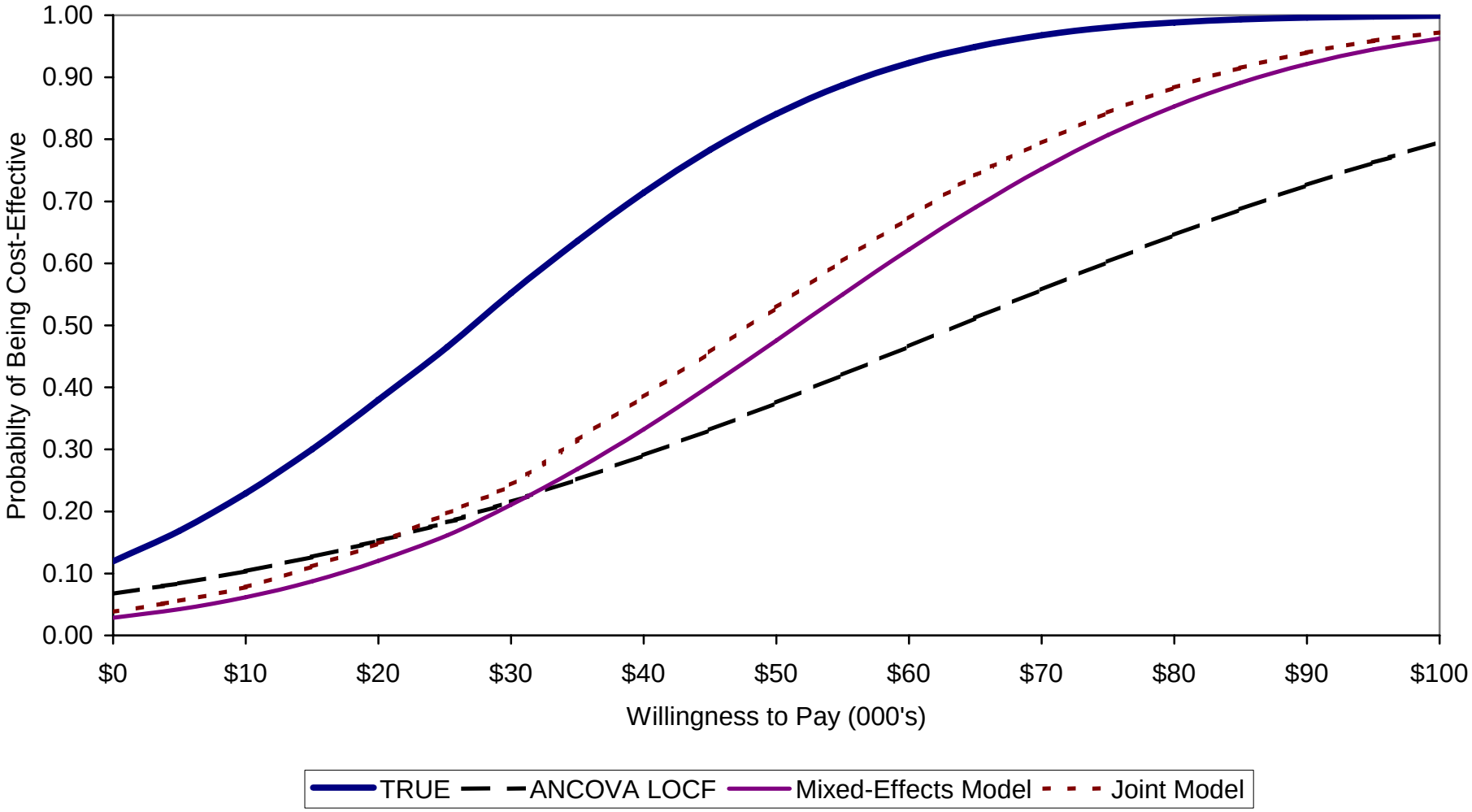

Table 5.1 Total annual $\hat{NMB}_\lambda$, $\hat{INMB}_\lambda$, and bias from complete data $INMB_\lambda$, post-hoc analysis

Λ		$\hat{INMB}_\lambda$ ($) (s.e.)	p value	Bias	Precision
$0	ANCOVA	-5,119.2 (3,411.3)	0.13	2,419.2	2.21
	ME	-5,264.0 (2,760.1)	0.06	2,564.0	1.45
	Joint ME	-4,878.6 (2,750.6)	0.08	2,178.6	1.20
	Complete data [a]	-2,700.0 (2,292.3)	0.24	--	--
$25000	ANCOVA	-3,110.1 (3,432.0)	0.37	2,909.1	2.24
	ME	-2,716.6 (2,746.1)	0.32	2,515.6	1.44
	Joint ME	-2,336.1 (2,737.6)	0.39	2,135.1	1.19
	Complete data [a]	-201.0 (2,292.1)	0.93	--	--
$50000	ANCOVA	-1,101.1 (3,458.3)	0.75	3,400.1	2.25
	ME	-166.8 (2,744.2)	0.95	2,465.8	1.42
	Joint ME	199.6 (2,734.9)	0.94	2,099.4	1.19
	Complete data [a]	2,299.0 (2,302.8)	0.32	--	--
$100000	ANCOVA	2,916.7 (3,530.0)	0.41	4,381.3	2.25
	ME	4,940.4 (2,771.5)	0.08	2,357.6	1.38
	Joint ME	5,314.8 (2,764.2)	0.06	1,983.2	1.17
	Complete data [a]	7,298.0 (2,355.6)	<0.01	--	--

(See Appendix II.P for ANCOVA model; Appendix II.Q for ME model; and Appendix II.R for Joint ME model SAS code.)

Dr. Fairclough (in a personal correspondence, February 2008) had cautioned that the joint model might have convergence problems with simulated data based on a threshold criterion. The reason for this was that the correlations among the random effects for NMB intercept and slope and the log of time-to-dropout might be too small for the model to converge. The correlations were significant, yet it was necessary to set one of the pairs of correlations (the correlation between the random effect for NMB intercept) to zero in order for the base case model to converge. Small correlations among these model parameters will pose an implementation barrier for a joint ME model, regardless of simulation criteria.

In her book, *Design and Analysis of Quality of Life Studies in Clinical Trials*, Dr. Fairclough discusses how selection model estimates are not robust to model

misspecification. She says, "…the lack of significant correlation implies that the missing data are ignorable *only if the model for dropout is correct*. If dropout was the result of a sudden change in the outcome rather than a gradual change (as measured by slopes), then the dropout model is misspecified and would not identify the nonignorable process." (Note: "Sudden change" could be implemented with a threshold criterion, and "gradual change" with a change or trajectory criterion.) The problem essentially is that the validity of the nonresponse mechanism component of the model is untestable because missing response is included as an explanatory variable. The comparison of base case and post-hoc results confirms that these estimation models are sensitive to the non-response mechanism. The challenge for analysis of actual clinical trial data is that the non-response mechanism is always unobserved, and these estimation models require strong assumptions concerning the unobserved nonreponse mechanism. Thus, the researcher can only conclude that, "If the non-response mechanism is thus, then this model provides a good estimate of the treatment effect." The researcher should never conclude that , "Because these estimates of treatment effect are good, then we can say that the non-response mechanism is thus." To draw this conclusion would be to make the Fallacy of Affirming the Consequent.

An additional lesson from the post-hoc analysis was that Rubin and Little's definitions of MAR and MNAR missingness may not sufficiently describe these nonresponse mechanisms. The definitions are so vague that they can be interpreted and implemented as thresholds, changes, hybrids of threshold and changes, or other. The true MAR and MNAR mechanisms are undoubtedly complex and are probably unique to each disease and clinical trial. Nevertheless, the definitions should be updated to at least

involve consideration for change in response overtime. An examination of these definitions could easily be the topic of another thesis.

A few issues in the current study need to be addressed. First, the dependent variable (*NMB*) was not normally distributed in this sample size of 600, even though its statistical properties suggest that it should be. The *NMB* probably would have been normally distributed in a larger sample, however, the sample size was chosen to be more representative of a typical clinical trial. Second, a log transformation of the *NMB* was not possible because the values of *NMB* can be less than zero. There are no transformations that work well on such variables, which is a potential methodological limitation to using the *NMB* in regression models. However, in regression analysis, it is not as important for the dependent variable be normally distributed as it is for the residual errors to be. In the current study, the residual errors were approximately normally distributed in each of the models. Last, the current study only addressed monotone patterns of missing. Monotone and intermittent patterns of missing are more likely to occur in clinical trials. Fairclough (2002) references a likelihood method described by Troxel (1997) that uses a Markovian correlation structure in a logistic model for analyzing intermittent patterns of missing.

A few additional findings from the current study are worth noting. The study provides further support for using the incremental net monetary benefit as an alternative to the incremental cost-effectiveness ratio in clinical trials. The response variable, *NMB*, can be used to assess cost-effectiveness in a regression model framework that may include treatment effect, covariates, and interactions between covariates and treatment effect. Cost-effectiveness from an analysis with the *NMB*, therefore, incorporates these effects as the linear combination of the parameter estimates involving treatment effect.

If a traditional ICER is desired, this measure can be derived from the CEAC at the willingness to pay level where probability of being cost-effective is 50 percent, i.e., where there is no treatment effect difference in net monetary benefit. (This point can be understood in terms of the *INMB*: there is no treatment effect difference when $\lambda\Delta\overline{E} - \Delta\overline{C} = 0$, or when $\lambda\Delta\overline{E} = \Delta\overline{C}$, or when $\lambda = \overline{\Delta C} / \overline{\Delta E} = \hat{ICER}$.)

The current study carefully examined the dropout patterns of patients with schizophrenia. The dropout pattern among the ROSE Study outpatient subgroup was suggestive of informative dropout, however, the pattern was very different from patterns that have been reported from cancer trials. An important first step in the analysis of longitudinal clinical trial data should be to examine the dropout patterns. Understanding how the disease and its treatments affect patients may help with the interpretation of the dropout patterns and how to model the nonresponse mechanism. Finally, this study illustrated how high proportions of missing data can dramatically alter unadjusted response values, and how different analytic approaches vary in their ability to produce good estimates under those data conditions. This is an important finding that has been reported in many published studies.

In conclusion, this study was the first to assess incremental net monetary benefit using simulated clinical trial data with monotone MAR and MNAR nonresponse mechanisms. The study demonstrated how the joint ME model can provide improved estimates of the $INMB_\lambda$ over ANCOVA and repeated measures ME models, but that the estimates are sensitive to the nonresponse mechanism. The study provides additional support for the use of the incremental net monetary benefit as an alternative to the traditional incremental cost-effectiveness ratio for assessing cost-effectiveness in clinical

trials. Moreover, selection models may be appropriate for evaluating *INMB* if there is good evidence of nonignorable missing data. When simulated MAR and MNAR nonresponse mechanisms are used in future simulation studies, careful consideration should be given to the definitions and implementation of these mechanisms. Further research is needed to examine and expand upon the definitions of MAR and MNAR nonresponse mechanisms that were first established by Rubin in 1976.

APPENDIX I. ABBREVIATIONS

AMCP	American Academy of Managed Care Pharmacy
ANCOVA	Analysis of covariance
b0	intercept term (SAS code)
b1	treatment group (SAS code)
b2	Month (SAS code)
b3	month interacted with treatment group (SAS code)
b4	month 4 (SAS code)
b5	month 4 interacted with treatment group (SAS code)
b6	month 8 (SAS code)
b7	month 8 interacted with treatment group (SAS code)
b8	age, centered at 40 (SAS code)
b9	previous hospitalizations (SAS code)
BL_NMB	variable name for baseline net monetary benefit
BPRSS	Brief Psychiatric Rating Scale Schizophrenia
C	cost measure
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CED	coverage with evidence development
CUA	cost-utility analysis
D22	variance of the random effect of the between patient NMB slope in the

	joint ME model (SAS code)
D2t	covariance between the random slopes and time-to-dropout for the joint ME model (SAS code)
E	effectiveness measure
EM algorithm	expectation maximization algorithm
GROUP	variable name for treatment group
ICER	incremental cost-effectiveness ratio
INMB	incremental net monetary benefit
ITT	intent-to-treat
Lambda 1 & 2	coefficients for the random effects in the time portion of the joint ME model (SAS code)
LOCF	last observation carried forward
LVCF	last value carried forward
LYG	life years gained
MAR	missing at random
MCAR	missing completely at random
MCS	mental component summary (of the SF-36)
ME	mixed-effects
MLR	maximum likelihood ratio
MNAR	missing not at random
mu0	joint ME model's fixed effect for the log time-of-dropout mean intercept (SAS code)
NHS	National Health Service

NICE	National Institute for Clinical Excellence
NMB	net monetary benefit
OLS	ordinary least squares
PHOSP	variable name for indicator of number of previous hospitalizations
PPP	purchasing power parity
QALY	quality-adjusted life year
QOL	quality of life
RH02T	correlation between NMB slope random effect and log time-to-dropout in the joint ME model (SAS code)
ROSE	Risperidone Outcomes Study of Effectiveness
s1, s12, s2	components of the Cholesky decomposition of the covariance matrix for the random effects in the joint ME model (SAS code)
s2t	residual error (variance) for log time-to-dropout in the joint ME model – same as Tau2 (SAS code)
s2w	variance of the residual error of NMB in the joint ME model (SAS code)
SD	standard deviation
s.e.	standard error
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SEE	standard error for the estimator
SG	standard gamble
Tau2	residual error (variance) for log time-to-dropout in the joint ME model, same as s2t (SAS code)

T_0	treatment group: standard of care
T_1	treatment group: experimental
USPHSP	U.S. Public Health Service Panel

APPENDIX II. SAS CODE

A. ANCOVA MODEL

```
  *  Program:      LOCF.SAS                                              ;
  *  Description:  This program reads the COMPLETE dataset and the       ;
  *  MISSING dataset and creates an LOCF dataset.  Baseline is           ;
  *  brought forward if there is not follow-up.                          ;
  *  Programmer:   Dennis D. Gagnon                                      ;
  *  Date:         02/24/2008                                            ;

libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat' ;
options pageno=1 ps=46 ls=150 center errors=2 ;
title 'LOCF.SAS                          Dissertation: Estimating INMB in
a Clinical Study With Missing Data' ;

  proc sort data=indat.complete out=complete(keep=patid month txgroup
age40 prevhospc month04 month08) ;
    by patid month ;
  run ;
  proc sort data=indat.missing out=missing ;
    by patid month ;
  run ;

  data full ;
    merge complete missing ;
      by patid month ;
  run ;

  proc print data=full(firstobs=2369) ;
    title3 'Last Observations of Full, Starting at 2369' ;
  run ;
  data locf ;
    set full ;
      by patid month ;
      array last {6} lc lu l0 l25 l50 l100 ;
      array current {6} cost util nmb_0 nmb_25 nmb_50 nmb_100 ;
      retain lc lu l0 l25 l50 l100 ;
      if first.patid then do ;
        do i = 1 to 6 ;
          last{i} = . ;
        end ;
      end ;
      do i = 1 to 6 ;
        if current{i} = . then current{i} = last{i} ;
      end ;
      do i = 1 to 6 ;
        last{i} = current{i} ;
      end ;
      drop i lc lu l0 l25 l50 l100 ;
  run ;

  proc print data=locf(firstobs=2369) ;
    title3 'Last Observations of LOCF, Starting at 2369' ;
  run ;
```

```
data indat.locf ;
  set locf ;
run ;

proc contents data=indat.locf ;
  title3 'Contents of LOCF' ;
run ;

proc print data=indat.locf(obs=20) ;
  title3 'First 20 Observations of LOCF' ;
run ;
```

A. ANCOVA MODEL (continued)

```
  *  Program:      Subject LOCF.SAS                                    ;
  *  Description:  This program reads the LOCF Dataset and creates a;
  *  subject-level complete dataset.  NMBs are summed across months ;
  *  4, 8, & 12.                                                       ;
  *  Programmer:   Dennis D. Gagnon                                    ;
  *  Date:         02/24/2008                                          ;
  libname indat  'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Subject LOCF.SAS                          Dissertation:
Estimating INMB in a Clinical Study With Missing Data' ;
  proc sort data=indat.locf out=locf (rename=(nmb_0=n_0 nmb_25=n_25
nmb_50=n_50 nmb_100=n_100)) ;
    by patid month ;
  run ;
  proc print data=locf(obs=20) ;
    title3 'First 20 Observations of LOCF' ;
  run ;

  data indat.subject_locf ;
    set locf ;
      by patid month ;
      retain nmb_0 nmb_25 nmb_50 nmb_100 bln0 bln25 bln50 bln100 0 ;
      array nmb{4} nmb_0 nmb_25 nmb_50 nmb_100 ;
      array bl{4} bln0 bln25 bln50 bln100 ;
      array nm{4} n_0 n_25 n_50 n_100 ;
      if first.patid then do ;
        do i=1 to 4 ;
          nmb{i} = 0 ;
            bl{i} = 0 ;
        end ;
    end ;
      if month = 0 then do ;
        do i=1 to 4 ;
          bl{i} = nm{i} ;
        end ;
      end ;
      else do ;
      do i=1 to 4 ;
          nmb{i} = nmb{i} + nm{i} ;
        end ;
      end ;
      drop i util cost month n_0 n_25 n_50 n_100 month month04 month08
;
      if last.patid then output ;
  run ;

  proc contents data=indat.subject_locf ;
    title3 'Contents of Subject_LOCF' ;
  run ;

  proc print data=indat.subject_locf(obs=20) ;
    title3 'First 20 Observations of Subject_LOCF' ;
  run ;
```

A. ANCOVA MODEL (continued)

```
*  Program: UNI LOCF, Mean BL.SAS                                    ;
*  Description:  This program creates the ANCOVA model estimates ;
*  by reading the SUBJECT_LOCF dataset and running analyses to   ;
*  determine the INMB. First a t-test is run,                    ;
*  then a simple GLM with no covariates, then GLMs with age40,   ;
*  previous hosps and baseline nmb. Baseline nmb is centered at  ;
*    the mean. Regressions modified to change categorical variables   ;
*  to numeric.  LS Means have been changed to ESTIMATE statements.;
*  Output residuals from ANCOVAs and plot them against the normal ;
*  curve. Plot NMBs against the normal curve.                    ;
*  Programmer:   Dennis D. Gagnon                                ;
*  Date: 06/15/2008                                              ;
  libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Uni LOCF, Mean BL.SAS                      Dissertation:
Estimating INMB in a Clinical Study With Missing Data' ;
  proc print data=indat.subject_locf(obs=20) ;
    title3 'First 20 Observations of Subject_LOCF' ;
  run ;

  proc means data=indat.subject_locf ;
    var bln0 bln25 bln50 bln100 txgroup age40 prevhospc ;
      title3 'Mean Baseline NMBs' ;
  run ;

  data subject_locf ;
    set indat.subject_locf ;
      bln0   = bln0   - -15.9882591 ;
      bln25  = bln25  - -10.8275510 ;
      bln50  = bln50  -  -5.6668430 ;
      bln100 = bln100 -   4.6545730 ;
  run ;

  proc ttest data=subject_locf ;
    class txgroup ;
      var nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 'T-Tests on LOCF Difference in Mean NMBs, Complete Data
Set' ;
  run ;

  proc glm data=subject_locf ;
      model nmb_0 = txgroup / solution ;
      estimate 'Tx=0' intercept 1 ;
      estimate 'Tx=1' intercept 1 txgroup 1 ;
      estimate 'Diff'             txgroup 1 ;
      title3 'OLS of NMB0 Against Treatment Only, LOCF' ;
  run ;

  proc glm data=subject_locf ;
      model nmb_25 = txgroup / solution ;
      estimate 'Tx=0' intercept 1 ;
      estimate 'Tx=1' intercept 1 txgroup 1 ;
      estimate 'Diff'             txgroup 1 ;
      title3 'OLS of NMB25 Against Treatment Only, LOCF' ;
  run ;
```

```
proc glm data=subject_locf ;
    model nmb_50 = txgroup / solution ;
    estimate 'Tx=0' intercept 1 ;
    estimate 'Tx=1' intercept 1 txgroup 1 ;
    estimate 'Diff'             txgroup 1 ;
    title3 'OLS of NMB50 Against Treatment Only, LOCF' ;
run ;

proc glm data=subject_locf ;
    model nmb_100 = txgroup / solution ;
    estimate 'Tx=0' intercept 1 ;
    estimate 'Tx=1' intercept 1 txgroup 1 ;
    estimate 'Diff'             txgroup 1 ;
    title3 'OLS of NMB100 Against Treatment Only, LOCF' ;
run ;

proc glm data=subject_locf ;
    model nmb_0 = txgroup age40 prevhospc bln0 / solution ;
    output out=nmb0 r=resid ;
    estimate 'Tx=0' intercept 1 ;
    estimate 'Tx=1' intercept 1 txgroup 1 ;
    estimate 'Diff'             txgroup 1 ;
    title3 'OLS of NMB0 Against Treatment And Covariates, LOCF' ;
    title5 'Baseline NMB Centered at Mean' ;
run ;

proc glm data=subject_locf ;
    model nmb_25 = txgroup age40 prevhospc bln25 / solution ;
    output out=nmb25 r=resid ;
    estimate 'Tx=0' intercept 1 ;
    estimate 'Tx=1' intercept 1 txgroup 1 ;
    estimate 'Diff'             txgroup 1 ;
    title3 'OLS of NMB25 Against Treatment And Covariates, LOCF' ;
    title5 'Baseline NMB Centered at Mean' ;
run ;

proc glm data=subject_locf ;
    model nmb_50 = txgroup age40 prevhospc bln50 / solution ;
    output out=nmb50 r=resid ;
    estimate 'Tx=0' intercept 1 ;
    estimate 'Tx=1' intercept 1 txgroup 1 ;
    estimate 'Diff'             txgroup 1 ;
    title3 'OLS of NMB50 Against Treatment And Covariates, LOCF' ;
    title5 'Baseline NMB Centered at Mean' ;
run ;

proc glm data=subject_locf ;
    model nmb_100 = txgroup age40 prevhospc bln100 / solution ;
    output out=nmb100 r=resid ;
    estimate 'Tx=0' intercept 1 ;
    estimate 'Tx=1' intercept 1 txgroup 1 ;
    estimate 'Diff'             txgroup 1 ;
    title3 'OLS of NMB100 Against Treatment And Covariates, LOCF' ;
    title5 'Baseline NMB Centered at Mean' ;
run ;
quit ;
```

```
title ;

PROC CAPABILITY DATA=nmb0 GRAPHICS;
  title3 'Residual Histogram from ANCOVA, Lambda 0' ;
  HISTOGRAM resid / NORMAL;
    var resid ;
RUN;

PROC CAPABILITY DATA=nmb25 GRAPHICS;
  title3 'Residual Histogram from ANCOVA, Lambda 25' ;
  HISTOGRAM resid / NORMAL;
    var resid ;
RUN;

PROC CAPABILITY DATA=nmb50 GRAPHICS;
  title3 'Residual Histogram from ANCOVA, Lambda 50' ;
  HISTOGRAM resid / NORMAL;
    var resid ;
RUN;

PROC CAPABILITY DATA=nmb100 GRAPHICS;
  title3 'Residual Histogram from ANCOVA, Lambda 100' ;
  HISTOGRAM resid / NORMAL;
    var resid ;
RUN;

PROC CAPABILITY DATA=subject_locf GRAPHICS;
  title3 'Histogram of Subject-Level NMB, Lambda 0' ;
  HISTOGRAM nmb_0 / NORMAL;
    var nmb_0 ;
RUN;

PROC CAPABILITY DATA=subject_locf GRAPHICS;
  title3 'Histogram of Subject-Level NMB, Lambda 25' ;
  HISTOGRAM nmb_25/ NORMAL;
    var nmb_25 ;
RUN;

PROC CAPABILITY DATA=subject_locf GRAPHICS;
  title3 'Histogram of Subject-Level NMB, Lambda 50' ;
  HISTOGRAM nmb_50 / NORMAL;
    var nmb_50 ;
RUN;

PROC CAPABILITY DATA=subject_locf GRAPHICS;
  title3 'Histogram of Subject-Level NMB, Lambda 100' ;
  HISTOGRAM nmb_100 / NORMAL;
    var nmb_100 ;
RUN;
```

B. ME MODEL

```
  *  Program:      MAR_Miss.SAS                                        ;
  *  Description:  This program creates the ME model estimates by;
  *  reading the MISSING dataset and creating the                      ;
  *  month & month knot variables (one knot at month                   ;
  *  4 and one know at month 8). A mixed effects model is then         ;
  *  run estimating the difference in the changes in NMB from          ;
  *  baseline across treatment groups. This program uses the data;
  *  simulated from Dr. Fairclough. NMB are divided by 1000.           ;
  *  Predicted values are output from each model and residual          ;
  *  are created. These residuals are then plotted against a           ;
  *  normal curve.                                                     ;
  *  Programmer:   Dennis D. Gagnon                                    ;
  *  Date:         06/22/2008                                          ;
  libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'MAR_Miss.SAS                    Dissertation: Estimating INMB
in a Clinical Study With Missing Data' ;
  proc print data=indat.missing(obs=20) ;
    title3 'First 20 Observations of Missing' ;
  run ;

  data missing ;
    set indat.missing ;
  run ;

  proc print data=missing(obs=20) ;
    title3 'Print of Missing with Month and Knots at Months 4 and 8
Derived' ;
  run ;

  *  Start Running of Mixed Models ;
  *  NMB_0 ;

  proc mixed data=missing covtest noclprint ;
    model NMB_0= age40 prevhospC txgroup month month*txgroup
                   month04 month04*txgroup month08 month08*txgroup
                  /solution outp=nmb0 ;
    random intercept month / subject = patid type =UN gc g gcorr v
vcorr ;

    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
   estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
```

```
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8

month08 4 month08*txgroup 4 ;
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
      estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12
month08 4 ;
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12

month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;

    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_0' ;
  run ;

  *  NMB_25 ;

  proc mixed data=missing covtest noclprint ;
    model NMB_25= age40 prevhospC txgroup month month*txgroup
                    month04 month04*txgroup month08 month08*txgroup
                   /solution outp=nmb25 ;
    random intercept month / subject = patid type =UN gc g gcorr v
vcorr;

    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
```

```
   estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8

month08 4 month08*txgroup 4 ;
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
      estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12
month08 4 ;
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12

month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;

    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_25' ;
  run ;

  *  NMB_50 ;

  proc mixed data=missing covtest noclprint ;
    model NMB_50= age40 prevhospC txgroup month month*txgroup
                     month04 month04*txgroup month08 month08*txgroup
                    /solution outp=nmb50 ;
 random intercept month / subject = patid type =UN gc g gcorr v vcorr;

    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
```

```
   estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8

month08 4 month08*txgroup 4 ;
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
      estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12
month08 4 ;
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12

month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;

    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_50' ;
  run ;

  *  NMB_100 ;

  proc mixed data=missing covtest noclprint ;
    model NMB_100= age40 prevhospC txgroup month month*txgroup
                    month04 month04*txgroup month08 month08*txgroup
                   /solution outp=nmb100 ;
    random intercept month / subject = patid type =UN gc g gcorr v
vcorr;

    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
```

```
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
   estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8

month08 4 month08*txgroup 4 ;
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
      estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12
month08 4 ;
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12

month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;

    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_100' ;
  run ;

  data nmb0 ;
    set nmb0 ;
      keep resid ;
  run ;

  data nmb25 ;
    set nmb25 ;
      keep resid ;
  run ;

  data nmb50 ;
    set nmb50 ;
      keep resid ;
  run ;

  data nmb100 ;
    set nmb100 ;
      keep resid ;
  run ;
```

```
title ;

PROC CAPABILITY DATA=nmb0 GRAPHICS;
 title3 'Histogram of Residuals from Mixed-Effects Model, Lambda 0' ;
  HISTOGRAM resid / NORMAL midpoints=-100 to 52 by 4 ;
    var resid ;
RUN;

PROC CAPABILITY DATA=nmb25 GRAPHICS;
title3 'Histogram of Residuals from Mixed-Effects Model, Lambda 25' ;
  HISTOGRAM resid / NORMAL midpoints=-100 to 52 by 4 ;
    var resid ;
RUN;

PROC CAPABILITY DATA=nmb50 GRAPHICS;
title3 'Histogram of Residuals from Mixed-Effects Model, Lambda 50' ;
  HISTOGRAM resid / NORMAL midpoints=-100 to 52 by 4 ;
    var resid ;
RUN;

PROC CAPABILITY DATA=nmb100 GRAPHICS;
title3 'Histogram of Residuals from Mixed-Effects Model, Lambda 100' ;
  HISTOGRAM resid / NORMAL midpoints=-100 to 52 by 4 ;
    var resid ;
RUN;
```

C. JOINT ME MODEL

```
  *  Program:  Joint_Miss.SAS                                          ;
  *  Description:  This program creates the joint ME model             ;
  *  estimates, by first obtaining estimates from the                  ;
  *  seperate models and then jointly estimates the parameters         ;
  *  Programmer:   Diane Fairclough                                    ;
  *  Date:         20/Dec/2007                                         ;
  *  Revised:      Dennis D. Gagnon                                    ;
  *  Date:         03/08/08                                            ;
  *  Revised:      Diane Fairclough                                    ;
  *  Date:         21Mar2008                                           ;
  *                Removed intercept random effect from Time to        ;
  *                DO model                                            ;
  *  Revised:      Dennis G. Gagnon                                    ;
  *  Date:         06/17/08                                            ;
  *                Add code sent by Diane Fairclough to print          ;
  *                out variance and correlation estimates.             ;
  *                (D11, D12, D22, Tau2, D1T, D2T, Rho1T, Rho2T        ;
  libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  *libname indat 'C:\Projects\Consult\Engelhart\SASlib' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;

  title 'Joint_Miss.SAS    Dissertation: Estimating INMB in a Clinical
Study With Missing Data' ;
  ****************************************************************
  PREPARE DATA ;

  proc print data=indat.missing(obs=20) ;
    title3 'First 20 Observations of Missing' ;
  run ;

proc summary data=indat.missing nway;  * Identifies time of last obs *;
    class patid;
      var month ;
      output out=work.last max=Last;
      run;

  proc freq data=work.last;
    table last/missing;
      run;

  data missing ;
    merge indat.missing work.last(keep=patid last);
      by patid;
      *** Time to last Assessment ***;
      if last eq 12 then Censor=1;
    else censor=0;
      L_Last=log(last+1);
      Label Censor='Completor (1=Yes, 0=No)'
            L_Last='Ln(Time to Last Obs + 1)';
  run ;

  proc print data=missing (obs=20);
    title3 'Print of Missing with Month and Knots at Months 4 and 8
Derived' ;
  run ;
```

```
*************************************************************************
  GET ESTIMATES FOR MU and SCALE (SAME FOR ALL NMBs ;

*** Initial Estimates for Time to DO portion of model ***;
proc lifereg data=work.missing;
  model L_last*Censor(1)=/ dist=normal; * Used Normal because already
logged *;
  where month eq 0;
  title3 'Estimate Mu and Scale' ;
run;
*************************************************************************
NMB_0 ;

*** Reference Model ***;
proc nlmixed data=work.missing ;
  title3 'Longitudinal and Time to Event with No correlation, NMB_0';
  where nmb_0 ne .;  * Proc does not deal well with missing values *;

  parms b0=-16.0633 b1=0.1251 b2=1.6403 b3=-0.2719 b4=-1.2449 b5=0.1560
b6=-0.0761 b7=0.0694 b8=0.0326 b9=-2.9063
        s1=16.9781 s12=-1.4833 s2=0.5905 s2w=137.27
        mu0=3.3075 st=1.695 lambda2=0;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_0-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_0 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
```

```
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;

  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                  ;

  estimate 'D11' D11;   *Var of between patient NMB intercept;

  estimate 'D12' D12;   *Covar of between patient NMB intercept and
slope;

  estimate 'D22' D22;   *Var of between patient NMB slope;

  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;

  estimate 'Tau2' lambda2**2*D22 + S2t;         *Residual error for log
time to dropout;

  *estimate 'D1T' lambda1*D11+Lambda2*D12;

  *estimate 'D2T' lambda1*D12+Lambda2*D22;

  estimate 'D2T' Lambda2*D22;                          *;

  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/

  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));

  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/

  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));

  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));      *Correlation between log time to dropout and NMB slope;

  run;

*** Joint Model with Two Random Effects ***;
*** Note this does not converge ... ****;
proc nlmixed data=work.missing ;
  title3 'Joint Longitudinal and Time to Event, NMB_0';
  where nmb_0 ne .;  * Proc does not deal well with missing values *;

  parms b0=-16.0633 b1=0.1251 b2=1.6403 b3=-0.2719 b4=-1.2449 b5=0.1560
b6=-0.0761 b7=0.0694 b8=0.0326 b9=-2.9063
        s1=16.9781 s12=-1.4833 s2=0.5905 s2w=137.27
        mu0=3.3075 st=1.695 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;

  *** Mixed effect Model for longitudinal outcome***;
```

```
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_0-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0  +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_0 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;

  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                  ;

  estimate 'D11' D11;

  estimate 'D12' D12;

  estimate 'D22' D22;

  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;

  estimate 'Tau2' lambda2**2*D22 + S2t;

  *estimate 'D1T' lambda1*D11+Lambda2*D12;

  *estimate 'D2T' lambda1*D12+Lambda2*D22;

  estimate 'D2T' Lambda2*D22;

  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/

  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
```

```
  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/

  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));

  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));
  run;
*************************************************************************
NMB_25 ;

*** Reference Model ***;
proc nlmixed data=work.missing;
  title3 'Longitudinal and Time to Event with No correlation, NMB_25';
  where nmb_25 ne .;  * Proc does not deal well with missing values *;

  parms b0=-10.9299 b1=0.1352 b2=1.6700 b3=-0.0707 b4=-1.2769 b5=-
0.0389 b6=-0.0746 b7=0.0674 b8=0.0250 b9=-3.0673
        s1=16.9721 s12=-1.5019 s2=0.5928 s2w=137.61
        mu0=3.3075 st=1.695 lambda2=0;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_25-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_25 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;
```

```
  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                  ;

  estimate 'D11' D11;

  estimate 'D12' D12;

  estimate 'D22' D22;

  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;

  estimate 'Tau2' lambda2**2*D22 + S2t;

  *estimate 'D1T' lambda1*D11+Lambda2*D12;

  *estimate 'D2T' lambda1*D12+Lambda2*D22;

  estimate 'D2T' Lambda2*D22;

  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/

  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));

  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/

  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));

  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));

  run;
*** Joint Mdel with Two Random Effects ***;
proc nlmixed data=work.missing;
  title3 'Joint Longitudinal and Time to Event, NMB_25';
  where nmb_25 ne .;  * Proc does not deal well with missing values *;

  parms b0=-10.9299 b1=0.1352 b2=1.6700 b3=-0.0707 b4=-1.2769 b5=-
0.0389 b6=-0.0746 b7=0.0674 b8=0.0250 b9=-3.0673
        s1=16.9721 s12=-1.5019 s2=0.5928 s2w=137.61
        mu0=3.3075 st=1.695 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_25-Pred)**2/s2w)/2;

  *** Time to Event ***;
```

```
  if month eq 0 then do;
    Pred_T=mu0 +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_25 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 + b2*24 + b4*12 + b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff' b1*3 + b3*24 + b5*12 +        b7*4 ;

  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                  ;

  estimate 'D11' D11;
  estimate 'D12' D12;
  estimate 'D22' D22;
  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;
  estimate 'Tau2' lambda2**2*D22 + S2t;
  *estimate 'D1T' lambda1*D11+Lambda2*D12;
  *estimate 'D2T' lambda1*D12+Lambda2*D22;
  estimate 'D2T' Lambda2*D22;
  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/
  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/
  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));   run;

*****************************************************************
NMB_50 ;
*** Reference Model ***;
proc nlmixed data=work.missing;
  title3 'Longitudinal and Time to Event with No correlation, NMB_50';
  where nmb_50 ne .;  * Proc does not deal well with missing values *;

  parms b0=-5.7967 b1=0.1453 b2=1.6968 b3=0.1285 b4=-1.3086 b5=-0.2339
b6=-0.0728 b7=0.0654 b8=0.0172 b9=-3.2265
        s1=16.9813 s12=-1.5202 s2=0.5983 s2w=138.56
        mu0=3.3075 st=1.695 lambda2=0;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
```

```
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_50-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_50 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;

  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                  ;

  estimate 'D11' D11;
  estimate 'D12' D12;
  estimate 'D22' D22;
  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;
  estimate 'Tau2' lambda2**2*D22 + S2t;
  *estimate 'D1T' lambda1*D11+Lambda2*D12;
  *estimate 'D2T' lambda1*D12+Lambda2*D22;
  estimate 'D2T' Lambda2*D22;
  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/
  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/
  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
```

```
  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));

  run;
*** Joint Mdel with Two Random Effects ***;
proc nlmixed data=work.missing ;
  title3 'Joint Longitudinal and Time to Event, NMB_50';
  where nmb_50 ne .;  * Proc does not deal well with missing values *;

  parms b0=-5.7967 b1=0.1453 b2=1.6968 b3=0.1285 b4=-1.3086 b5=-0.2339
b6=-0.0728 b7=0.0654 b8=0.0172 b9=-3.2265
        s1=16.9813 s12=-1.5202 s2=0.5983 s2w=138.56
        mu0=3.3075 st=1.695 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_50-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0 +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_50 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;

  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                  ;
  estimate 'D11' D11;
  estimate 'D12' D12;
  estimate 'D22' D22;
```

```
  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;
  estimate 'Tau2' lambda2**2*D22 + S2t;
  *estimate 'D1T' lambda1*D11+Lambda2*D12;
  *estimate 'D2T' lambda1*D12+Lambda2*D22;
  estimate 'D2T' Lambda2*D22;
  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/
  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/
  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));  run;

*****************************************************************
NMB_100 ;

*** Reference Model ***;
proc nlmixed data=work.missing;
  title3 'Longitudinal and Time to Event with No correlation, NMB_100';
  where nmb_100 ne .;  * Proc does not deal well with missing values *;

  parms b0=4.4688 b1=0.1653 b2=1.7504 b3=0.5291 b4=-1.3714 b5=-0.6239
b6=-0.0679 b7=0.0616 b8=0.0013 b9=-3.5388
        s1=17.0574 s12=-1.5562 s2=0.6197 s2w=142.21
        mu0=3.3075 st=1.695 lambda2=0;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_100-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_100 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;
```

```
  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;

  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                  ;

  estimate 'D11' D11;
  estimate 'D12' D12;
  estimate 'D22' D22;
  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;
  estimate 'Tau2' lambda2**2*D22 + S2t;
  *estimate 'D1T' lambda1*D11+Lambda2*D12;
  *estimate 'D2T' lambda1*D12+Lambda2*D22;
  estimate 'D2T' Lambda2*D22;
 *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/
  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/
  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));
  run;
*** Joint Mdel with Two Random Effects ***;
proc nlmixed data=work.missing;
  title3 'Joint Longitudinal and Time to Event, NMB_100';
  where nmb_100 ne .;  * Proc does not deal well with missing values *;

  parms b0=4.4688 b1=0.1653 b2=1.7504 b3=0.5291 b4=-1.3714 b5=-0.6239
b6=-0.0679 b7=0.0616 b8=0.0013 b9=-3.5388
        s1=17.0574 s12=-1.5562 s2=0.6197 s2w=142.21
        mu0=3.3075 st=1.695 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_100-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0 +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
```

```
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_100 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;

  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                    ;
  estimate 'D11' D11;
  estimate 'D12' D12;
  estimate 'D22' D22;
  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;
  estimate 'Tau2' lambda2**2*D22 + S2t;
  *estimate 'D1T' lambda1*D11+Lambda2*D12;
  *estimate 'D2T' lambda1*D12+Lambda2*D22;
  estimate 'D2T' Lambda2*D22;
  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/
  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/
  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));   run;
```

D. Build the Mixed Effects Model to Estimate the Joint Parameters for Costs and Utilities

```
  ****************************************************************;
  *  Program:      MAR_CostUtil.SAS                                ;
  *  Description:  This program jointly estimates Cost and Utility ;
  *  so that NMBs at different levels of lamba can be generated from ;
  *  a single dataset, for the simulation of the dataset           ;
  *                                                                ;
  *  Programmer:   Diane Fairclough                                ;
  *  Date:         18/Jan/2007                                     ;
  ****************************************************************;
  *libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  *libname indat 'H:\Consulting\Engelhart' ;
  libname indat 'C:\Projects\Consult\Engelhart' ;
  options pageno=1 ps=46 ls=150 center errors=2 nofmterr;
  title 'MAR_CostUtil.SAS' ;

  proc contents data=indat.missing2; * Missing dataset renamed *;
  run;
  proc print data=indat.missing2(obs=20);
  run;
  proc means data=indat.missing2;
     where month eq 0 and meas eq 2;
       var age prevhosp group;
       run;

* Estimate parameter estimates for cost to find the variables that;
* best predict log of cost. Start by creating indicator variables ;
* for cost and utilities, center variables, transform cost to log ;
  * cost, and rescale utilities to 10 X utilities. ;

 data work.missing2;
    set indat.missing2;
      visit=month;  * Allows One variable to be continous and the other
                      to be categorical *;
      Cost=(Meas eq 1);  * Indicator of Cost Data *;
      Util=(Meas eq 2);  * Indicator of Utility Data *;
      Age40=Age-40;      * Age Centered *;
      PrevHospC=PrevHosp-.5;  * PrevHosp Centered *;
      GroupC=Group-1.5;   * Group Centered;
      *** Log of Cost Data ***;
      if Meas eq 1 then LValue=log(Value+.1);
      *** Rescaled Utility ***;
      if Meas eq 2 then LValue=10*Value;
      *** Deletes Missing Data ***;
      if Value eq . then delete;
      run;

  proc means data=missing2 nway mean median stddev skewness;
     title 'Measure 1 (Cost) only';
     where meas eq 1;
       class group visit;
       var value LValue;
       run;
  proc univariate data=missing2 plot;
     title2 'Check Distribution of Log of Cost';
```

```
     where meas eq 1;
       var value LValue;
       run;
       title2 '  ';

  * Begin with full model for log cost to find independent variables;
  * that best predict log of cost.                                   ;
  * Note: The variable COST is always 1.  Although not necessary at ;
  * this point, the indicator will be useful in the joint model at  ;
  * the end of this program.                                         ;

  proc mixed data=work.missing2 method=ml noclprint covtest ;
      title2 'Full model for Log Cost';
       where meas eq 1;

       class PatID ;

       model LValue=Cost Cost*Age40 Cost*PrevHospc
             Cost*Month Cost*Month*GroupC Cost*Month*age40
Cost*Month*PrevHospC
                  Cost*Month08 Cost*GroupC*Month08
       /noint solution ;
      random Cost Cost*Month/subject=PatID type=UN g gcorr gc v=2
Vcorr=2;
        contrast 'Group' Cost*MOnth*GroupC 1, Cost*Month08*GroupC 1;
        contrast 'Month8' Cost*Month08 1, Cost*Month08*GroupC 1;
        run;

*** End with reduced model for log cost.   ;

  proc mixed data=work.missing2 method=ml noclprint covtest ;
      title2 'Reduced model for Log Cost';
       where meas eq 1;
       class PatID ;
       model LValue=Cost Cost*PrevHospc  Cost*Month
       /noint solution ;
      random Cost Cost*Month/subject=PatID type=UN g gcorr gc v=2
Vcorr=2;
        run;

  proc means data=missing2 nway;
      title 'Measure 2 (Utility) only';
     where meas eq 2;
       class group visit;
       var value;
       run;
  proc univariate data=missing2 plot;
     title2 'Check Distribution of Utility';
     where meas eq 2;
       var value;
       run;
       title2 '  ';

* Estimate parameter estimates for utilities to find the variables ;
*  that best predict utilities. Begin with full model for utilities.;
   proc mixed data=work.missing2 method=ml noclprint covtest ;
      title2 'Full Model for Utilities';
```

```
        where meas eq 2;

       class PatID ;

       model LValue=Util Util*age40 Util*PrevHospC
Util*Month Util*Month*GroupC
Util*Month*Age40 Util*Month*PrevHospC
                  Util*Month04 Util*Month04*GroupC
                  Util*Month08 Util*Month08*GroupC
       /noint solution ;
   random Util Util*Month/subject=PatID type=un g gcorr gc v=2 Vcorr=2;
   contrast 'Group Effects' Util*Month*GroupC 1, Util*Month04*GroupC 1,
              Util*Month08*GroupC 1;
      contrast 'Age Effects' Util*age40 1, Util*Month*Age40 1;
      contrast 'Prev Hosp'  Util*PrevHospC 1, Util*Month*PrevHospC 1;
      Contrast 'Month 8'   Util*Month08 1, Util*Month08*GroupC 1;
        Contrast 'Month 4'    Util*Month04 1, Util*Month04*GroupC 1;
      run;

*** End with reduced model for utilities.   ;

   proc mixed data=work.missing2 method=ml noclprint covtest ;
      title2 'Reduced Model for Utilities';
        where meas eq 2;
       class PatID ;
       model LValue=Util Util*age40
                  Util*Month Util*Month*PrevHospC
       /noint solution ;
      random Util Util*Month/subject=PatID type=un g gcorr gc v=2
Vcorr=2;
      run;

* Combine the reduced Log of Cost and Utilities models into one      *;
* mixed effects model to jointly estimate the parameters for the     *;
* fixed effects of age, previous hospitalizations, and month, and    *;
* the random effects of the covariance between intercept & slope.    *;
* The output datasets of parameter estimates, covariance parameters  *;
* and residuals for costs and utilities will be used in Step 2 of    *;
* the data simulation.                                               *;
  proc mixed data=work.missing2 method=ml noclprint covtest ;
       title 'Mixed Effects on Costs & Utilities' ;

       class PatID Meas Visit;

       model LValue=Cost Cost*PrevHospc  Cost*Month
                     Util Util*age40  Util*Month Util*Month*PrevHospC
       /noint solution outpred=indat.resid_costutil;
      random Cost Util Cost*Month Util*Month/subject=PatID type=FA0(4)
             g gcorr gc;
      repeated Meas/subject=PatID(visit) type=FA0(2) rc=2 r=2 rcorr=2;

        *** Output Solutions for Fixed Effects and Covariance
Parameters ***;
      ods output covparms=indat.cp_costutil;
      ods output solutionf=indat.sf_costutil;
        run;
```

```
*** Parameters for Simulation ***;
proc print data=indat.sf_costutil;

proc print data=indat.cp_costutil;
proc print data=indat.resid_costutil(obs=20);
run;
proc univariate data=indat.resid_costutil plot;
  title 'Cost Residuals';
    where Meas eq 1;
    var Resid;
run;
  proc univariate data=indat.resid_costutil plot;
  title 'Utility Residuals';
    where Meas eq 2;
    var Resid;
run;
```

E. Generate Complete Simulated Dataset from Random ME Model

```
*****************************=************************************;
* Program:     Gen_Complete2.SAS                                   ;
* Description: This program generates a complete simulated dataset  ;
* with parameters estimated from a random effects model of the      ;
* cost and utility data (Step 1, MAR_CostUtil.sas) and from         ;
* bootstrap samples of the patient characteristics and              ;
* residual errors. For the simulation of the dataset.               ;
* MAR_CostUtil.sas                                                  ;
* Programmer:   Diane Fairclough                                    ;
* Date:         19/Jan/2007                                         ;
*********************************************************************;
  *libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  *libname indat 'H:\Consulting\Engelhart' ;
  libname indat 'C:\Projects\Consult\Engelhart' ;
  options pageno=1 ps=46 ls=150 center errors=2 nofmterr ;
  footnote 'Gen_Complete2.SAS' ;
* Generate random sample with replacement of baseline covariates   ;
* and create dataset with 4 obs per subject and Std Norm Random    ;
* Errors. Maintain the correlations between covariates.            ;

  /* proc print data=indat.resid_costutil(obs=20); run; */
  proc summary data=indat.resid_costutil nway print;
    where LValue ne .;
      class Meas;
    var  Pred Resid;
      run;

  *** Baseline Covariates (Age and PrevHosp) ***;

  data work.covariates;
    set indat.resid_costutil;
      by PatID;
      if first.PatID;         * Selects One Record *;
      Age40=Age-40;           * Centered Age *;
      PrevHospC=PrevHosp-.5;  * Centered Previous Hospitalization *;
      keep PatID Age40 PrevHospC;
      run;

  *** Double check that IDs go from 1 to 232 and Average Age and
PrevHosp ***;

  proc summary data=work.covariates print n mean std min max;
    title 'Characteristics of Source Data';
    var PatID Age40 PrevHospC;
    run;

  *** Generates 600 new case IDs between 1 and N ***;

  data work.boot;
    SEED=37373;  N=232; * Max of IDs between 1 and N *;
    do NewID=1 to 600; * Generates 600 new cases *;
      LINK_ID=ceil(ranuni(SEED)*N); * Ceil creates integers;
      output;
    end;
    run;
```

```
  *** Selects cases from Source Dataset ***;

  proc sql;  * Allows many to many merge;
    create table work.boot2(keep=NewID Age40 PrevHospC)
      as select *
      from work.boot as l left join work.covariates as r
      on l.LINK_ID=r.PatID
      order by NewID;
    quit;

  proc summary data=work.boot2 print  n mean std min max;
    title 'Characteristics of Random Sample with Replacement Data';
    var NewID Age40 PrevHospC;
    run;

*** Create dataset with 4 observations per subject and Std Norm  ***;
*** Random Errors. Each of the 4 randomly generated observations ***;
*** must be specific to each sampled subject.                    ***;

  data work.boot3;
    set work.boot2;
      *** Group Assignment 1:1 Allocation ***;
      Group=mod(NewID,2)-.5; * Even ID => Group=-0.5, Odd ID =>
Group=0.5 *;
      *** 4 Standard Normal Errors for Random Effects ***;
      Z1=rannor(77777); Z2=rannor(97531); Z3=rannor(12345);
Z4=rannor(131313);
      do Month=0 to 12 by 4;
         Month04=max(Month-4,0);
         Month08=max(Month-8,0);
         output;
      end;
      run
/* proc print data=work.boot3(obs=12); run; */

  ****************************************************************;
*   Create random sample with replacement of Cost residuals.       ;
*   Maintain correlations between covariates and costs.            ;
  ****************************************************************;

  data work.Cresid;
    set indat.resid_costutil(where=(resid ne . and meas eq 1) keep=meas
resid);
      CostID=_N_;
      rename resid=CResid;
      run;
  proc summary data=work.Cresid print N min max mean std median Q1 Q3;
    title 'Characteristics of Residuals';
      var CostID CResid;      run;

  *** Generates 2400 link IDs between 1 and 641 ***;

  data work.clink;
    SEED=17171;  N=641; * Max of IDs between 1 and N *;
    do ResidID=1 to 2400; * Generates 2400 Link IDs *;
      LINK_ID=ceil(ranuni(SEED)*N);
```

```
      output;
    end;
    run;

  *** Selects cases from Source Dataset using LINK.ID ***;

  proc sql;
    create table work.cresid2(keep=CResid)
      as select *
      from work.clink as l left join work.cResid as r
      on l.LINK_ID=r.CostID
      order by ResidID;
    quit;
  proc summary data=work.cresid2 print  n mean std min max median Q1
Q3;
    title 'Characteristics of Bootstrapped Cost Residuals';
    var CResid;
    run;
*********************************************************************;
*   Create random sample with replacement of Utility residuals.     ;
*   Maintain correlations between covariates and utilities.         ;
*********************************************************************;

  data work.Uresid;
    set indat.resid_costutil(where=(resid ne . and meas eq 2) keep=meas
resid);
      UtilID=_N_;
      rename resid=UResid;
      run;
  proc summary data=work.Uresid print N min max mean std median Q1 Q3;
    title 'Characteristics of Residuals';
      var UtilID UResid;
      run;

  *** Generates 2400 link IDs between 1 and 641 ***;

  data work.Ulink;
    SEED=818181;  N=763; * Max of IDs between 1 and N *;
    do ResidID=1 to 2400; * Generates 240 Link IDs *;
      LINK_ID=ceil(ranuni(SEED)*N);
      output;
    end;
    run;

  *** Selects cases from Source Dataset using LINK_ID ***;

  proc sql;
    create table work.Uresid2(keep=UResid)
      as select *
      from work.Ulink as l left join work.UResid as r
      on l.LINK_ID=r.UtilID
      order by ResidID;
    quit;
  proc summary data=work.Uresid2 print  n mean std min max median Q1
Q3;
    title 'Characteristics of Bootstrapped Utility Residuals';
    var UResid;
```

```
    run;

  *** Transpose Datasets with the beta Parameters and covariances  ***;
  *** between the covariates for age and previous hospitalizations ***;

  /* proc print data=indat.sf_costutil; run; */
  proc transpose data=indat.sf_costutil out=work.beta prefix=B;
    var Estimate;
  run;
  /* proc print data=work.beta; run; */
  /* proc print data=indat.cp_costutil; run; */
  proc transpose data=indat.cp_costutil out=work.Sig prefix=Sig;
    var Estimate;
  run;
  /* proc print data=work.sig; run; */

  *** Merge Bootstrap Covariates parameters ***;

  proc sql;
    create table work.boot4(drop=_Name_)
      as select *
      from work.boot3, work.beta, work.sig;
    quit;

  *** Merge Cost and Utility Residuals ***;

  data work.merged;
    merge work.boot4 work.Cresid2 work.Uresid2;
      run;
  /* Proc print data=work.merged(obs=12); run; */

*****************************************************************;
* Generate New Data Values using parameter estimates for cost and   ;
* utility, and adding to these the random effects (i.e., intercepts ;
* and slope variations for each month) and residual error effects   ;
* for both cost and utility.                                        ;

  data work.simdata;
    set work.merged;
      *** Generage XBeta terms ***;
      CXBeta=B1+B2*PrevHospC+B3*Month; *These are cost model
parameters;
      UXBeta=B4+B5*Age40+B6*Month+B7*Month*PrevHospC; *Utility model
parameters;

      *** Generate Random Effects ***;
      ZiD1=Sig1*Z1;               *1st Random Effect (RE) - Cost
Intercept*;
      ZiD2=Sig2*Z1+Sig3*Z2;       *2nd RE - Utility Intercept*;

    *** The slope effects are the random variations for each month;
    ZiD3=Month*(Sig4*Z1+Sig5*Z2+Sig6*Z3);  * 3rd RE - Cost Slope *;
    ZiD4=Month*(Sig7*Z1+Sig8*Z2+Sig9*Z3+Sig10*Z4);  *4th RE - Utility
Slope *;

* Generate REsidual Errors (if residuals were correlated, would do ;
* random sample with replacement of the residuals)                  ;
```

```
      Z5=rannor(88888); Z6=Rannor(22222);
      E1=Sig11*Z5;            * Residual for Cost *;
      E2=Sig12*Z5+Sig13*Z6;   * Residual for Utility *;

      ***  Put the all together and transform back ***;
      Cost1=exp(CXBeta+ZiD1+ZiD3+Cresid); *Retransformed costs;
      Cost2=exp(CXBeta+ZiD1+ZiD3+E1);
      Util1=(UXBeta+ZiD2+ZiD4+Uresid)/10;
      Util2=(UXBeta+ZiD2+ZiD4+E2)/10;

      *** Add group specific cost and utility information ***;
      if month gt 0 then do;
       Cost1=Cost1+Group*900;
       Util1=Util1+Group*.033;
       Cost2=Cost2+Group*900;
       Util2=Util2+Group*.033;
      end;
    run;
  /* proc print data=work.simdata(obs=10); run; */
  proc univariate data=work.simdata plot;
    title 'Check on Randomly Generated Data';
    var Cost1 Cost2 Util1 Util2;
      run;

* Output the final complete simulated dataset with calculated NMB ;
* values for lambda equal to 0, 25k, 50k, and 100k.               ;

  data indat.Complete2(label="Complete data from Cost and Utilities");
    set work.simdata;
  *** Divide NMBs by 1000 to make the parameter estimates ;
  *** from subsequent models smaller numbers             ;
    NMB0=(Util1/3*0-Cost1)/1000;
    NMB25=(Util1/3*25000-Cost1)/1000;
    NMB50=(Util1/3*50000-Cost1)/1000;
    NMB100=(Util1/3*100000-Cost1)/1000;
      Age=Age40+age;
      label NMB0='NMB0/1 K'
          NMB25='NMB25/1 K'
              NMB50='NMB50/1 K'
              NMB100='NMB1000/1 K';
      rename Group=GroupC Cost1=Cost Util1=Util;
      keep NewID group month Age40 PrevHospC
         Month Month04 Month08 Cost1 Util1 NMB0 NMB25 NMB50 NMB100;
      label Group='Centered Group Indicator'
            PrevHospC='Centered Prev Hosp Indicator'
              Age40='Age centered at 40 years';
      run;
  proc mixed data=indat.Complete2 covtest noclprint ;
    title 'Examine Mixed effect Model for Complete Data';
    model NMB50= age40 prevhospC groupC month month*groupC
                    month04 month04*groupC month08 month08*groupC
                   /solution;
    random intercept month / subject = NewID type =UN gc g gcorr v
vcorr;
    title3 'Piecewise Linear Regression Analysis: NMB_50' ;
  run ;
```

F. MAR/MNAR ALGORITHMS

```
*  Program:      Missing.SAS (base case)                        ;
*  Description:  This program reads the COMPLETE dataset and    ;
*  creates the missing dataset based upon the NMB_50.           ;
*  The cutoff value for determining MAR and mnar is NMB_50 of   ;
*  75th percentile of month 8 (8.91569 for group = 0).          ;
*  Programmer:   Dennis D. Gagnon                               ;
*  Date:         02/02/2008                                     ;
  libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Missing.SAS Dissertation: Estimating INMB in a Clinical Study
With Missing Data' ;

  proc sort data=indat.complete out=complete ;
    by patid month ;
  run ;

  data tx0 ;
    set complete ;
      if txgroup = 0 ;
  run ;

  data tx1 ;
    set complete ;
      if txgroup = 1 ;
  run ;

  data tx0_1 tx0_2 tx0_3 ;
    set tx0 ;
          if _n_ le 400                then output tx0_1 ;
      else if _n_ gt 400 and _n_ le 800 then output tx0_2 ;
      else                                   output tx0_3 ;
  run ;

  data tx1_1 tx1_2 tx1_3 ;
    set tx1 ;
          if _n_ le 400                then output tx1_1 ;
      else if _n_ gt 400 and _n_ le 800 then output tx1_2 ;
      else                                   output tx1_3 ;
  run ;

  data mar ;
    set tx0_2 tx1_2 ;
      by patid month ;
      retain flag 0 ;
      if first.patid then flag = 0 ;
      if flag = 1 then delete ;
      output ;
      if flag = 0 & nmb_50 > 8.91569 then flag = 1 ;
  run ;

  data mnar ;
    set tx0_3 tx1_3 ;
    by patid month ;
    retain flag 0 ;
```

```
  if first.patid then flag = 0 ;
  if month ne 0 & flag = 0 & nmb_50 > 8.91569 then flag = 1 ;
  if flag = 1 then delete ;
run ;

data missing ;
  set tx0_1 tx1_1 mar mnar ;
    drop flag ;
run ;

proc sort data=missing out=indat.missing ;
  by patid month ;
run ;

proc sort data=indat.missing out=missing ;
  by txgroup month ;
run ;

proc means data=missing ;
  by txgroup month ;
  var nmb_0 nmb_25 nmb_50 nmb_100 ;
    title3 'Mean NMB by Treatment Group and Visit' ;
    title4 'Simulated Dataset with Missing Data' ;
run ;

proc univariate data=missing ;
  by txgroup month ;
  var cost util nmb_0 nmb_25 nmb_50 nmb_100 ;
    title3 'Mean Cost, Util, and NMB by Treatment Group and Visit' ;
    title4 'Simulated Dataset with Missing Data' ;
run ;
```

F. MAR/MNAR ALGORITHMS (continued)

```
*  Program:      Missing, MAR Sensitivity                              ;
*  Description:  This program reads the COMPLETE dataset and creates;
*  the missing dataset based upon the NMB_50.  The cutoff value for ;
*  determining MAR is NMB_50 of 75th percentile of month 8 (8.91569 ;
*  for group = 0).                                                     ;
*  ALL SUBJECTS ARE PUT THROUGH THE MAR ALGORITHM FOR THIS             ;
*  SENSITIVITY ANALYSIS !!                                             ;
*  Programmer:   Dennis D. Gagnon                                      ;
*  Date:         05/24/2008                                            ;
  libname indat  'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  libname outdat 'C:\UMDNJ\Dissertation\NMB\V802dat\Sensitivity, MAR' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Missing, MAR Sensitivity.SAS              Dissertation:
Estimating INMB in a Clinical Study With Missing Data' ;

  proc sort data=indat.complete out=complete ;
    by patid month ;   run ;

  data mar ;
    set complete ;
      by patid month ;
      retain flag 0 ;
      if first.patid then flag = 0 ;
      if flag = 1 then delete ;
      output ;
      if flag = 0 & nmb_50 > 8.91569 then flag = 1 ;   run ;

  data missing ;
    set mar ;
      drop flag ;   run ;

  proc sort data=missing out=outdat.missing ;
    by patid month ;   run ;

  proc sort data=outdat.missing out=missing ;
    by txgroup month ;   run ;

  proc means data=missing ;
    by txgroup month ;
    var nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 'Mean NMB by Treatment Group and Visit' ;
      title4 'Simulated Dataset with Missing Data' ;
      title6 'SENSITIVITY ANALYSIS, ALL DATA RUN THROUGH MAR ALGORITHM'
;   run ;

  proc univariate data=missing ;
    by txgroup month ;
    var cost util nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 'Mean Cost, Util, and NMB by Treatment Group and Visit' ;
      title4 'Simulated Dataset with Missing Data' ;
      title6 'SENSITIVITY ANALYSIS, ALL DATA RUN THROUGH MAR ALGORITHM'
;   run ;
```

F. MAR/MNAR ALGORITHMS (continued)

```
  *  Program:   Missing, Trajectory.SAS (post hoc)                    ;
  *  Description:  This program reads the COMPLETE dataset and       ;
  *  creates the missing dataset based upon the NMB_50.  This        ;
  *  program is much like MISSING.SAS, but uses change from baseline;
  *  instead of a threshold value.                                   ;
  *  Programmer:   Dennis D. Gagnon                                  ;
  *  Date:         06/30/2008                                        ;
  libname indat  'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  libname outdat 'C:\UMDNJ\Dissertation\NMB\V802dat\Trajectory' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Missing, Trajectory.SAS                    Dissertation:
Estimating INMB in a Clinical Study With Missing Data' ;

  proc sort data=indat.complete out=complete ;
    by patid month ;   run ;

  proc contents data=complete ;
    title3 'Contents of Complete' ;   run ;

  proc print data=complete(obs=20) ;
    title3 'First 20 Observations of Complete' ;   run ;

  data bl ;
    set complete ;
      if month = 0 ;
    bl0 = nmb_0 ;
    bl25 = nmb_25 ;
    bl50 = nmb_50 ;
    bl100 = nmb_100 ;
    keep patid bl0 bl25 bl50 bl100 ;   run ;

  data complete ;
    merge complete bl ;
    by patid ;   run ;

  proc print data=complete(obs=20) ;
    title3 'First 20 Observations of Complete, with Baseline' ;
  run ;

  data tx0 ;
    set complete ;
      if txgroup = 0 ;   run ;

  data tx1 ;
    set complete ;
      if txgroup = 1 ;   run ;

  data tx0_1 tx0_2 tx0_3 ;
    set tx0 ;
          if _n_ le 400                then output tx0_1 ;
      else if _n_ gt 400 and _n_ le 800 then output tx0_2 ;
      else                                   output tx0_3 ;
  run ;

  data tx1_1 tx1_2 tx1_3 ;
```

```
  set tx1 ;
         if _n_ le 400                then output tx1_1 ;
    else if _n_ gt 400 and _n_ le 800 then output tx1_2 ;
    else                                   output tx1_3 ;
run ;

data mar ;
  set tx0_2 tx1_2 ;
    by patid month ;
    retain flag 0 ;
    if first.patid then flag = 0 ;
    if flag = 1 then delete ;
    output ;
    if flag = 0 & (nmb_50 - bl50) > 2.0 then flag = 1 ;
run ;

data mnar ;
  set tx0_3 tx1_3 ;
  by patid month ;
  retain flag 0 ;
  if first.patid then flag = 0 ;
  if month ne 0 & flag = 0 & (nmb_50 - bl50) > 2.0 then flag = 1 ;
  if flag = 1 then delete ;   run ;

data missing ;
  set tx0_1 tx1_1 mar mnar ;
    drop flag ;   run ;

proc sort data=missing out=outdat.missing ;
  by patid month ;   run ;

proc sort data=outdat.missing out=missing ;
  by txgroup month ;   run ;

proc means data=missing ;
  by txgroup month ;
  var nmb_0 nmb_25 nmb_50 nmb_100 ;
    title3 'Mean NMB by Treatment Group and Visit' ;
    title4 'Simulated Dataset with Missing Data' ;
    title5 'Trajectory Technique' ;
run ;

proc univariate data=missing ;
  by txgroup month ;
  var cost util nmb_0 nmb_25 nmb_50 nmb_100 ;
    title3 'Mean Cost, Util, and NMB by Treatment Group and Visit' ;
    title4 'Simulated Dataset with Missing Data' ;
run ;
```

F. MAR/MNAR ALGORITHMS (continued)

```
*  Program:      Missing, MNAR Sensitivity.SAS              ;
*  Description:  This program reads the COMPLETE dataset and ;
*  creates the missing dataset based upon the NMB_50.       ;
*  The cutoff value for determining MNAR is NMB_50 of 75th  ;
*  percentile of month 8 (8.91569 for group = 0).           ;
*  ALL SUBJESTS ARE RUN THROUGH THE MNAR ALGORITHM FOR THIS  ;
*  SENSITIVITY ANALYSIS !                                   ;
*  Programmer:   Dennis D. Gagnon                           ;
*  Date:         05/24/2008                                 ;
 libname indat  'C:\UMDNJ\Dissertation\NMB\V802dat' ;
 libname outdat 'C:\UMDNJ\Dissertation\NMB\V802dat\Sensitivity, MNAR' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Missing, MNAR Sensitivity.SAS
Dissertation: Estimating INMB in a Clinical Study With Missing Data' ;

  proc sort data=indat.complete out=complete ;
    by patid month ;   run ;
  data mnar ;
    set complete ;
    by patid month ;
    retain flag 0 ;
    if first.patid then flag = 0 ;
    if month ne 0 & flag = 0 & nmb_50 > 8.91569 then flag = 1 ;
    if flag = 1 then delete ;   run ;

  data missing ;
    set mnar ;
      drop flag ;   run ;

  proc sort data=missing out=outdat.missing ;
    by patid month ;   run ;

  proc sort data=outdat.missing out=missing ;
    by txgroup month ;   run ;

  proc means data=missing ;
    by txgroup month ;
    var nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 'Mean NMB by Treatment Group and Visit' ;
      title4 'Simulated Dataset with Missing Data' ;
      title6 'ALL SUBJECTS RUN THROUGH MNAR ALGORITHM FOR THIS
SENSITIVITY ANALYSIS' ;
  run ;

  proc univariate data=missing ;
    by txgroup month ;
    var cost util nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 'Mean Cost, Util, and NMB by Treatment Group and Visit' ;
      title4 'Simulated Dataset with Missing Data' ;
      title6 'ALL SUBJECTS RUN THROUGH MNAR ALGORITHM FOR THIS
SENSITIVITY ANALYSIS' ;
  run ;
```

G. DESCRIPTIVE STATISTICS

```
  *  Program:      ROSE, Descriptive Stats, Outpatients.SAS          ;
  *  Description:  This program pulls the utility data and cost data ;
  *  and creates a patient-level dataset with utility and costs for  ;
  *  each visit.  It then creates a a patient/visit-level dataset and;
  *  runs descriptive stats on the outcome variables.                ;
  *  Programmer:   Dennis D. Gagnon                                  ;
  *  Date:         05/24/2008                                        ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  libname indat  'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  libname indat2 'C:\UMDNJ\Dissertation\NMB\V612dat\Original Data' ;
  title 'ROSE, Descriptive Stats, Outpatients.SAS        Dissertation:
Estimating INMB in a Clinical Study With Missing Data' ;

  proc format ;
    value $zrace
      " " = " " ;
    value $zsex
      " " = " " ;
    value $zyesno
      " " = " " ;
      value $ZRISPTG
        " " = " " ;
      value $ZPHSE
      " " = " " ;
    value tag2a
      . = " " ;
    value tag1a
      . = " " ;
    run ;
    /*
      proc contents data=indat2.patittii ;
        title3 'Contents of PATITTII' ;
      run ;  */
    *  Bring in Dataset that Flags Patients as Being Randomized from
Hospital or as Outpatients ;
    data hosp ;
      set indat2.patittii ;
      length pat $4 ;
      pat =substr(idn,1,4) ;
      if substr(pat,1,1)= '0' then substr(pat,1,1)=' ' ;
        if numprev ge 2 then prevhosp = 1 ;
        else                 prevhosp = 0 ;
      keep pat rih age numprev numprevr prevhosp group ;    run ;

      proc sort data=hosp ;
        by pat ;  run ;

    proc freq data=hosp ;
        tables numprev*numprevr*prevhosp / list ;
        where rih = 1 ;
        title3 'Frequency of Number of Previous Hospitalizaitons,
Inpatients' ;     run ;

      proc freq data=hosp ;
        tables numprev*numprevr*prevhosp / list ;
```

```
        where rih = 0 ;
        title3 'Frequency of number of Previous hospitalizaitons,
Outpatients' ;    run ;

      proc means data=hosp ;
        var age ;
        where rih = 1 ;
        title3 'Mean Age, Inpatients' ;   run ;

      proc means data=hosp ;
        var age ;
        where rih = 0 ;
        title3 'Mean age, Outpatients' ;  run ;
      *  Bring in Cohort Dataset.  Cohort (1,2,3, or 4) is Derived from
Days on Study and Reflects
Which was Last Visit for the Patient.                              ;

      proc sort data=indat.cohort out=cohort ;
        by pat ;  run ;

      *  Create a patient-level dataset for utilities ;
      data utility ;
        set indat.utility ;
        pat = right(pat) ;
        if substr(pat,1,1)= '0' then substr(pat,1,1)=' ' ;
        if sfindex = . then delete ;
        keep pat vnbr sfindex ;    run ;

      proc sort data=utility ;
        by pat vnbr ;   run ;

      data util_v ;
        merge utility(in=keep) cohort ;
        by pat ;
        if keep ;
        if vnbr > cohort then delete ;    run ;

      data util_p ;
        set util_v ;
        by pat ;
        retain util_1 util_2 util_3 util_4 ;
        if first.pat then do ;
          util_1 = . ;
          util_2 = . ;
          util_3 = . ;
          util_4 = . ;
        end ;
        if vnbr = 1 then util_1 = sfindex ;
        if vnbr = 2 then util_2 = sfindex ;
        if vnbr = 3 then util_3 = sfindex ;
        if vnbr = 4 then util_4 = sfindex ;
        if last.pat then output ;
        keep pat util_1 util_2 util_3 util_4 ;  run ;

      proc print data=util_p(obs=20) ;
        title3 'First 20 Observations of UTIL_P' ;    run ;
```

```
*  Create a Patient-Level Dataset of Costs ;

data cost ;
  set indat.cost ;
  pat= right(pat) ;
  if cost = . then delete ;
  keep pat vnbr cost completr ;     run ;

proc sort data=cost ;
  by pat vnbr ;   run ;

data cost_v ;
  merge cost(in=keep) cohort ;
  by pat ;
  if keep ;
  if vnbr > cohort then delete ;    run ;

data cost_p ;
  set cost_v ;
  by pat ;
  retain cost_1 cost_2 cost_3 cost_4 ;
  if first.pat then do ;
    cost_1 = . ;
    cost_2 = . ;
    cost_3 = . ;
    cost_4 = . ;
  end ;
  if vnbr = 1 then cost_1 = cost ;
  if vnbr = 2 then cost_2 = cost ;
  if vnbr = 3 then cost_3 = cost ;
  if vnbr = 4 then cost_4 = cost ;
  cost_1 = cost_2 ;
  if last.pat then output ;
  keep pat cost_1 cost_2 cost_3 cost_4 ;
run ;

proc print data=cost_p(obs=20) ;
  title3 'First 20 Observations of COST_P' ;
run ;

*  Merge Utilities, Costs, and Hospital Randomization data ;

data patient ;
  merge util_p(in=util) cost_p(in=cost) hosp ;
  by pat ;
  if util or cost ;
run ;

data patient ;
  set patient ;
  if rih=0 ;   *  <--- Select Outpatients ;
run ;

proc print data=patient(obs=20) ;
  title3 'First 20 Observations of Patient' ;
run ;
```

```
      * Create month-level data with derived NMBs ;
      data month ;
        set patient ;
        patid = _n_ ;
        do i=1 to 4 ;
          if i=1 then do ;
              month = 0 ;
          cost = l ;
              util = util_1 ;
          output ;
            end ;
          if i=2 then do ;
              month = 4 ;
          cost = cost_2 ;
              util = util_2 ;
          output ;
            end ;
          if i=3 then do ;
              month = 8 ;
          cost = cost_3 ;
              util = util_3 ;
          output ;
            end ;
          if i=4 then do ;
              month = 12 ;
          cost = cost_4 ;
              util = util_4 ;
          output ;
            end ;
        end ;
        keep patid age prevhosp group cost util month ;
      run ;

      proc print data=month(obs=20) ;
        title3 'First 20 Observations of Month' ;
      run ;

      proc sort data=month ;
        by group month ;
      run ;

      proc means data=month n nmiss mean std median min max ;
      var cost util age prevhosp ;
        by group month ;
        title3 'Descriptive Statistics of ROSE Cost and Utility Data,
By Group and Month' ;
      run ;
```

G. DESCRIPTIVE STATISTICS (continued)

```
  *  Program:      Univariate.SAS                                        ;
  *  Description:  This program reads the COMPLETE dataset and runs     ;
  *  some uni-variate analyses by txgroup and month on nmb_0, nmb_25,   ;
  *  nmb_50, and nmb_100.  NMBs have been divided by 1000.              ;
  *  Programmer:   Dennis D. Gagnon                                     ;
  *  Date:         04/12/2008                                           ;
  libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Univariate.SAS                  Dissertation: Estimating INMB
in a Clinical Study With Missing Data' ;

  proc sort data=indat.complete out=complete ;
    by month ;
  run ;

  proc corr data=complete spearman ;
    by month ;
    var cost util age40 prevhospc ;
    title3'Spearman Rank Correlations, by Month(Treatments Combined)' ;
  run ;

  proc sort data=complete ;
    by txgroup month ;
  run ;

  PROC MEANS DATA=COMPLETE;
   BY TXGROUP ;
   where month = 0 ;
   VAR age40 prevhospc;
   TITLE3 'Means of age40 and previous hospitalizations by treatment
group';
   title4 'Complete simulated data';
   run;

  PROC MEANS DATA=COMPLETE;
   BY TXGROUP month ;
   VAR UTIL COST;
   TITLE3 'Means of utilities and costs by treatment group and month';
   title4 'Complete simulated data';
   run;

  proc univariate data=complete plot normal ;
    by txgroup month ;
      var util cost ;
      title3 'Univariate Statistics of utilities and costs by Treatment
Group and Visit' ;
      title4 'Complete Simulated Data' ;
  run ;

  proc means data=complete ;
    by txgroup month ;
      var nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 'Means of NMBs by Treatment Group and Visit' ;
      title4 'Complete Simulated Data' ;
  run ;
```

```
  proc univariate data=complete plot normal ;
    by txgroup month ;
      var nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 'Univariate Statistics of NMBs by Treatment Group and
Visit' ;
      title4 'Complete Simulated Data' ;
  run ;

  proc sort data=complete ;
    by month ;
  run ;

  proc ttest data=complete ;
    by month ;
      class txgroup ;
      var cost util nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 '**Independent Sample T-tests for Differences in Costs,
Utils, and NMB by Visit**' ;
      title4 'Complete Simulated Data' ;   run ;

  proc sort data=complete ;
    by patid month ;   run ;

  data total ;
    set complete ;
      by patid month ;
    retain tnmb_0 tnmb_25 tnmb_50 tnmb_100 0 ;
      if first.patid then do ;
        tnmb_0   = 0 ;
        tnmb_25  = 0 ;
        tnmb_50  = 0 ;
        tnmb_100 = 0 ;
      end ;
      tnmb_0   = tnmb_0   + nmb_0   ;
      tnmb_25  = tnmb_25  + nmb_25  ;
      tnmb_50  = tnmb_50  + nmb_50  ;
      tnmb_100 = tnmb_100 + nmb_100 ;
      if last.patid then output ;
      keep patid txgroup tnmb_0 tnmb_25 tnmb_50 tnmb_100 ;   run ;

  proc sort data=total ;
    by txgroup ;   run ;

  proc univariate data=total plot normal ;
    by txgroup ;
    var tnmb_0 tnmb_25 tnmb_50 tnmb_100 ;
      title3 'Univariate Statistics of Total NMBs by Treatment Group' ;
    title4 'Complete Simulated Dataset' ;
  run ;
  proc ttest data=total ;
    class txgroup ;
      var tnmb_0 tnmb_25 tnmb_50 tnmb_100 ;
      title3 'Independent Sample T-tests for Difference in Total NMB' ;
      title4 'Complete Simulated Data' ;
  run ;
```

G. DESCRIPTIVE STATISTICS (continued)

```
  *  Program:      Univariate LOCF.SAS                                  ;
  *  Description:  This program reads the LOCF dataset and runs some  ;
  *  univariate analyses by txgroup and month on nmb_0, nmb_25,       ;
  *  nmb_50, and nmb_100.  NMBs have been divided by 1000.            ;
  *  Programmer:   Dennis D. Gagnon                                   ;
  *  Date:         04/12/2008                                         ;
  libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Univariate LOCF.SAS          Dissertation: Estimating INMB in
a Clinical Study With LOCF Data' ;
  proc sort data=indat.locf out=locf ;
    by month ;
  run ;
  proc corr data=locf spearman ;
    by month ;
    var cost util age40 prevhospc ;
    title3 'Spearman Rank Correlations, by Month (Treatments Combined)'
;
      title4 'Simulated LOCF' ;
  run ;
  proc sort data=locf ;
    by txgroup month ;
  run ;
  PROC MEANS DATA=locf;
   BY TXGROUP ;
   where month = 0 ;
   VAR age40 prevhospc;
   TITLE3 'Means of age40 and previous hospitalizations by treatment
group';
   title4 'LOCF simulated data';
   run;
  PROC MEANS DATA=locf;
   BY TXGROUP month ;
   VAR UTIL COST;
   TITLE3 'Means of utilities and costs by treatment group and month';
   title4 'LOCF simulated data';
   run;
  proc univariate data=locf plot normal ;
    by txgroup month ;
      var util cost ;
      title3 'Univariate Statistics of utilities and costs by Treatment
Group and Visit' ;
      title4 'LOCF Simulated Data' ;
  run ;
  proc means data=locf ;
    by txgroup month ;
      var nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 'Means of NMBs by Treatment Group and Visit' ;
      title4 'LOCF Simulated Data' ;
  run ;
  proc univariate data=locf plot normal ;
    by txgroup month ;
      var nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 'Univariate Statistics of NMBs by Treatment Group and
Visit' ;
```

```
      title4 'LOCF Simulated Data' ;
  run ;
  proc sort data=locf ;
    by month ;
  run ;
  proc ttest data=locf ;
    by month ;
      class txgroup ;
      var cost util nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 '**Independent Sample T-tests for Differences in Costs,
Utils, and NMB by Visit**' ;
      title4 'LOCF Simulated Data' ;
  run ;
  proc sort data=locf ;
    by patid month ;
  run ;
  data total ;
    set locf ;
      by patid month ;
    retain tnmb_0 tnmb_25 tnmb_50 tnmb_100 0 ;
      if first.patid then do ;
        tnmb_0   = 0 ;
        tnmb_25  = 0 ;
        tnmb_50  = 0 ;
        tnmb_100 = 0 ;
      end ;
      tnmb_0   = tnmb_0   + nmb_0   ;
      tnmb_25  = tnmb_25  + nmb_25  ;
      tnmb_50  = tnmb_50  + nmb_50  ;
      tnmb_100 = tnmb_100 + nmb_100 ;
      if last.patid then output ;
      keep patid txgroup tnmb_0 tnmb_25 tnmb_50 tnmb_100 ;
  run ;
  proc sort data=total ;
    by txgroup ;
  run ;
  proc univariate data=total plot normal ;
    by txgroup ;
    var tnmb_0 tnmb_25 tnmb_50 tnmb_100 ;
      title3 'Univariate Statistics of Total NMBs by Treatment Group' ;
    title4 'LOCF Simulated Dataset' ;
  run ;
  proc ttest data=total ;
    class txgroup ;
      var tnmb_0 tnmb_25 tnmb_50 tnmb_100 ;
      title3 'Independent Sample T-tests for Difference in Total NMB' ;
      title4 'LOCF Simulated Data' ;
  run ;
```

G. DESCRIPTIVE STATISTICS (continued)

```
*  Program:      Missing.SAS                                          ;
*  Description:  This program reads the COMPLETE dataset and          ;
*  creates the missing dataset based upon the NMB_50.  The cutoff     ;
*  value for determining MAR and mnar is NMB_50 of 75th percentile    ;
*  of month 8 (8.91569 for group = 0).                                ;
*  Programmer:   Dennis D. Gagnon                                     ;
*  Date:         02/02/2008                                           ;
libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat' ;
options pageno=1 ps=46 ls=150 center errors=2 ;
title 'Missing.SAS  Dissertation: Estimating INMB in a Clinical Study
With Missing Data' ;

  proc sort data=indat.complete out=complete ;
    by patid month ;
  run ;

  data tx0 ;
    set complete ;
      if txgroup = 0 ;
  run ;

  data tx1 ;
    set complete ;
      if txgroup = 1 ;
  run ;

  data tx0_1 tx0_2 tx0_3 ;
    set tx0 ;
          if _n_ le 400                then output tx0_1 ;
      else if _n_ gt 400 and _n_ le 800 then output tx0_2 ;
      else                                   output tx0_3 ;
  run ;

  data tx1_1 tx1_2 tx1_3 ;
    set tx1 ;
          if _n_ le 400                then output tx1_1 ;
      else if _n_ gt 400 and _n_ le 800 then output tx1_2 ;
      else                                   output tx1_3 ;
  run ;

  data mar ;
    set tx0_2 tx1_2 ;
      by patid month ;
      retain flag 0 ;
      if first.patid then flag = 0 ;
      if flag = 1 then delete ;
      output ;
      if flag = 0 & nmb_50 > 8.91569 then flag = 1 ;
  run ;

  data mnar ;
    set tx0_3 tx1_3 ;
    by patid month ;
    retain flag 0 ;
    if first.patid then flag = 0 ;
```

```
  if month ne 0 & flag = 0 & nmb_50 > 8.91569 then flag = 1 ;
  if flag = 1 then delete ;
run ;

data missing ;
  set tx0_1 tx1_1 mar mnar ;
    drop flag ;
run ;

proc sort data=missing out=indat.missing ;
  by patid month ;
run ;

proc sort data=indat.missing out=missing ;
  by txgroup month ;
run ;

proc means data=missing ;
  by txgroup month ;
  var nmb_0 nmb_25 nmb_50 nmb_100 ;
    title3 'Mean NMB by Treatment Group and Visit' ;
    title4 'Simulated Dataset with Missing Data' ;
run ;

proc univariate data=missing ;
  by txgroup month ;
  var cost util nmb_0 nmb_25 nmb_50 nmb_100 ;
    title3 'Mean Cost, Util, and NMB by Treatment Group and Visit' ;
    title4 'Simulated Dataset with Missing Data' ;
run ;
```

H. MISSINGNESS PATTERNS

```
  *  Program:      Cohort_Sim.SAS                                          ;
  *  Description:  This program uses the simulated data once missing       ;
  *  has been imposed and derives a cohort flag for each subject in        ;
  *  the simulated data.                                                   ;
  *  Programmer:   Dennis D. Gagnon                                        ;
  *  Date:         02/23/2008                                              ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  title 'Cohort_Sim.SAS                 Dissertation: Estimating INMB
in a Clinical Study With Missing Data' ;

  proc sort data=indat.missing out=missing;
     by patid month ;  run ;

data cohort_sim ;
  set missing ;
  by patid month ;
  if last.patid then do ;
    cohort = month ;
      output ;
  end ;
  keep patid cohort ;run ;

data indat.cohort_sim ;
  merge missing cohort_sim ;
  by patid ;run ;

proc print data=indat.cohort_sim(obs=20) ;
  title3 'First 20 Observations of Cohort_Sim' ;run ;

proc contents data=indat.cohort_sim ;
  title3 'Contents of Cohort_Sim' ;run ;

proc sort data=indat.cohort_sim out=cohort_sim ;
  by cohort month ;run ;

proc freq data=cohort_sim ;
  tables cohort*month / list ;
  title3 'Numbers for Cohort by Visit' ;
  title4 'Treatment Groups Combined' ;run ;
proc freq data=cohort_sim ;
  tables txgroup*cohort*month / list ;
  title3 'Numbers for Treatment Group by Cohort by Visit' ;run ;
proc means data=cohort_sim ;
  by cohort month ;
  var nmb_0 nmb_25 nmb_50 nmb_100 ;
  title3 'Mean NMB by Cohort, by Visit' ;
  title4 'Both Treatment Groups Combined' ;run ;
proc sort data=cohort_sim ;
  by txgroup cohort month ;run ;
proc means data=cohort_sim ;
  by txgroup cohort month ;
  var nmb_0 nmb_25 nmb_50 nmb_100 ;
  title3 'Mean NMB by Treatment, by Cohort, by Visit' ;run ;
```

I. TRUE

```
  *  Program:      True.SAS                                              ;
  *  Description:  This program reads the SUBJECT_COMP dataset and       ;
  *  runs analyses to determine the true INMB.  First a t-test is run;
  *  then a simple GLM with no covariates, then GLMs with age40,         ;
  *  previous hosps and baseline nmb.                                    ;
  *  Programmer:   Dennis D. Gagnon                                      ;
  *  Date:         02/23/2008                                            ;
  libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'True.SAS                                    Dissertation:
Estimating INMB in a Clinical Study With Missing Data' ;

  proc print data=indat.subject_comp(obs=20) ;
    title3 'First 20 Observations of Subject_Comp' ;
  run ;

  proc ttest data=indat.subject_comp ;
    class txgroup ;
      var nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 'T-Tests on True Difference in Mean NMBs, Complete Data
Set' ;
  run ;

  proc glm data=indat.subject_comp ;
    class txgroup ;
      model nmb_0 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB0 Against Treatment Only' ;
  run ;

  proc glm data=indat.subject_comp ;
    class txgroup ;
      model nmb_25 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB25 Against Treatment Only' ;
  run ;

  proc glm data=indat.subject_comp ;
    class txgroup ;
      model nmb_50 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB50 Against Treatment Only' ;
  run ;

  proc glm data=indat.subject_comp ;
    class txgroup ;
      model nmb_100 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB100 Against Treatment Only' ;
  run ;

  proc glm data=indat.subject_comp ;
    class txgroup prevhospc ;
      model nmb_0 = txgroup age40 prevhospc bln0 / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
```

```
    title3 'OLS of NMB0 Against Treatment And Covariates' ;
run ;

proc glm data=indat.subject_comp ;
  class txgroup prevhospc ;
    model nmb_25 = txgroup age40 prevhospc bln25 / solution ;
    lsmeans txgroup / stderr tdiff pdiff cl ;
    title3 'OLS of NMB25 Against Treatment And Covariates' ;
run ;

proc glm data=indat.subject_comp ;
  class txgroup prevhospc ;
    model nmb_50 = txgroup age40 prevhospc bln50 / solution ;
    lsmeans txgroup / stderr tdiff pdiff cl ;
    title3 'OLS of NMB50 Against Treatment And Covariates' ;
run ;

proc glm data=indat.subject_comp ;
  class txgroup prevhospc ;
    model nmb_100 = txgroup age40 prevhospc bln100 / solution ;
    lsmeans txgroup / stderr tdiff pdiff cl ;
    title3 'OLS of NMB100 Against Treatment And Covariates' ;
run ;
quit ;
```

J. SENSITIVITY ANALYSIS 1 ANCOVA MODEL

```
*  Program: LOCF, MAR Sensitivity.SAS                                  ;
*  Description:  This program reads the COMPLETE dataset and the       ;
*  MISSING dataset and creates an LOCF dataset.  Baseline is           ;
*  brought forward if there is not follow-up.                          ;
*     THIS IS THE MAR SENSITIVITY ANALYSIS !                           ;
*  Programmer:   Dennis D. Gagnon                                      ;
*  Date:         05/24/2008                                            ;
  libname indat  'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  libname outdat 'C:\UMDNJ\Dissertation\NMB\V802dat\Sensitivity, MAR' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'LOCF, MAR Sensitivity.SAS       Dissertation: Estimating INMB
in a Clinical Study With Missing Data' ;

  proc sort data=indat.complete out=complete(keep=patid month txgroup
age40 prevhospc month04 month08) ;
    by patid month ;  run ;

  proc sort data=outdat.missing out=missing ;
    by patid month ;  run ;

  data full ;
    merge complete missing ;
      by patid month ;  run ;

  proc print data=full(firstobs=2369) ;
    title3 'Last Observations of Full, Starting at 2369' ;  run ;

  data locf ;
    set full ;
      by patid month ;
      array last {6} lc lu l0 l25 l50 l100 ;
      array current {6} cost util nmb_0 nmb_25 nmb_50 nmb_100 ;
      retain lc lu l0 l25 l50 l100 ;
      if first.patid then do ;
        do i = 1 to 6 ;
          last{i} = . ;
        end ;
      end ;
      do i = 1 to 6 ;
        if current{i} = . then current{i} = last{i} ;
      end ;
      do i = 1 to 6 ;
        last{i} = current{i} ;
      end ;
      drop i lc lu l0 l25 l50 l100 ;  run ;

  data outdat.locf ;
    set locf ;  run ;

  proc contents data=outdat.locf ;
    title3 'Contents of LOCF, Sensitivity MAR' ;  run ;

  proc print data=outdat.locf(obs=20) ;
    title3 'First 20 Observations of LOCF, Sensitivity MAR' ;  run ;
```

J. SENSITIVITY ANALYSIS 1 ANCOVA MODEL (continued)

```
*  Program:  Subject LOCF, MAR Sensitivity.SAS                          ;
*  Description:  This program reads the LOCF dataset and creates       ;
*  a subject-level complete dataset.  NMBs are summed across months    ;
*  4, 8, & 12.                                                         ;
*     THIS IS THE MAR SENSITIVITY ANALYSIS !!!!                        ;
*  Programmer:   Dennis D. Gagnon                                      ;
*  Date:         05/24/2008                                            ;
  libname indat  'C:\UMDNJ\Dissertation\NMB\V802dat\Sensitivity, MAR' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Subject LOCF, MAR Sensitivity.SAS
Dissertation: Estimating INMB in a Clinical Study With Missing Data' ;
  proc sort data=indat.locf out=locf (rename=(nmb_0=n_0 nmb_25=n_25
nmb_50=n_50 nmb_100=n_100)) ;
    by patid month ;
  run ;

  proc print data=locf(obs=20) ;
    title3 'First 20 Observations of LOCF' ;
  run ;

  data indat.subject_locf ;
    set locf ;
      by patid month ;
      retain nmb_0 nmb_25 nmb_50 nmb_100 bln0 bln25 bln50 bln100 0 ;
      array nmb{4} nmb_0 nmb_25 nmb_50 nmb_100 ;
      array bl{4} bln0 bln25 bln50 bln100 ;
      array nm{4} n_0 n_25 n_50 n_100 ;
      if first.patid then do ;
        do i=1 to 4 ;
          nmb{i} = 0 ;
            bl{i} = 0 ;
        end ;
    end ;
      if month = 0 then do ;
        do i=1 to 4 ;
          bl{i} = nm{i} ;
        end ;
      end ;
      else do ;
      do i=1 to 4 ;
          nmb{i} = nmb{i} + nm{i} ;
        end ;
      end ;
      drop i util cost month n_0 n_25 n_50 n_100 month month04 month08
;
      if last.patid then output ;   run ;

  proc contents data=indat.subject_locf ;
    title3 'Contents of Subject_LOCF' ;
      title5 'MAR Sensitivity Analysis' ;   run ;

  proc print data=indat.subject_locf(obs=20) ;
    title3 'First 20 Observations of Subject_LOCF' ;
      title5 'MAR Sensitivity Analysis' ;
  run ;
```

J. SENSITIVITY ANALYSIS 1 ANCOVA MODEL (continued)

```
*  Program: UNI LOCF, MAR Sensitivity.SAS                                ;
*  Description: his program reads the SUBJECT_LOCF dataset and runs  ;
*  analyses to determine the INMB.  First a t-test is run, then a    ;
*  simple GLM with No covariates, then GLMs with age40, previous     ;
*  hosps and baseline nmb.                                           ;
*     THIS IS THE MAR SENSITIVITY ANALYSIS !!!!                      ;
*  Programmer:   Dennis D. Gagnon                                    ;
*  Date:         05/24/2008                                          ;
  libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat\Sensitivity, MAR' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Uni LOCF, MAR Sensitivity.SAS              Dissertation:
Estimating INMB in a Clinical Study With Missing Data' ;

  proc print data=indat.subject_locf(obs=20) ;
    title3 'First 20 Observations of Subject_LOCF' ;
  run ;
  proc ttest data=indat.subject_locf ;
    class txgroup ;
      var nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 'T-Tests on LOCF Difference in Mean NMBs, Complete Data
Set' ;
      title5 'MAR Sensitivity Analysis' ;
  run ;
  proc glm data=indat.subject_locf ;
    class txgroup ;
      model nmb_0 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB0 Against Treatment Only, LOCF' ;
      title5 'MAR Sensitivity Analysis' ;
  run ;
  proc glm data=indat.subject_locf ;
    class txgroup ;
      model nmb_25 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB25 Against Treatment Only, LOCF' ;
      title5 'MAR Sensitivity Analysis' ;
  run ;
  proc glm data=indat.subject_locf ;
    class txgroup ;
      model nmb_50 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB50 Against Treatment Only, LOCF' ;
      title5 'MAR Sensitivity Analysis' ;
  run ;
  proc glm data=indat.subject_locf ;
    class txgroup ;
      model nmb_100 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB100 Against Treatment Only, LOCF' ;
      title5 'MAR Sensitivity Analysis' ;
  run ;
  proc glm data=indat.subject_locf ;
    class txgroup prevhospc ;
      model nmb_0 = txgroup age40 prevhospc bln0 / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
```

```
    title3 'OLS of NMB0 Against Treatment And Covariates, LOCF' ;
    title5 'MAR Sensitivity Analysis' ;
run ;
proc glm data=indat.subject_locf ;
  class txgroup prevhospc ;
    model nmb_25 = txgroup age40 prevhospc bln25 / solution ;
    lsmeans txgroup / stderr tdiff pdiff cl ;
    title3 'OLS of NMB25 Against Treatment And Covariates, LOCF' ;
    title5 'MAR Sensitivity Analysis' ;
run ;
proc glm data=indat.subject_locf ;
  class txgroup prevhospc ;
    model nmb_50 = txgroup age40 prevhospc bln50 / solution ;
    lsmeans txgroup / stderr tdiff pdiff cl ;
    title3 'OLS of NMB50 Against Treatment And Covariates, LOCF' ;
    title5 'MAR Sensitivity Analysis' ;
run ;
proc glm data=indat.subject_locf ;
  class txgroup prevhospc ;
    model nmb_100 = txgroup age40 prevhospc bln100 / solution ;
    lsmeans txgroup / stderr tdiff pdiff cl ;
    title3 'OLS of NMB100 Against Treatment And Covariates, LOCF' ;
    title5 'MAR Sensitivity Analysis' ;
run ;
quit ;
```

K. SENSITIVITY ANALYSIS 1 ME MODEL

```
*  Program:      MAR_Miss, MAR Sensitivity.SAS                          ;
*  Description:  This program reads the MISSING dataset and creates     ;
*  the month & month knot variables (one knot at month 4 and one knot   ;
*  at month 8). A mixed effects model is then run estimating the        ;
*  difference in the changes in NMB from baseline across treatment      ;
*  groups.                                                              ;
*     This program uses the data simulated from Dr. Fairclough.        ;
*     NMB are divided by 1000.                                         ;
*     MAR SENSITIVITY ANALYSES !!!!                                    ;
*  Programmer:   Dennis D. Gagnon                                       ;
*  Date:         05/26/2008                                             ;
    libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat\Sensitivity, MAR';
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'MAR_Miss, MAR Sensitivity.SAS                 Dissertation:
Estimating INMB in a Clinical Study With Missing Data' ;

  proc print data=indat.missing(obs=20) ;
    title3 'First 20 Observations of Missing' ;
  run ;
  data missing ;
    set indat.missing ;
  run ;
  proc print data=missing(obs=20) ;
    title3 'Print of Missing with Month and Knots at Months 4 and 8
Derived' ;
  run ;

  *  Start Running of Mixed Models ;
  *  NMB_0 ;
  proc mixed data=missing covtest noclprint ;
    model NMB_0= age40 prevhospC txgroup month month*txgroup
                     month04 month04*txgroup month08 month08*txgroup
                    /solution;
random intercept month / subject = patid type =UN gc g gcorr v vcorr;
    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12 month*txgroup
12 month04 8 month04*txgroup 8
month08 4 month08*txgroup 4 ;
estimate 'Month 12, Diff' txgroup 1 month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
```

```
estimate 'Total FU NMB,Tx=0' intercept 3 month 24 month04 12 month08 4
;
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12

month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;
    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_0' ;
      title5 'MAR SENSITIVITY ANALYSES !!' ;
  run ;

  *  NMB_25 ;
  proc mixed data=missing covtest noclprint ;
    model NMB_25= age40 prevhospC txgroup month month*txgroup
                     month04 month04*txgroup month08 month08*txgroup
                    /solution;
random intercept month / subject = patid type =UN gc g gcorr v vcorr;
    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8

month08 4 month08*txgroup 4 ;
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
      estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12
month08 4 ;
```

```
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12

month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;
    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_25' ;
      title5 'MAR SENSITIVITY ANALYSES !!' ;
  run ;

  *  NMB_50 ;
  proc mixed data=missing covtest noclprint ;
    model NMB_50= age40 prevhospC txgroup month month*txgroup
                    month04 month04*txgroup month08 month08*txgroup
                   /solution;
random intercept month / subject = patid type =UN gc g gcorr v vcorr;
    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8

month08 4 month08*txgroup 4 ;
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
      estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12
month08 4 ;
```

```
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12
month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;
    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_50' ;
      title5 'MAR SENSITIVITY ANALYSES !!' ;
  run ;

  *  NMB_100 ;
  proc mixed data=missing covtest noclprint ;
    model NMB_100= age40 prevhospC txgroup month month*txgroup
                    month04 month04*txgroup month08 month08*txgroup
                   /solution;
random intercept month / subject = patid type =UN gc g gcorr v vcorr;
      contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8
month08 4 month08*txgroup 4 ;
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
      estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12
month08 4 ;
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12
month08 4  month08*txgroup 4 ;
```

```
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;
    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_100' ;
      title5 'MAR SENSITIVITY ANALYSES !!' ;
  run ;
```

L. SENSITIVITY ANALYSIS 1 JOINT ME MODEL

```
*  Program: Joint_Miss, MAR Sensitivity.SAS                          ;
*  Description:  This program first obtains estimats from the        ;
*  separate models and then jointly estimates the parameters         ;
*  Programmer:   Diane Fairclough;
*  Date:         20/Dec/2007     ;
*  Revised:      Dennis D. Gagnon;
*  Date:         03/08/08        ;
*  Revised:      Diane Fairclough;
*  Date:         21Mar2008       ;
*  Removed intercept random effect from Time to DO model             ;
*  Revised:      Dennis D. Gagnon                                    ;
*                05/26/08                                            ;
*                MAR SENSITIVITY ANALYSES !!                         ;
  libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat\Sensitivity, MAR' ;
  *libname indat 'C:\Projects\Consult\Engelhart\SASlib' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Joint_Miss, MAR Sensitivity.SAS    Dissertation: Estimating
INMB in a Clinical Study With Missing Data' ;
*********************************************************************
  PREPARE DATA ;

  proc print data=indat.missing(obs=20) ;
    title3 'First 20 Observations of Missing' ;
  run ;

  proc summary data=indat.missing nway;  * Identifies time of last obs;
    class patid;
      var month ;
      output out=work.last max=Last;
      run;

  proc freq data=work.last;
    table last/missing;
      run;

  data missing ;
    merge indat.missing work.last(keep=patid last);
      by patid;
      *** Time to last Assessment ***;
      if last eq 12 then Censor=1;
    else censor=0;
      L_Last=log(last+1);
      Label Censor='Completor (1=Yes, 0=No)'
            L_Last='Ln(Time to Last Obs + 1)';
  run ;

    proc print data=missing (obs=20);
    title3 'Print of Missing with Month and Knots at Months 4 and 8
Derived' ;
  run ;

*********************************************************************
  GET ESTIMATES FOR MU and SCALE (SAME FOR ALL NMBs) ;

*** Initial Estimates for Time to DO portion of model ***;
```

```
proc lifereg data=work.missing;
  model L_last*Censor(1)=/ dist=normal; * Used Normal because already
logged *;
  where month eq 0;
  title3 'Estimate Mu and Scale' ;
  title5 'MAR Sensitivity Analysis' ;
run;
************************************************************************
NMB_0 ;
*** Reference Model ***;
proc nlmixed data=work.missing ;
  title3 'Longitudinal and Time to Event with No correlation, NMB_0';
  title5 'MAR Sensitivity Analyses' ;
  where nmb_0 ne .;  * Proc does not deal well with missing values *;

  parms b0=-16.1150 b1=0.1349 b2=1.6742 b3=-0.2045 b4=-1.2214 b5=0.0888
b6=-0.2484 b7=-0.0677 b8=0.0132 b9=-2.9815
        s1=16.9651 s12=-1.5065 s2=0.6207 s2w=140.59
        mu0=2.8497 st=1.2775;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_0-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_0 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;
  run;

*** Joint Model with Two Random Effects ***;
```

```
*** Note this does not converge ... ****;
proc nlmixed data=work.missing ;
  title3 'Joint Longitudinal and Time to Event, NMB_0';
  title5 'MAR Sensitivity Analyses' ;
  where nmb_0 ne .;  * Proc does not deal well with missing values *;

  parms b0=-16.1150 b1=0.1349 b2=1.6742 b3=-0.2045 b4=-1.2214 b5=0.0888
b6=-0.2484 b7=-0.0677 b8=0.0132 b9=-2.9815
        s1=16.9651 s12=-1.5065 s2=0.6207 s2w=140.59
        mu0=2.8497 st=1.2775 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_0-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0  +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_0 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;
  run;

*************************************************************************
NMB_25 ;
*** Reference Model ***;
proc nlmixed data=work.missing;
  title3 'Longitudinal and Time to Event with No correlation, NMB_25';
  title5 'MAR Sensitivity Analyses' ;
  where nmb_25 ne .;  * Proc does not deal well with missing values *;

  parms b0=-10.9848 b1=0.1451 b2=1.7083 b3=-0.0032 b4=-1.2555 b5=-
0.1069 b6=-0.2634 b7=-0.0821 b8=0.0041 b9=-3.1334
```

```
        s1=16.9599 s12=-1.5232 s2=0.6186 s2w=141.25
        mu0=2.8497 st=1.2775;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_25-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_25 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;
  run;
*** Joint Mdel with Two Random Effects ***;
proc nlmixed data=work.missing;
  title3 'Joint Longitudinal and Time to Event, NMB_25';
  title5 'MAR Sensitivity Analyses' ;
  where nmb_25 ne .;  * Proc does not deal well with missing values *;

  parms b0=-10.9848 b1=0.1451 b2=1.7083 b3=-0.0032 b4=-1.2555 b5=-
0.1069 b6=-0.2634 b7=-0.0821 b8=0.0041 b9=-3.1334
        s1=16.9599 s12=-1.5232 s2=0.6186 s2w=141.25
        mu0=2.8497 st=1.2775 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
```

```
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_25-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0 +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_25 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;
  run;
*****************************************************************
NMB_50 ;
*** Reference Model ***;
proc nlmixed data=work.missing;
  title3 'Longitudinal and Time to Event with No correlation, NMB_50';
  title5 'MAR Sensitivity Analyses' ;
  where nmb_50 ne .;  * Proc does not deal well with missing values *;

  parms b0=-5.8547 b1=0.1552 b2=1.7423 b3=0.1982 b4=-1.2893 b5=-0.3026
b6=-0.2778 b7=-0.0957 b8=-0.0051 b9=-3.2842
        s1=16.9738 s12=-1.5397 s2=0.6199 s2w=142.52
        mu0=2.8497 st=1.2775;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_50-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
```

```
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_50 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;
  run;

*** Joint Mdel with Two Random Effects ***;
proc nlmixed data=work.missing ;
  title3 'Joint Longitudinal and Time to Event, NMB_50';
  title5 'MAR Sensitivity Analyses' ;
  where nmb_50 ne .;  * Proc does not deal well with missing values *;

  parms b0=-5.8547 b1=0.1552 b2=1.7423 b3=0.1982 b4=-1.2893 b5=-0.3026
b6=-0.2778 b7=-0.0957 b8=-0.0051 b9=-3.2842
        s1=16.9738 s12=-1.5397 s2=0.6199 s2w=142.52
        mu0=2.8497 st=1.2775 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_50-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0 +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_50 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;
```

```
  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;
  run;
*************************************************************************
NMB_100 ;
*** Reference Model ***;
proc nlmixed data=work.missing;
  title3 'Longitudinal and Time to Event with No correlation, NMB_100';
  title5 'MAR Sensitivity Analyses' ;
  where nmb_100 ne .;  * Proc does not deal well with missing values *;

  parms b0=4.4047 b1=0.1755 b2=1.8101 b3=0.6010 b4=-1.3562 b5=-0.6940
b6=-0.3043 b7=-0.1209 b8=-0.0239 b9=-3.5817
        s1=17.0551 s12=-1.5726 s2=0.6320 s2w=146.91
        mu0=2.8497 st=1.2775;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_100-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_100 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;
  run;
```

```
*** Joint Mdel with Two Random Effects ***;
proc nlmixed data=work.missing;
  title3 'Joint Longitudinal and Time to Event, NMB_100';
  title5 'MAR Sensitivity Analyses' ;
  where nmb_100 ne .;  * Proc does not deal well with missing values *;

  parms b0=4.4047 b1=0.1755 b2=1.8101 b3=0.6010 b4=-1.3562 b5=-0.6940
b6=-0.3043 b7=-0.1209 b8=-0.0239 b9=-3.5817
        s1=17.0551 s12=-1.5726 s2=0.6320 s2w=146.91
        mu0=2.8497 st=1.2775 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_100-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0 +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_100 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;
  run;
```

M. SENSITIVITY ANALYSIS 2 ANCOVA MODEL

```
*  Program:      LOCF, MNAR Sensitivity.SAS                          ;
*  Description:  This program reads the COMPLETE dataset and the ;
*  MISSING dataset and creates an LOCF dataset.  Baseline is     ;
*  brought forward if there is not follow-up.                    ;
*     THIS IS THE MNAR SENSITIVITY ANALYSIS !                    ;
*  Programmer:   Dennis D. Gagnon                                ;
*  Date:         05/26/2008                                      ;
libname indat  'C:\UMDNJ\Dissertation\NMB\V802dat' ;
libname outdat 'C:\UMDNJ\Dissertation\NMB\V802dat\Sensitivity, MNAR' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'LOCF, MNAR Sensitivity.SAS      Dissertation: Estimating INMB
in a Clinical Study With Missing Data' ;
  proc sort data=indat.complete out=complete(keep=patid month txgroup
age40 prevhospc month04 month08) ;
    by patid month ; run ;

  proc sort data=outdat.missing out=missing ;
    by patid month ; run ;

  data full ;
    merge complete missing ;
      by patid month ;  run ;

  proc print data=full(firstobs=2369) ;
    title3 'Last Observations of Full, Starting at 2369' ;   run ;

  data locf ;
    set full ;
      by patid month ;
      array last {6} lc lu l0 l25 l50 l100 ;
      array current {6} cost util nmb_0 nmb_25 nmb_50 nmb_100 ;
      retain lc lu l0 l25 l50 l100 ;
      if first.patid then do ;
        do i = 1 to 6 ;
          last{i} = . ;
        end ;
      end ;
      do i = 1 to 6 ;
        if current{i} = . then current{i} = last{i} ;
      end ;
      do i = 1 to 6 ;
        last{i} = current{i} ;
      end ;
      drop i lc lu l0 l25 l50 l100 ;  run ;

  data outdat.locf ;
    set locf ;
  run ;

  proc contents data=outdat.locf ;
    title3 'Contents of LOCF, Sensitivity MNAR' ;
  run ;

  proc print data=outdat.locf(obs=20) ;
    title3 'First 20 Observations of LOCF, Sensitivity MNAR' ;   run ;
```

M. SENSITIVITY ANALYSIS 2 ANCOVA MODEL (CONTINUED)

```
*  Program:      Subject LOCF, MNAR Sensitivity.SAS                  ;
*  Description:  This program reads the LOCF dataset and creates a   ;
*  SUBJect-Level complete dataset.  NMBs are summed across months 4, ;
*  8, 12.                                                            ;
*     THIS IS THE MNAR SENSITIVITY ANALYSIS !!!!                     ;
*  Programmer:   Dennis D. Gagnon                                    ;
*  Date:         05/26/2008                                          ;
libname indat  'C:\UMDNJ\Dissertation\NMB\V802dat\Sensitivity, MNAR' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Subject LOCF, MNAR Sensitivity.SAS
Dissertation: Estimating INMB in a Clinical Study With Missing Data' ;

  proc sort data=indat.locf out=locf (rename=(nmb_0=n_0 nmb_25=n_25
nmb_50=n_50 nmb_100=n_100)) ;
    by patid month ;   run ;

  proc print data=locf(obs=20) ;
    title3 'First 20 Observations of LOCF' ;   run ;

  data indat.subject_locf ;
    set locf ;
      by patid month ;
      retain nmb_0 nmb_25 nmb_50 nmb_100 bln0 bln25 bln50 bln100 0 ;
      array nmb{4} nmb_0 nmb_25 nmb_50 nmb_100 ;
      array bl{4} bln0 bln25 bln50 bln100 ;
      array nm{4} n_0 n_25 n_50 n_100 ;
      if first.patid then do ;
        do i=1 to 4 ;
          nmb{i} = 0 ;
            bl{i} = 0 ;
        end ;
    end ;
      if month = 0 then do ;
        do i=1 to 4 ;
          bl{i} = nm{i} ;
        end ;
      end ;
      else do ;
      do i=1 to 4 ;
          nmb{i} = nmb{i} + nm{i} ;
        end ;
      end ;
      drop i util cost month n_0 n_25 n_50 n_100 month month04 month08
;
      if last.patid then output ;   run ;

  proc contents data=indat.subject_locf ;
    title3 'Contents of Subject_LOCF' ;
      title5 'MNAR Sensitivity Analysis' ;   run ;

  proc print data=indat.subject_locf(obs=20) ;
    title3 'First 20 Observations of Subject_LOCF' ;
      title5 'MNAR Sensitivity Analysis' ;   run ;
```

M. SENSITIVITY ANALYSIS 2 ANCOVA MODEL (CONTINUED)

```
*  Program:  UNI LOCF, MNAR Sensitivity.SAS                          ;
*  Description:  This program reads the SUBJECT_LOCF dataset and runs;
*  to determine the INMB. First a t-test is run, then a simple GLM   ;
*  with no covariates, then GLMs with age40, previous hosps and      ;
*  baseline nmb.                                                     ;
*  THIS IS THE MNAR SENSITIVITY ANALYSIS !!!!                        ;
*  Programmer:   Dennis D. Gagnon                                    ;
*  Date:         05/26/2008                                          ;
libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat\Sensitivity, MNAR' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Uni LOCF, MNAR Sensitivity.SAS              Dissertation:
Estimating INMB in a Clinical Study With Missing Data' ;

  proc print data=indat.subject_locf(obs=20) ;
    title3 'First 20 Observations of Subject_LOCF' ;   run ;

  proc ttest data=indat.subject_locf ;
    class txgroup ;
      var nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 'T-Tests on LOCF Difference in Mean NMBs, Complete Data
Set' ;
      title5 'MNAR Sensitivity Analysis' ;   run ;

  proc glm data=indat.subject_locf ;
    class txgroup ;
      model nmb_0 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB0 Against Treatment Only, LOCF' ;
      title5 'MNAR Sensitivity Analysis' ;   run ;

  proc glm data=indat.subject_locf ;
    class txgroup ;
      model nmb_25 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB25 Against Treatment Only, LOCF' ;
      title5 'MNAR Sensitivity Analysis' ;   run ;

  proc glm data=indat.subject_locf ;
    class txgroup ;
      model nmb_50 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB50 Against Treatment Only, LOCF' ;
      title5 'MNAR Sensitivity Analysis' ;   run ;

  proc glm data=indat.subject_locf ;
    class txgroup ;
      model nmb_100 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB100 Against Treatment Only, LOCF' ;
      title5 'MNAR Sensitivity Analysis' ;
  run ;

  proc glm data=indat.subject_locf ;
    class txgroup prevhospc ;
      model nmb_0 = txgroup age40 prevhospc bln0 / solution ;
```

```
    lsmeans txgroup / stderr tdiff pdiff cl ;
    title3 'OLS of NMB0 Against Treatment And Covariates, LOCF' ;
    title5 'MNAR Sensitivity Analysis' ;
run ;

proc glm data=indat.subject_locf ;
  class txgroup prevhospc ;
    model nmb_25 = txgroup age40 prevhospc bln25 / solution ;
    lsmeans txgroup / stderr tdiff pdiff cl ;
    title3 'OLS of NMB25 Against Treatment And Covariates, LOCF' ;
    title5 'MNAR Sensitivity Analysis' ;
run ;

proc glm data=indat.subject_locf ;
  class txgroup prevhospc ;
    model nmb_50 = txgroup age40 prevhospc bln50 / solution ;
    lsmeans txgroup / stderr tdiff pdiff cl ;
    title3 'OLS of NMB50 Against Treatment And Covariates, LOCF' ;
    title5 'MNAR Sensitivity Analysis' ;
run ;

proc glm data=indat.subject_locf ;
  class txgroup prevhospc ;
    model nmb_100 = txgroup age40 prevhospc bln100 / solution ;
    lsmeans txgroup / stderr tdiff pdiff cl ;
    title3 'OLS of NMB100 Against Treatment And Covariates, LOCF' ;
    title5 'MNAR Sensitivity Analysis' ;
run ;
quit ;
```

N. SENSITIVITY ANALYSIS 2 ME MODEL

```
*  Program:  MAR_Miss, MNAR Sensitivity.SAS                          ;
*  Description:  This program reads the MISSING dataset and creates;
*  the month & month knot variables (one knot at month 4 and one   ;
*  know at month 8). A mixed effects model is then run estimating  ;
*  the difference in the changes in NMB from baseline across       ;
*  treatment groups. This program uses the data simulated from     ;
*  Dr. Fairclough.                                                 ;
*     NMB are divided by 1000.                                     ;
*     MNAR SENSITIVITY ANALYSES !!!!                               ;
*  Programmer:   Dennis D. Gagnon                                  ;
*  Date:         05/26/2008                                        ;
  libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat\Sensitivity, MNAR' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'MAR_Miss, MNAR Sensitivity.SAS                Dissertation:
Estimating INMB in a Clinical Study With Missing Data' ;

  proc print data=indat.missing(obs=20) ;
    title3 'First 20 Observations of Missing' ;
  run ;
  data missing ;
    set indat.missing ;
  run ;
  proc print data=missing(obs=20) ;
    title3 'Print of Missing with Month and Knots at Months 4 and 8
Derived' ;   run ;

  *  Start Running of Mixed Models ;
  *  NMB_0 ;

  proc mixed data=missing covtest noclprint ;
    model NMB_0= age40 prevhospC txgroup month month*txgroup
                     month04 month04*txgroup month08 month08*txgroup
                    /solution;
random intercept month / subject = patid type =UN gc g gcorr v vcorr;

    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8

month08 4 month08*txgroup 4 ;
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
```

```
      estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12
month08 4 ;
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12

month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;

    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_0' ;
      title5 'MNAR SENSITIVITY ANALYSES !!' ;
  run ;

  *  NMB_25 ;

  proc mixed data=missing covtest noclprint ;
    model NMB_25= age40 prevhospC txgroup month month*txgroup
                    month04 month04*txgroup month08 month08*txgroup
                   /solution;
random intercept month / subject = patid type =UN gc g gcorr v vcorr;

    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8

month08 4 month08*txgroup 4 ;
```

```
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
      estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12
month08 4 ;
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12

month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;

    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_25' ;
      title5 'MNAR SENSITIVITY ANALYSES !!' ;
  run ;

  *  NMB_50 ;

  proc mixed data=missing covtest noclprint ;
    model NMB_50= age40 prevhospC txgroup month month*txgroup
                    month04 month04*txgroup month08 month08*txgroup
                   /solution;
random intercept month / subject = patid type =UN gc g gcorr v vcorr;

    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8
```

```
month08 4 month08*txgroup 4 ;
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
      estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12
month08 4 ;
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12

month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;

    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_50' ;
      title5 'MNAR SENSITIVITY ANALYSES !!' ;
  run ;

  *  NMB_100 ;

  proc mixed data=missing covtest noclprint ;
    model NMB_100= age40 prevhospC txgroup month month*txgroup
                    month04 month04*txgroup month08 month08*txgroup
                   /solution;
random intercept month / subject = patid type =UN gc g gcorr v vcorr;

    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
```

```
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8

month08 4 month08*txgroup 4 ;
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
      estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12
month08 4 ;
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12

month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;

    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_100' ;
      title5 'MNAR SENSITIVITY ANALYSES !!' ;
  run ;
```

O. SENSITIVITY ANALYSIS 2 JOINT ME MODEL

```
*  Program:  Joint_Miss, MNAR Sensitivity.SAS                          ;
*  Description:  This program first obtains estimats from the          ;
*  separate models and then jointly estimates the parameters           ;
*  Programmer:   Diane Fairclough                                      ;
*  Date:         20/Dec/2007                                           ;
*  Revised:      Dennis D. Gagnon                                      ;
*  Date:         03/08/08                                              ;
*  Revised:      Diane Fairclough                                      ;
*  Date:         21Mar2008                                             ;
*                Removed intercept random effect from Time to DO       ;
*                model                                                 ;
*  Revised:      Dennis D. Gagnon                                      ;
*                05/26/08                                              ;
*                MNAR SENSITIVITY ANALYSES !!                          ;
  libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat\Sensitivity, MNAR' ;
  *libname indat 'C:\Projects\Consult\Engelhart\SASlib' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Joint_Miss, MNAR Sensitivity.SAS    Dissertation: Estimating
INMB in a Clinical Study With Missing Data' ;
*********************************************************************
  PREPARE DATA ;
    proc print data=indat.missing(obs=20) ;
    title3 'First 20 Observations of Missing' ;
  run ;

proc summary data=indat.missing nway;  * Identifies time of last obs *;
    class patid;
      var month ;
      output out=work.last max=Last;
      run;

  proc freq data=work.last;
    table last/missing;
      run;

  data missing ;
    merge indat.missing work.last(keep=patid last);
      by patid;
      *** Time to last Assessment ***;
      if last eq 12 then Censor=1;
    else censor=0;
      L_Last=log(last+1);
      Label Censor='Completor (1=Yes, 0=No)'
            L_Last='Ln(Time to Last Obs + 1)';
  run ;

  proc print data=missing (obs=20);
    title3 'Print of Missing with Month and Knots at Months 4 and 8
Derived' ;
  run ;

*********************************************************************
  GET ESTIMATES FOR MU and SCALE (SAME FOR ALL NMBs) ;
*** Initial Estimates for Time to DO portion of model ***;
proc lifereg data=work.missing;
```

```
  model L_last*Censor(1)=/ dist=normal; * Used Normal because already
logged *;
  where month eq 0;
  title3 'Estimate Mu and Scale' ;
  title5 'MNAR Sensitivity Analysis' ;
run;
************************************************************************
NMB_0 ;
*** Reference Model ***;
proc nlmixed data=work.missing ;
  title3 'Longitudinal and Time to Event with No correlation, NMB_0';
  title5 'MNAR Sensitivity Analyses' ;
  where nmb_0 ne .;  * Proc does not deal well with missing values *;

  parms b0=-16.0748 b1=0.1140 b2=1.4719 b3=-0.2941 b4=-1.2006 b5=-
0.1134 b6=-0.0909 b7=0.0961 b8=0.0215 b9=-2.6116
        s1=16.8619 s12=-1.5543 s2=0.7354 s2w=160.68
        mu0=2.2591 st=1.4175;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_0-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_0 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;
  run;

*** Joint Model with Two Random Effects ***;
*** Note this does not converge ... ****;
```

```
proc nlmixed data=work.missing ;
  title3 'Joint Longitudinal and Time to Event, NMB_0';
  title5 'MNAR Sensitivity Analyses' ;
  where nmb_0 ne .;  * Proc does not deal well with missing values *;

  parms b0=-16.0748 b1=0.1140 b2=1.4719 b3=-0.2941 b4=-1.2006 b5=-
0.1134 b6=-0.0909 b7=0.0961 b8=0.0215 b9=-2.6116
        s1=16.8619 s12=-1.5543 s2=0.7354 s2w=160.68
        mu0=2.2591 st=1.4175 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_0-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0  +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_0 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;
  run;

*****************************************************************
NMB_25 ;
*** Reference Model ***;
proc nlmixed data=work.missing;
  title3 'Longitudinal and Time to Event with No correlation, NMB_25';
  title5 'MNAR Sensitivity Analyses' ;
  where nmb_25 ne .;  * Proc does not deal well with missing values *;
  parms b0=-10.9384 b1=0.1219 b2=1.4828 b3=-0.0958 b4=-1.2267 b5=-
0.3190 b6=-0.1133 b7=0.1009 b8=0.0136 b9=-2.7044
        s1=16.8415 s12=-1.5726 s2=0.7179 s2w=160.81
        mu0=2.2591 st=1.4175;
```

```
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_25-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_25 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 + b2*24 + b4*12 + b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff' b1*3 + b3*24 +  b5*12 + b7*4 ;
  run;

*** Joint Mdel with Two Random Effects ***;
proc nlmixed data=work.missing;
  title3 'Joint Longitudinal and Time to Event, NMB_25';
  title5 'MNAR Sensitivity Analyses' ;
  where nmb_25 ne .;  * Proc does not deal well with missing values *;
  parms b0=-10.9384 b1=0.1219 b2=1.4828 b3=-0.0958 b4=-1.2267 b5=-
0.3190 b6=-0.1133 b7=0.1009 b8=0.0136 b9=-2.7044
        s1=16.8415 s12=-1.5726 s2=0.7179 s2w=160.81
        mu0=2.2591 st=1.4175 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup +b8*age40
+b9*prevhospc +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_25-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0 +lambda2*d2;
```

```
    *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_25 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;
  estimate 'Total FU NMB, Tx=0' b0*3 + b2*24 + b4*12 + b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'b1*3 + b3*24 + b5*12 +        b7*4 ;
  run;

*************************************************************************
NMB_50 ;
*** Reference Model ***;
proc nlmixed data=work.missing;
  title3 'Longitudinal and Time to Event with No correlation, NMB_50';
  title5 'MNAR Sensitivity Analyses' ;
  where nmb_50 ne .;  * Proc does not deal well with missing values *;
  parms b0=-5.8020 b1=0.1289 b2=1.4937 b3=0.1026 b4=-1.2527 b5=-0.5242
b6=-0.1361 b7=0.1053 b8=0.0058 b9=-2.7967
        s1=16.8356 s12=-1.5905 s2=0.7017 s2w=161.58
        mu0=2.2591 st=1.4175;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup +b8*age40
+b9*prevhospc +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_50-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_50 ~ general(ll_Y+ll_T);
```

```
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;
  estimate 'Total FU NMB, Tx=0' b0*3 + b2*24 + b4*12 +    b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;   run;

*** Joint Mdel with Two Random Effects ***;
proc nlmixed data=work.missing ;
  title3 'Joint Longitudinal and Time to Event, NMB_50';
  title5 'MNAR Sensitivity Analyses' ;
  where nmb_50 ne .;  * Proc does not deal well with missing values *;
  parms b0=-5.8020 b1=0.1289 b2=1.4937 b3=0.1026 b4=-1.2527 b5=-0.5242
b6=-0.1361 b7=0.1053 b8=0.0058 b9=-2.7967
        s1=16.8356 s12=-1.5905 s2=0.7017 s2w=161.58
        mu0=2.2591 st=1.4175 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_50-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0 +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_50 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 + b2*24 + b4*12 + b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff' b1*3 + b3*24 + b5*12 + b7*4 ;
  run;


*****************************************************************
NMB_100 ;

*** Reference Model ***;
proc nlmixed data=work.missing;
```

```
  title3 'Longitudinal and Time to Event with No correlation, NMB_100';
  title5 'MNAR Sensitivity Analyses' ;
  where nmb_100 ne .;  * Proc does not deal well with missing values *;

  parms b0=4.4707 b1=0.1429 b2=1.5152 b3=0.4994 b4=-1.3045 b5=-0.9334
b6=-0.1819 b7=0.1137 b8=-0.0100 b9=-2.9806
        s1=16.8764 s12=-1.6249 s2=0.6756 s2w=164.90
        mu0=2.2591 st=1.4175;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_100-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_100 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;
  run;

*** Joint Mdel with Two Random Effects ***;
proc nlmixed data=work.missing;
  title3 'Joint Longitudinal and Time to Event, NMB_100';
  title5 'MNAR Sensitivity Analyses' ;
  where nmb_100 ne .;  * Proc does not deal well with missing values *;

  parms b0=4.4707 b1=0.1429 b2=1.5152 b3=0.4994 b4=-1.3045 b5=-0.9334
b6=-0.1819 b7=0.1137 b8=-0.0100 b9=-2.9806
        s1=16.8764 s12=-1.6249 s2=0.6756 s2w=164.90
        mu0=2.2591 st=1.4175 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
```

```
  s2t=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_100-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0 +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_100 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +        b2*24 +         b4*12 +
b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;
  run;
```

P. POST HOC ANALYSIS ANCOVA MODEL

```
*  Program:      LOCF, Trajectory.SAS                                    ;
*  Description:  This program reads the COMPLETE dataset and the         ;
*  MISSSING Dataset and creates an LOCF dataset.  Baseline is brought;
*  forward if there is not follow-up.                                    ;
*     THIS IS THE TRAJECTORY SENSITIVITY ANALYSIS !                      ;
*  Programmer:   Dennis D. Gagnon                                        ;
*  Date:         06/30/2008                                              ;
  libname indat  'C:\UMDNJ\Dissertation\NMB\V802dat' ;
  libname outdat 'C:\UMDNJ\Dissertation\NMB\V802dat\Trajectory' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'LOCF, Trajectory.SAS           Dissertation: Estimating INMB
in a Clinical Study With Missing Data' ;

  proc sort data=indat.complete out=complete(keep=patid month txgroup
age40 prevhospc month04 month08) ;
    by patid month ;  run ;

  proc sort data=outdat.missing out=missing ;
    by patid month ;  run ;

  data full ;
    merge complete missing ;
      by patid month ;  run ;

  proc print data=full(firstobs=2369) ;
    title3 'Last Observations of Full, Starting at 2369' ;  run ;

  data locf ;
    set full ;
      by patid month ;
      array last {6} lc lu l0 l25 l50 l100 ;
      array current {6} cost util nmb_0 nmb_25 nmb_50 nmb_100 ;
      retain lc lu l0 l25 l50 l100 ;
      if first.patid then do ;
        do i = 1 to 6 ;
          last{i} = . ;
        end ;
      end ;
      do i = 1 to 6 ;
        if current{i} = . then current{i} = last{i} ;
      end ;
      do i = 1 to 6 ;
        last{i} = current{i} ;
      end ;
      drop i lc lu l0 l25 l50 l100 ;   run ;

  data outdat.locf ;
    set locf ;   run ;

  proc contents data=outdat.locf ;
    title3 'Contents of LOCF, Trajectory Sensitivity Analysis' ;  run ;

  proc print data=outdat.locf(obs=20) ;
    title3 'First 20 Observations of LOCF, Trajectory Sensitivity
Analysis' ;   run ;
```

P. POST HOC ANALYSIS ANCOVA MODEL (CONTINUED)

```
*  Program:      Subject LOCF, Trajectory.SAS                          ;
*  Description:  This program reads the LOCF dataset and creates A     ;
*  subject-level complete dataset.  NMBs are summed across months 4,   ;
*  8, & 12.                                                            ;
*     THIS IS THE TRAJECTORY SENSITIVITY ANALYSIS !!                   ;
*  Programmer:   Dennis D. Gagnon                                      ;
*  Date:         06/30/2008                                            ;
  libname indat  'C:\UMDNJ\Dissertation\NMB\V802dat\Trajectory' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Subject LOCF, Trajectory.SAS
Dissertation: Estimating INMB in a Clinical Study With Missing Data' ;

  proc sort data=indat.locf out=locf (rename=(nmb_0=n_0 nmb_25=n_25
nmb_50=n_50 nmb_100=n_100)) ;
    by patid month ;
  run ;
  proc print data=locf(obs=20) ;
    title3 'First 20 Observations of LOCF' ;   run ;

  data indat.subject_locf ;
    set locf ;
      by patid month ;
      retain nmb_0 nmb_25 nmb_50 nmb_100 bln0 bln25 bln50 bln100 0 ;
      array nmb{4} nmb_0 nmb_25 nmb_50 nmb_100 ;
      array bl{4} bln0 bln25 bln50 bln100 ;
      array nm{4} n_0 n_25 n_50 n_100 ;
      if first.patid then do ;
        do i=1 to 4 ;
          nmb{i} = 0 ;
            bl{i} = 0 ;
        end ;
    end ;
      if month = 0 then do ;
        do i=1 to 4 ;
          bl{i} = nm{i} ;
        end ;
      end ;
      else do ;
      do i=1 to 4 ;
          nmb{i} = nmb{i} + nm{i} ;
        end ;
      end ;
      drop i util cost month n_0 n_25 n_50 n_100 month month04 month08
;
      if last.patid then output ;   run ;

  proc contents data=indat.subject_locf ;
    title3 'Contents of Subject_LOCF' ;
      title5 'Trajectory Sensitivity Analysis' ;  run ;

  proc print data=indat.subject_locf(obs=20) ;
    title3 'First 20 Observations of Subject_LOCF' ;
      title5 'Trajectory Sensitivity Analysis' ;  run ;
```

P. POST HOC ANALYSIS ANCOVA MODEL (CONTINUED)

```
*  Program:      UNI LOCF, Trajectory.SAS                              ;
*  Description:  This program reads the SUBJECT_LOCF dataset and       ;
*  runs analyses to determine the INMB. First a t-test is run,         ;
*  then a simple GLM with no covariates, then GLMs with age40,         ;
*  previous hosps and baseline nmb.                                    ;
*     THIS IS THE TRAJECTORY SENSITIVITY ANALYSIS !!!!                 ;
*  Programmer:   Dennis D. Gagnon                                      ;
*  Date:         06/30/2008                                            ;
  libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat\Trajectory' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Uni LOCF, Trajectory.SAS                    Dissertation:
Estimating INMB in a Clinical Study With Missing Data' ;
  proc print data=indat.subject_locf(obs=20) ;
    title3 'First 20 Observations of Subject_LOCF' ;
  run ;

  proc ttest data=indat.subject_locf ;
    class txgroup ;
      var nmb_0 nmb_25 nmb_50 nmb_100 ;
      title3 'T-Tests on LOCF Difference in Mean NMBs, Complete Data
Set' ;
      title5 'Trajectory Sensitivity Analysis' ;
  run ;

  proc glm data=indat.subject_locf ;
    class txgroup ;
      model nmb_0 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB0 Against Treatment Only, LOCF' ;
      title5 'Trajectory Sensitivity Analysis' ;
  run ;

  proc glm data=indat.subject_locf ;
    class txgroup ;
      model nmb_25 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB25 Against Treatment Only, LOCF' ;
      title5 'Trajectory Sensitivity Analysis' ;
  run ;

  proc glm data=indat.subject_locf ;
    class txgroup ;
      model nmb_50 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB50 Against Treatment Only, LOCF' ;
      title5 'Trajectory Sensitivity Analysis' ;
  run ;

  proc glm data=indat.subject_locf ;
    class txgroup ;
      model nmb_100 = txgroup / solution ;
      lsmeans txgroup / stderr tdiff pdiff cl ;
      title3 'OLS of NMB100 Against Treatment Only, LOCF' ;
      title5 'Trajectory Sensitivity Analysis' ;
  run ;
```

```
proc glm data=indat.subject_locf ;
  class txgroup prevhospc ;
    model nmb_0 = txgroup age40 prevhospc bln0 / solution ;
    lsmeans txgroup / stderr tdiff pdiff cl ;
    title3 'OLS of NMB0 Against Treatment And Covariates, LOCF' ;
    title5 'Trajectory Sensitivity Analysis' ;   run ;

proc glm data=indat.subject_locf ;
  class txgroup prevhospc ;
    model nmb_25 = txgroup age40 prevhospc bln25 / solution ;
    lsmeans txgroup / stderr tdiff pdiff cl ;
    title3 'OLS of NMB25 Against Treatment And Covariates, LOCF' ;
    title5 'Trajectory Sensitivity Analysis' ;  run ;

proc glm data=indat.subject_locf ;
  class txgroup prevhospc ;
    model nmb_50 = txgroup age40 prevhospc bln50 / solution ;
    lsmeans txgroup / stderr tdiff pdiff cl ;
    title3 'OLS of NMB50 Against Treatment And Covariates, LOCF' ;
    title5 'Trajectory Sensitivity Analysis' ;  run ;

proc glm data=indat.subject_locf ;
  class txgroup prevhospc ;
    model nmb_100 = txgroup age40 prevhospc bln100 / solution ;
    lsmeans txgroup / stderr tdiff pdiff cl ;
    title3 'OLS of NMB100 Against Treatment And Covariates, LOCF' ;
    title5 'Trajectory Sensitivity Analysis' ;  run ;
quit ;
```

Q. POST HOC ANALYSIS ME MODEL

```
*  Program:      MAR_Miss, Trajectory.SAS                              ;
*  Descriptin:  This program reads the MISSING dataset and creates  ;
*  the month & month knot variables (one knot at month 4 and one    ;
*  know at month 8). A mixed effects model is then run estimating   ;
*  the difference in the changes in the NMB from baseline across    ;
*  treatment groups.                                                 ;
*     This program uses the data simulated from Dr. Fairclough.     ;
*     NMB are divided by 1000.                                       ;
*     TRAJECTORY SENSITIVITY ANALYSIS !!!                            ;
*  Programmer:   Dennis D. Gagnon                                    ;
*  Date:         06/30/2008                                          ;
  libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat\Trajectory' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'MAR_Miss, Trajectory.SAS                       Dissertation:
Estimating INMB in a Clinical Study With Missing Data' ;
  proc print data=indat.missing(obs=20) ;
    title3 'First 20 Observations of Missing' ;
  run ;

  data missing ;
    set indat.missing ;
  run ;

  proc print data=missing(obs=20) ;
    title3 'Print of Missing with Month and Knots at Months 4 and 8
Derived' ;
  run ;

  *  Start Running of Mixed Models ;
  *  NMB_0 ;
  proc mixed data=missing covtest noclprint ;
    model NMB_0= age40 prevhospC txgroup month month*txgroup
                    month04 month04*txgroup month08 month08*txgroup
                   /solution;
    random intercept month / subject = patid type =UN gc g gcorr v
vcorr;

    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
    estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4
;
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8
```

```
month08 4 month08*txgroup 4 ;
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
      estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12
month08 4 ;
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12

month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;

    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_0' ;
      title5 'TRAJECTORY SENSITIVITY ANALYSES !!' ;   run ;

  *  NMB_25 ;
  proc mixed data=missing covtest noclprint ;
    model NMB_25= age40 prevhospC txgroup month month*txgroup
                    month04 month04*txgroup month08 month08*txgroup
                   /solution;
random intercept month / subject = patid type =UN gc g gcorr v vcorr;

    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
  estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8
```

```
month08 4 month08*txgroup 4 ;
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12 month08 4
;
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12

month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;
    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_25' ;
      title5 'TRAJECTORY SENSITIVITY ANALYSES !!' ;
  run ;

  *  NMB_50 ;
  proc mixed data=missing covtest noclprint ;
    model NMB_50= age40 prevhospC txgroup month month*txgroup
                    month04 month04*txgroup month08 month08*txgroup
                   /solution;
 random intercept month / subject = patid type =UN gc g gcorr v vcorr;
    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
   estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8

month08 4 month08*txgroup 4 ;
```

```
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
      estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12
month08 4 ;
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12

month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;

    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_50' ;
      title5 'TRAJECTORY SENSITIVITY ANALYSES !!' ;   run ;



  *  NMB_100 ;
  proc mixed data=missing covtest noclprint ;
    model NMB_100= age40 prevhospC txgroup month month*txgroup
                    month04 month04*txgroup month08 month08*txgroup
                   /solution;
 random intercept month / subject = patid type =UN gc g gcorr v vcorr;
    contrast 'Tx Diff at Baseline' txgroup 1 ;
    estimate 'Intercept, Tx=0' intercept 1 ;
    estimate 'Intercept, Tx=1' intercept 1 txgroup 1 ;
      estimate 'Intercept, Diff' txgroup 1 ;
    estimate 'Month 4, Tx=0' intercept 1 month 4 ;
    estimate 'Month 4, TX=1' intercept 1 txgroup 1 month 4
month*txgroup 4 ;
      estimate 'Month 4, Diff' txgroup 1 month*txgroup 4 ;
    estimate 'Month 8, Tx=0' intercept 1 month 8 month04 4 ;
    estimate 'Month 8, TX=1' intercept 1 txgroup 1 month 8
month*txgroup 8 month04 4 month04*txgroup 4 ;
      estimate 'Month 8, Diff' txgroup 1 month*txgroup 8
month04*txgroup 4 ;
   estimate 'Month 12, Tx=0' intercept 1 month 12 month04 8 month08 4 ;
    estimate 'Month 12, TX=1' intercept 1 txgroup 1 month 12
month*txgroup 12 month04 8 month04*txgroup 8
month08 4 month08*txgroup 4 ;
```

```
      estimate 'Month 12, Diff' txgroup 1 month*txgroup 12
month04*txgroup 8 month08*txgroup 4 ;
      estimate 'Total FU NMB, Tx=0' intercept 3 month 24 month04 12
month08 4 ;
      estimate 'Total FU NMB, Tx=1' intercept 3 txgroup 3 month 24
month*txgroup 24 month04 12 month04*txgroup 12

month08 4  month08*txgroup 4 ;
      estimate 'Total FU NMB, Diff' txgroup 3 month*txgroup 24
month04*txgroup 12 month08*txgroup 4 ;
    estimate 'Chg Mo4, Tx=0' month 4 ;
    estimate 'Chg Mo4, TX=1' month 4 month*txgroup 4 ;
      estimate 'Chg Mo4, Diff' month*txgroup 4 ;
    estimate 'Chg Mo8, Tx=0' month 8 month04 4 ;
    estimate 'Chg Mo8, TX=1' month 8 month*txgroup 8 month04 4
month04*txgroup 4 ;
      estimate 'Chg Mo8, Diff' month*txgroup 8 month04*txgroup 4 ;
    estimate 'Chg Mo12, Tx=0' month 12 month04 8 month08 4 ;
    estimate 'Chg Mo12, TX=1' month 12 month*txgroup 12 month04 8
month04*txgroup 8 month08 4 month08*txgroup 4 ;
      estimate 'Chg Mo12, Diff' month*txgroup 12 month04*txgroup 8
month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Tx=0' month 24 month04 12 month08 4 ;
      estimate 'Chg T_FU NMB, Tx=1' month 24 month*txgroup 24 month04
12 month04*txgroup 12 month08 4  month08*txgroup 4 ;
      estimate 'Chg T_FU NMB, Diff' month*txgroup 24 month04*txgroup 12
month08*txgroup 4 ;
    title3 'Piecewise Linear Regression Analysis: NMB_100' ;
      title5 'TRAJECTORY SENSITIVITY ANALYSES !!' ; run ;
```

R. POST HOC ANALYSIS JOINT ME MODEL

```
*  Program:      Joint_Miss, Trajectory.SAS                          ;
*  Description:  This program first obtains estimats from the        ;
*  seperate models and then jointly estimates the parameters         ;
*  Programmer:   Diane Fairclough                                    ;
*  Date:         20/Dec/2007                                         ;
*  Revised:      Dennis D. Gagnon                                    ;
*  Date:         03/08/08                                            ;
*  Revised:      Diane Fairclough                                    ;
*  Date:         21Mar2008                                           ;
*                Removed intercept random effect from Time to DO     ;
*                model                                               ;
*  Revised:      Dennis D. Gagnon                                    ;
*                08/21/08                                            ;
*                TRAJECTORY SENSITIVITY ANALYSIS !!                  ;
  libname indat
'L:\Raritan\PGSM\PGSMHE&P\PUBLIC\DGagnon\NMB\Trajectory\V802dat\Traject
ory' ;
  *libname indat 'C:\UMDNJ\Dissertation\NMB\V802dat\Trajectory' ;
  *libname indat 'C:\Projects\Consult\Engelhart\SASlib' ;
  options pageno=1 ps=46 ls=150 center errors=2 ;
  title 'Joint_Miss, Trajectory.SAS         Dissertation: Estimating
INMB in a Clinical Study With Missing Data' ;
************************************************************************
  PREPARE DATA ;
    proc print data=indat.missing(obs=20) ;
    title3 'First 20 Observations of Missing' ;
  run ;

  proc summary data=indat.missing nway;  * Identifies time of last obs
*;
    class patid;
      var month ;
      output out=work.last max=Last; run;
    proc freq data=work.last;
    table last/missing; run;
  data missing ;
    merge indat.missing work.last(keep=patid last);
      by patid;
      *** Time to last Assessment ***;
      if last eq 12 then Censor=1;
    else censor=0;
      L_Last=log(last+1);
      Label Censor='Completor (1=Yes, 0=No)'
            L_Last='Ln(Time to Last Obs + 1)';
  run ;
  proc print data=missing (obs=20);
    title3 'Print of Missing with Month and Knots at Months 4 and 8
Derived' ;
  run ;
************************************************************************
  GET ESTIMATES FOR MU and SCALE (SAME FOR ALL NMBs) ;
  *** Initial Estimates for Time to DO portion of model ***;
proc lifereg data=work.missing;
  model L_last*Censor(1)=/ dist=normal; * Used Normal because already
logged *;
```

```
  where month eq 0;
  title3 'Estimate Mu and Scale' ;
  title5 'Trajectory Sensitivity Analysis' ;
run;
*************************************************************************
NMB_0 ;
*** Reference Model ***;
proc nlmixed data=work.missing ;
  title3 'Longitudinal and Time to Event with No correlation, NMB_0';
  title5 'Trajectory Sensitivity Analyses' ;
  where nmb_0 ne .;  * Proc does not deal well with missing values *;

  parms b0=-16.0498 b1=0.1070 b2=1.5262 b3=-0.4298 b4=-0.9284 b5=0.3531
b6=-0.0813 b7=0.1235 b8=0.0292 b9=-2.4951
        s1=18.0371 s12=-1.5875 s2=0.4572 s2w=132.19
        mu0=2.4541 st=1.6194 lambda2=0 ;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_0-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_0 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 + b2*24 + b4*12 + b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff' b1*3 + b3*24 + b5*12 + b7*4 ;

  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                ;
  estimate 'D11' D11;         *Var of between patient NMB intercept;
  estimate 'D12' D12;         *Covar of between patient NMB intercept
and slope;
```

```
  estimate 'D22' D22;         *Var of between patient NMB slope;
  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;
  estimate 'Tau2' lambda2**2*D22 + S2t;         *Residual error for log
time to dropout;
  *estimate 'D1T' lambda1*D11+Lambda2*D12;
  *estimate 'D2T' lambda1*D12+Lambda2*D22;
  estimate 'D2T' Lambda2*D22;                          *;
  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/
  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/
  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t)); *Correlation between log time to dropout and NMB slope;
  run;

*** Joint Model with Two Random Effects ***;
*** Note this does not converge ... ****;
proc nlmixed data=work.missing ;
  title3 'Joint Longitudinal and Time to Event, NMB_0';
  title5 'Trajectory Sensitivity Analyses' ;
  where nmb_0 ne .;  * Proc does not deal well with missing values *;

  parms b0=-16.0498 b1=0.1070 b2=1.5262 b3=-0.4298 b4=-0.9284 b5=0.3531
b6=-0.0813 b7=0.1235 b8=0.0292 b9=-2.4951
        s1=18.0371 s12=-1.5875 s2=0.4572 s2w=132.19
        mu0=2.4541 st=1.6194 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_0-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0  +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_0 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;
```

```
    estimate 'Total FU NMB, Tx=0' b0*3 + b2*24 + b4*12 + b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff' b1*3 + b3*24 + b5*12 +        b7*4 ;

  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                  ;
  estimate 'D11' D11;         *Var of between patient NMB intercept;
  estimate 'D12' D12;         *Covar of between patient NMB intercept
and slope;
  estimate 'D22' D22;         *Var of between patient NMB slope;
  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;
  estimate 'Tau2' lambda2**2*D22 + S2t;         *Residual error for log
time to dropout;
  *estimate 'D1T' lambda1*D11+Lambda2*D12;
  *estimate 'D2T' lambda1*D12+Lambda2*D22;
  estimate 'D2T' Lambda2*D22;                           *;
  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/
  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/
  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));      *Correlation between log time to dropout and NMB slope;
  run;

************************************************************************
NMB_25 ;
*** Reference Model ***;
proc nlmixed data=work.missing;
  title3 'Longitudinal and Time to Event with No correlation, NMB_25';
  title5 'Trajectory Sensitivity Analyses' ;
  where nmb_25 ne .;  * Proc does not deal well with missing values *;
  parms b0=-10.9154 b1=0.1179 b2=1.5492 b3=-0.2216 b4=-0.9438 b5=0.1439
b6=-0.0724 b7=0.1303 b8=0.0225 b9=-2.6785
        s1=18.0248 s12=-1.6097 s2=0.4639 s2w=132.53
        mu0=2.4541 st=1.6194 lambda2=0 ;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_25-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
```

```
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_25 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 + b2*24 + b4*12 +  b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff' b1*3 + b3*24 + b5*12 + b7*4 ;

  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                  ;

  estimate 'D11' D11;         *Var of between patient NMB intercept;
  estimate 'D12' D12;         *Covar of between patient NMB intercept
and slope;
  estimate 'D22' D22;         *Var of between patient NMB slope;
  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;
  estimate 'Tau2' lambda2**2*D22 + S2t;         *Residual error for log
time to dropout;
  *estimate 'D1T' lambda1*D11+Lambda2*D12;
  *estimate 'D2T' lambda1*D12+Lambda2*D22;
  estimate 'D2T' Lambda2*D22;                            *;
  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/
  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/
  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));      *Correlation between log time to dropout and NMB slope;
  run;

*** Joint Mdel with Two Random Effects ***;
proc nlmixed data=work.missing;
  title3 'Joint Longitudinal and Time to Event, NMB_25';
  title5 'Trajectory Sensitivity Analyses' ;
  where nmb_25 ne .;  * Proc does not deal well with missing values *;
  parms b0=-10.9154 b1=0.1179 b2=1.5492 b3=-0.2216 b4=-0.9438 b5=0.1439
b6=-0.0724 b7=0.1303 b8=0.0225 b9=-2.6785
        s1=18.0248 s12=-1.6097 s2=0.4639 s2w=132.53
        mu0=2.4541 st=1.6194 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;
```

```
  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_25-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0 +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_25 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;
  estimate 'Total FU NMB, Tx=0' b0*3 + b2*24 +  b4*12 + b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;

  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                  ;
  estimate 'D11' D11;         *Var of between patient NMB intercept;
  estimate 'D12' D12;         *Covar of between patient NMB intercept
and slope;
  estimate 'D22' D22;         *Var of between patient NMB slope;
  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;
  estimate 'Tau2' lambda2**2*D22 + S2t;         *Residual error for log
time to dropout;
  *estimate 'D1T' lambda1*D11+Lambda2*D12;
  *estimate 'D2T' lambda1*D12+Lambda2*D22;
  estimate 'D2T' Lambda2*D22;                           *;
  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/
  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/
  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));      *Correlation between log time to dropout and NMB slope;
  run;

*****************************************************************
NMB_50 ;
```

```
*** Reference Model ***;
proc nlmixed data=work.missing;
  title3 'Longitudinal and Time to Event with No correlation, NMB_50';
  title5 'Trajectory Sensitivity Analyses' ;
  where nmb_50 ne .;  * Proc does not deal well with missing values *;

  parms b0=-5.7818 b1=0.1289 b2=1.5719 b3=-0.0133 b4=-0.9594 b5=-0.0653
b6=-0.0638 b7=0.1374 b8=0.0155 b9=-2.8636
        s1=18.0353 s12=-1.6312 s2=0.4744 s2w=133.46
        mu0=2.4541 st=1.6194 lambda2=0 ;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_50-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_50 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 + b2*24 + b4*12 + b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'b1*3 + b3*24 +    b5*12 +        b7*4 ;

  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                  ;
  estimate 'D11' D11;         *Var of between patient NMB intercept;
  estimate 'D12' D12;         *Covar of between patient NMB intercept
and slope;
  estimate 'D22' D22;         *Var of between patient NMB slope;
 *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;
  estimate 'Tau2' lambda2**2*D22 + S2t;         *Residual error for log
time to dropout;
  *estimate 'D1T' lambda1*D11+Lambda2*D12;
```

```
  *estimate 'D2T' lambda1*D12+Lambda2*D22;
  estimate 'D2T' Lambda2*D22;                          *;
  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/
  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/
  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));      *Correlation between log time to dropout and NMB slope;
  run;

*** Joint Mdel with Two Random Effects ***;
proc nlmixed data=work.missing ;
  title3 'Joint Longitudinal and Time to Event, NMB_50';
  title5 'Trajectory Sensitivity Analyses' ;
  where nmb_50 ne .;  * Proc does not deal well with missing values *;

  parms b0=-5.7818 b1=0.1289 b2=1.5719 b3=-0.0133 b4=-0.9594 b5=-0.0653
b6=-0.0638 b7=0.1374 b8=0.0155 b9=-2.8636
        s1=18.0353 s12=-1.6312 s2=0.4744 s2w=133.46
        mu0=2.4541 st=1.6194 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_50-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0 +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_50 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 + b2*24 + b4*12 + b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;
```

```
  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                  ;
  estimate 'D11' D11;         *Var of between patient NMB intercept;
  estimate 'D12' D12;         *Covar of between patient NMB intercept
and slope;
  estimate 'D22' D22;         *Var of between patient NMB slope;
  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;
  estimate 'Tau2' lambda2**2*D22 + S2t;         *Residual error for log
time to dropout;
  *estimate 'D1T' lambda1*D11+Lambda2*D12;
  *estimate 'D2T' lambda1*D12+Lambda2*D22;
  estimate 'D2T' Lambda2*D22;                          *;
  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/
  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/
  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));

  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));      *Correlation between log time to dropout and NMB slope;
  run;

*************************************************************************
NMB_100 ;
*** Reference Model ***;
proc nlmixed data=work.missing;
  title3 'Longitudinal and Time to Event with No correlation, NMB_100';
  title5 'Trajectory Sensitivity Analyses' ;
  where nmb_100 ne .;  * Proc does not deal well with missing values *;

  parms b0=4.4830 b1=0.1515 b2=1.6175 b3=0.4032 b4=-0.9910 b5=-0.4833
b6=-0.0471 b7=0.1520 b8=0.0006 b9=-3.2371
        s1=18.0964 s12=-1.6718 s2=0.5060 s2w=137.08
        mu0=2.4541 st=1.6194 lambda2=0 ;
  bounds s2w>0, st>0; * Variance of D constrained to be PD *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  S2T=st*st;

  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
       +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_100-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
```

```
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_100 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 + b2*24 + b4*12 +   b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;

  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                  ;

  estimate 'D11' D11;         *Var of between patient NMB intercept;

  estimate 'D12' D12;         *Covar of between patient NMB intercept
and slope;
  estimate 'D22' D22;         *Var of between patient NMB slope;
  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;
  estimate 'Tau2' lambda2**2*D22 + S2t;         *Residual error for log
time to dropout;
  *estimate 'D1T' lambda1*D11+Lambda2*D12;
  *estimate 'D2T' lambda1*D12+Lambda2*D22;
  estimate 'D2T' Lambda2*D22;                           *;
  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/
  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/
  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));      *Correlation between log time to dropout and NMB slope;
  run;

*** Joint Mdel with Two Random Effects ***;
proc nlmixed data=work.missing;
  title3 'Joint Longitudinal and Time to Event, NMB_100';
  title5 'Trajectory Sensitivity Analyses' ;
  where nmb_100 ne .;  * Proc does not deal well with missing values *;

  parms b0=4.4830 b1=0.1515 b2=1.6175 b3=0.4032 b4=-0.9910 b5=-0.4833
b6=-0.0471 b7=0.1520 b8=0.0006 b9=-3.2371
        s1=18.0964 s12=-1.6718 s2=0.5060 s2w=137.08
        mu0=2.4541 st=1.6194 lambda2=0;
  bounds s2w>0, st>0; * Variance constrained to be Positive *;
  D11=S1*S1; D12=S1*S12; D22=S12*S12 + S2*S2;
  s2t=st*st;
```

```
  *** Mixed effect Model for longitudinal outcome***;
  Pred=b0 +b1*txgroup +b2*month +b3*month*txgroup +b4*month04
+b5*month04*txgroup +b6*month08 +b7*month08*txgroup
      +b8*age40 +b9*prevhospc
      +d1 +d2*month;
  ll_Y= -(log(2*3.14159) + log(s2w) + (nmb_100-Pred)**2/s2w)/2;

  *** Time to Event ***;
  if month eq 0 then do;
    Pred_T=mu0 +lambda2*d2;
      *** Residual of Measure of Ancillary Variable ***;
    Z_T=(L_Last-Pred_T)/sqrt(s2t);
    *** Left censored ***;
    *if Censor eq -1 then ll_t=log(probnorm(Z_T));
    *** Uncensored ***;
    if Censor eq 0 then ll_T=-(log(2*3.14159)+log(s2t)+Z_T**2)/2;
    *** Right censored ***;
    if Censor eq 1 then ll_T=log(1-probnorm(Z_T));
  end;
  else ll_T=0;

  *** General Log Likelihood ***;
  model nmb_100 ~ general(ll_Y+ll_T);
  random d1 d2 ~ normal([0,0],[D11,D12,D22]) sub=patid;

  estimate 'Total FU NMB, Tx=0' b0*3 +  b2*24 + b4*12 + b6*4        ;
  estimate 'Total FU NMB, Tx=1' b0*3 + b1*3 + b2*24 + b3*24 + b4*12 +
b5*12 + b6*4 + b7*4 ;
  estimate 'Total FU NMB, Diff'        b1*3 +         b3*24 +
b5*12 +        b7*4 ;

  * These are the statements you need to add to the joint models to get
the variance and correlation estimates.  ;
  *  The ones that are commented out are if any of your models include
lambda1.                                  ;
  estimate 'D11' D11;         *Var of between patient NMB intercept;
  estimate 'D12' D12;         *Covar of between patient NMB intercept
and slope;
  estimate 'D22' D22;         *Var of between patient NMB slope;
  *estimate 'Tau2' lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t;
  estimate 'Tau2' lambda2**2*D22 + S2t;         *Residual error for log
time to dropout;
  *estimate 'D1T' lambda1*D11+Lambda2*D12;
  *estimate 'D2T' lambda1*D12+Lambda2*D22;
  estimate 'D2T' Lambda2*D22;                           *;
  *estimate 'Rho1T' (lambda1*D11+Lambda2*D12)/
  (sqrt(D11)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));
  *estimate 'Rho2T' (lambda1*D12+Lambda2*D22)/
  (sqrt(D22)*sqrt(lambda1**2*D11 + 2*lambda1*lambda2*D12
+lambda2**2*D22 + S2t));

  estimate 'Rho2T' (Lambda2*D22)/(sqrt(D22)*sqrt(lambda2**2*D22 +
S2t));      *Correlation between log time to dropout and NMB slope;
  run;
```

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CURRICULUM VITA

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EDUCATION

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1990 **UNIVERSITY OF CALIFORNIA, Santa Barbara, California**
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PROFESSIONAL EXPERIENCE

2006-Present **CORDIS CORPORATION, a Johnson & Johnson Company**
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PUBLICATIONS

Ryan JW, Linde-Zwirble W, Engelhart L, Cooper L, Cohen D. Temporal trends in coronary revascularization procedures, outcomes, and costs: results from the U.S. Medicare program. Manuscript in development.

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