CHAPTER 15

STUDY MONITORING

15.1 INTRODUCTION

The T3 study is composed of two randomized, multicenter, international clinical trials T3A and T3B. T3A will compare the relative efficacy of t-PA in changing angiographic findings. In T3B, the clinical efficacy of t-PA will be assessed, in addition to testing the clinical efficacy of two follow-up management strategies. Thus, T3B is a 2 by 2 factorial design that has been designed to determine the best combination of initial therapy (t-PA plus conventional therapy versus conventional therapy only) and subsequent management strategy (invasive versus conservative) using a single study design.

There will be two types of data analyses carried out in both of these studies. First, analyses will be performed to determine if initial treatment or follow-up management outcome differences are present which indicate that one of the randomized groups has a better outcome than the other groups. This type of data analysis will include interim data analyses for efficacy, and the final data analysis of study results. In Sections 15.2 and 15.3 are presented the plans to monitor for beneficial and/or side effects for T3A and T3B. In Section 15.3, the final analytical plans are presented for T3A and T3B. The second type of data analyses to be carried out in these studies are analyses to determine if the two T3 protocols are being performed as planned. In Section 15.4, there is a description of plans to monitor the performance and quality of data acquisition in the Clinical Centers, Data Coordinating Center, and Core Laboratories.

15.2 MONITORING FOR DECISIONS OF TREATMENT EFFECTS

The data reports prepared for both T3A and T3B will include information on the patients enrolled with emphasis on baseline comparability of patient characteristics in the treatment groups; reports on end point and results during the course of study to assess the treatment effects; analyses of the occurrence of major end points in subgroups defined by baseline findings; and reports on overall study and individual Clinical Center performance with regard to patient intake and follow-up.

The DSMB will be scheduled to meet at six-month intervals up to 36 months after recruitment starts to review interim results. Two months before reports are to be presented, the T3 data base will be extracted to provide an unchanging interim analysis file which will be permanently archived. Prior to any scheduled meeting, table shells for proposed analyses will be constructed and submitted to members of the Operations Committee for review. Suggestions will be incorporated, and the table shells will be filled in using the extracted data base. These results will be distributed to the Study Chairman, and the Director of the Data Coordinating Center to check for inconsistencies and errors. One week prior to the scheduled DSMB meeting, the report will be mailed to the DSMB members for their review.

T3A recruitment will last 12 months. One formal interim analysis and one final analysis are for T3A to determine the angiographic efficacy of t-PA. Inferences concerning the clinical efficacy and toxicity of t-PA, and the clinical efficacy of the Invasive Strategy will be made at six time points over the course of the T3B investigation. Significance testing for sequentially monitored data in both the studies will be accomplished: 1) without regard for Type I error rates if the variable being compared is a baseline variable, and 2) using a group sequential monitoring methodology if the variable being compared is a primary end point.

Interim Monitoring for both of the T3B primary end points and the T3A end point will be accomplished using a two-sided boundary. The method employed will be that of Fleming-Harrington-O'Brien (1). The major strength associated with the Fleming-Harrington-O'Brien plan is that monitoring can take place, but the final comparisons (two-sided 5% or one-sided 2.5%) made at the end of the study (should the investigation proceed to completion) can be made at nearly the same alpha level as the alpha level for a study that has no monitoring plan. The boundaries are wide for the early period of recruitment and narrow to an approximate 5% level two-sided test at the conclusion of the study.

The Boundaries for T3A are:

	Sequential Data Reviews	
Month after Start of Recruitment	6	12
Critical Value Z	2.81	1.97

The boundaries to be used for T3B are:

	Sequential Data Reviews					
	1	2	3	4	5	6
Month after Start of Recruitment	6	12	18	24	30	36
Critical Value Z	3.28	3.26	3.19	3.14	3.13	1.97

As can be seen from the above listed critical values for the proposed monitoring plan, the final comparison is very close to the Z value for standard 5% level two-sided test (Z = 1.96). If t-PA (in T3A or T3B) or the Invasive Strategy were found in an interim analysis to be greatly superior (or inferior) to placebo or the Conservative Strategy, this would be detected, and subsequent actions taken.

Each primary end point will be monitored independently. Should a significant treatment effect be found for either of the two compari-

sons in T3B, randomization for that therapy could be discontinued, while continuing to randomize patients for the other therapy. In this case standard treatment of patients would be changed to accommodate the superior treatment for the discontinued randomization.

15.3 MONITORING FOR SIDE EFFECTS OF TREATMENT

Monitoring for rare and severe side effects (such as intracranial hemorrhage) will be accomplished by evaluating the two comparisons (initial treatment and subsequent management) separately. For comparing initial therapy, the results of T3A will be combined with the results of T3B. Data Coordinating Center (DCC) staff will report every occurrence of intracranial hemorrhage to the members of the Operations Committee within two days of receipt of the Adverse Drug Reaction Report from the Clinical Center. Even one occurrence of this event is significant, and therefore, will be reported to the appropriate individuals promptly.

The next most important adverse event that can be anticipated before the onset of this trial is the appearance of major hemorrhage. Major hemorrhage will be defined as any intracranial hemorrhage, pericardial hemorrhage with tamponade, at least a five gram drop in the patients hemoglobin or at least a 15% decrease in the patient's hematocrit. The frequency of this event will be compared between initial therapy groups and between the follow-up management groups as part of the DSMB Monitoring Report. The significance of any observed differences will be reported as part of the periodic review of this report.

For all other adverse events encountered in T3, the DCC staff plan to notify the DSMB by letter if any single complication is found six times in one treatment group, without a single occurrence in the other group.

The rationale for choosing six complications in one group and no complications in the other group is based upon the following statisti-

cal considerations. Consider a 2x2 table with the rows labeled as the study groups (e.g., t-PA and placebo) and the columns labeled as the presence or absence of complications. The row marginal totals will be large relative to the number of complications observed. Let X be the number of complications observed in the t-PA group. If a total of six complications have been observed, then, using the binomial approximation to the hypergeometric distribution, X is distributed as a binomial random variable with parameters N = 6 and p = 0.5 under the assumption that the risk of complication is equal in each study drug group. If X = 0 or 6, rejecting the null hypothesis has an alpha level of 0.03 and would indicate that the risk of complication in the t-PA group is not equal to the risk of complication in the placebo group based on the observation that all six complications occurred in the t-PA group.

If complications occur in both the t-PA and placebo groups, then a monitoring scheme will be set up to insure that the incidence of this complication in the t-PA group is not significantly than the incidence of the complication in the placebo-treated group. If a 95% confidence interval for the difference in complication rates failed to include zero, DCC staff would notify the DSMB by letter to arrange for subsequent actions.

15.4 DATA ANALYSIS

15.4.1 Introduction

For primary analyses, all patients will be counted in the group to which they were randomized regardless of actual treatment received (analysis by "Intention to treat"). Data analysis at the DCC will be ongoing from the beginning of patient recruitment. Initially, analysis variables will be constructed and tested using data derived from the first patients entering T3. Subsequently, analyses of these variables will proceed, according to the plans presented below, for each of the interim analyses and the final report.

15.4.2 T3A

15.4.2.1 Primary End Point

The primary end point will be the successful result of therapy, defined as whether an improvement in TIMI perfusion by two grades (from 0 to 2 or 3, or from 1 to 3) or a 10% reduction in the severity of stenosis. The reduction will be based on a comparison between the initial angiogram and the follow-up angiogram obtained 18 to 48 hours later with regard to the severity of the presumed culprit lesion. This comparison of the primary end point will be accomplished using a test for two proportions carried out at the 5% alpha level.

15.4.2.2 Analysis of Secondary Outcomes

Various other outcomes from the angiography results are of interest in comparing t-PA to placebo. Each component of the primary end point will be compared between the two treatment groups. The categorical variables of substantial improvement ($\geq$ 20% reduction of stenosis or 2 TIMI grade improvement in perfusion) and measurable worsening (> 10% increase in stenosis or 2 TIMI grade worsening in perfusion) will be analyzed. In addition the continuous outcomes of: stenosis, change in stenosis, lumen diameter, and change in lumen diameter will be compared between the two treatment groups.

In addition to angiographic end points, patients in T3A will be followed for: vital status, occurrence of myocardial infarction, occurrence of ischemia (spontaneous or provokable ischemia, see Chapter 4), occurrence of hemorrhagic events, performance of: catheterization, Percutaneous Transluminal Coronary Angioplasty, and Coronary Artery Bypass Graft Surgery. The clinical events of death and myocardial infarction will be reviewed by a Mortality and Morbidity Classification Committee.

Comparisons between treatment groups of categorical variables and continuous variables will use the chi-square and t-test respectively. When testing for treatment effects within specified subgroups, in

addition to calculating simple test statistics within each subgroup, a test for homogeneity will be performed across complementary subgroups. If the outcome variable is categorical, the Breslow-Day test for homogeneity of the odds ratio will be used as the test of homogeneity. If the outcome is continuous, an interaction term will be included in an analysis of variance model to test for interaction between treatment and the subgroup being investigated.

15.4.2.3 Adjusted Analyses for the Primary and Secondary End Points

Adjusted analyses will be accomplished using linear or logistic regression. Candidate variables for inclusion into the linear or logistic regression model will be those that upon univariate correlation with the outcome are significant at the 0.1 alpha level. Candidate variable will be included into the regression model using a stepwise addition procedure; those variables remaining in the model with a p-value of 0.01 will be counted as important adjustment variables.

15.4.3 T3B

15.4.3.1 Primary End Points

There are two primary end points for the T3B investigation. The primary end point for the comparison of t-PA versus placebo (initial therapy end point) will be the composite during the first six weeks of: 1) death, 2) subsequent myocardial infarction or 3) severe recurrent ischemia in-hospital defined as failure to control spontaneous ischemia or existence of provokable ischemia prior to hospital discharge. The efficacy of t-PA will be tested at the 5% (two-sided) level using the above end point. The primary end point for the Invasive versus Conservative Strategy comparison (follow-up management end point) is the composite of: 1) death or 2) subsequent myocardial infarction within the first six weeks, 3) the occurrence of rest-angina requiring rehospitalization or Canadian Class III or IV angina confirmed by ETT between hospital discharge and six weeks, and 4) unsatisfactory outcome of a standard Bruce exercise tolerance test

(ETT) performed at six weeks. The efficacy of the Invasive Strategy will be tested at the 5% (two-sided) level using the above end point. The follow-up management primary end point will not be considered as the primary end point in the evaluation of initial therapy and the initial therapy primary end point not be a primary end point for the comparison of follow-up management. This separation of end points for the primary analyses is necessary due to the differing goals of initial therapy and follow-up management. Specifically, the initial therapy comparison is designed to ascertain if the administration of t-PA can affect the short-term incidence of severe recurrent ischemia. The follow-up management comparison is designed to ascertain if the Invasive Strategy can affect longer-term recurrence of severe ischemia.

Tests for initial therapy - follow-up management interactions will be carried out using a 5% level test. Thus, it is planned to maintain the factorial design in making initial therapy and follow-up management comparisons for both of the above end points. The model, assumptions and specific analytic details associated with the proposed comparisons can be found in Appendix 1.

Under the assumption that the initial therapy and follow-up management treatment effects are independent for both end point analyses, initial therapy results will be pooled across follow-up management strategies, and follow-up management effects will be pooled across initial therapy.

In addition to the initial therapy and follow-up management comparisons, there is a plan to test, for both end points, whether t-PA and Invasive Strategy act synergistically or antagonistically when given in combination. The details for how this test will be accomplished can be found in Appendix 1. This test will also be conducted at the 5% level, and should a significant result be found, main effects for initial therapy will be evaluated within each follow-up management strategy and main effects for the follow-up management

comparisons will be evaluated within each initial therapy group. Specifically should t-PA have different effects when patients are assigned to the Invasive Strategy than when patients are assigned to the Conservative Strategy, comparisons of t-PA versus placebo will be performed within each follow-up management group. Since two independent initial therapy comparisons (t-PA versus placebo) will be performed once within each follow-up management group, each of these comparisons will be conducted at the 2.5% level. Similarly, since the follow-up management comparisons would be performed within each initial therapy group. Each of these comparisons would also be performed at the 2.5% level.

15.4.3.2 Analysis of Secondary End Points

Secondary end points are listed in Chapter 13. As mentioned in Chapter 2, Section 2.4 the analytic technique for these end points will be similar to the analyses of the primary end points except that the level of the test to determine significance will be set at 1% rather than 5%.

All binary end points in T3B will be analyzed according to the analytic design stated in Section 15.3.3 and in Appendix 1. Secondary end points which are continuous in nature will be analyzed using a standard 2x2 factorial design for Analysis of Variance (ANOVA). End points which are recorded as times to event will be analyzed using the log-rank test or Gehan test, whichever is appropriate.

Estimations of "survival" functions for time-to-event data (such as: time to death, time to occurrence of death or myocardial infarction or time to major hemorrhagic event) will be constructed using the methods of Kaplan and Meier (2). Cumulative incidence at any point in time will be estimated from these distributions and standard deviations for these point estimates will be estimated using Greenwood's formula (3).

Much of the data collected over the course of the study will consist of quantitative or qualitative measurements. These measurements may be taken only once, or they may be repeated measurements of the same variable. For instance ECGs will be repeated at baseline, hospital discharge, and six weeks. Depending on the type of outcome measure being analyzed (quantitative or qualitative), means, medians, or proportions will be estimated at each time point. Appropriate confidence intervals will be calculated using standard methods or, if necessary, more complicated models. In all cases interval estimates will be constructed as 99% confidence intervals.

When testing for treatment effects in subgroups, in addition to calculating simple test statistics within each subgroup, a test for homogeneity will be performed across complimentary subgroups. If the outcome variable is categorical, the Breslow-Day test for homogeneity of the odds ratio will be used as the test of homogeneity. If the outcome is continuous or a time to event (e.g., time to death), an subgroup-treatment interaction term will be included in an analysis of variance or Cox proportional hazards model respectively. The statistical significance of this term will be used to assess the significance of the subgroup-treatment interaction.

15.4.3.3 Adjusted Analyses for the Primary and Secondary End Points

Adjusted analyses will be accomplished using linear, logistic, or Cox proportional hazards regression models. Candidate variables for inclusion into a regression model will be those that are significantly related to the outcome at the 0.1 alpha level. Candidate variable will be added to the regression model using a stepwise addition procedure; those variables remaining in the model with a p-value of 0.01 will be considered important adjustment variables.

15.5 SUBGROUPS FOR ANALYSIS

The primary and secondary end points will be analyzed for the T3A and T3B population as a whole and for several subgroups based on the

time of occurrence of their pain and results of CK-MB measurements. These groups are defined below.

Group I: No pain within the four hours prior to randomization (i.e., the qualifying pain occurred four to 12 hours prior to randomization)

AND

No CK-MB elevation in blood samples obtained at randomization and four hours after randomization.

Group II: Pain within the four hours prior to randomization

AND

No CK-MB elevation in blood samples obtained at randomization and four hours after randomization.

Group III: Pain at any time within the 12 hours prior to randomization

AND

CK-MB elevation in at least one of the two samples.

Thus, patients in Groups I and II will presumably be free of ongoing MI at the time of randomization. Exclusion of pre-randomization infarction will be most certain in Group I (i.e., no pain in the four hours prior to randomization). In this group, lack of an elevation of CK-MB at the time of randomization will reliably identify patients without infarction prior to treatment, since over four hours would have elapsed since the last episode of pain, and the biologic time delay for CK-MB to enter the blood stream would have elapsed prior to treatment. In Group II (i.e., pain during the four hours prior to randomization), CK-MB values may be somewhat less reliable as indicators of pre-randomization infarct status because therapy would be initiated after the occurrence of myocardial necrosis but before the appearance of CK-MB in the peripheral circulation. Analysis in this group must therefore take into account the possibility that treatment might affect the CK-MB as a marker of myocardial necrosis.

This will be determined by comparison of the CK-MB results among the various treatment groups. Group III patients, all of whom will have documented CK-MB elevation, will have primarily non-Q-wave infarction, since patients with new Q-waves and persistent ST-segment elevation are excluded from the study. The various end points will be analyzed in each of these three groups of patients.

Other subgroups for analysis will include (1) patients whose acute ischemic syndrome occurred despite prior aspirin therapy versus those whose disorder began without prior aspirin therapy, (2) patients older than 70 versus those age 70 or less, (3) those with symptom onset within one week versus those with symptom onset more than one week prior to enrollment, (4) males versus females, and (5) those with versus those without a history of prior MI, (6) those with ST-segment elevation versus those with ST-segment depression, (7) those with only T-wave changes versus those with only ST-segment changes, (8) those with continued rest pain on maximal medical therapy, (9) those whose last episode of pain was within four hours of enrollment versus those with pain from four to 12 hours prior to enrollment, and (10) those with versus those without an angiographically visualized thrombus in the invasive group.

15.6 MONITORING STUDY PERFORMANCE AND QUALITY CONTROL

15.6.1 Introduction

Monitoring study performance and instituting adequate quality control procedures for the conduct of the Thrombolysis in Myocardial Ischemia Trial is a very important function of the DCC. The DCC staff propose to meet their responsibilities in this area by instituting three types of reports: 1) Performance Reports; 2) Quality Control Reports; and 3) Recruitment and End Point Summaries. These reports will be generated on a weekly (recruitment report), monthly (end point summary), or biannually (complete performance report). Reports will be generated for the Clinical Centers, the Data Coordinating Center,

and the Core Laboratories and reported to the Operations Committee and the DSMB.

15.6.2 Clinical Centers

15.6.2.1 Performance Reports

The Data Coordinating Center will produce reports monthly on critical components for the overall completion of the T3 Clinical Trial. These reports will include information concerning: 1) the number of patients recruited into both of the T3 Clinical Trials, 2) the number of major protocol violations which occurred during that month, 3) the number of forms and study materials that have been submitted, and 4) the number of studies submitted to the relevant Core Laboratories. This will include holter and thallium studies, angiograms, and ECG's documenting recurrent angina. Each of the above Items (1-4) will be reported in aggregate and for each Clinical Center.

15.6.2.2 Monitoring Procedures

I. Monitoring of Recruitment

Individual Clinical Centers will be monitored for the number of patients recruited during each quarter. A Clinical Center is expected to recruit at least one patient per week at a minimum. The Data Coordinating Center will notify the Study Chairman's Office of those Clinical Centers that have not enrolled within an eight-week period.

II. Monitoring for Major Protocol Violations

As part of the monthly summary of events, the Data Coordinating Center will notify the Study Chairman's Office of the possible major protocol violations that have occurred in the prior month. The identification of these possible violations will be based on information from the Hospitalization Form (Form 10), missing procedure forms, and forms received indicating that a procedure was not performed. The staff of the Study Chairman's Office will follow-up on each of these

notifications; instructing Clinical Center staff how to correct information if the protocol violation did not occur, and providing guidance in filling out a non-performance of protocol procedure form if that is required.

Biannually, the Data Coordinating Center will produce a summary of the major protocol violations that have occurred at each Clinical Center. This report will be based only on the confirmed receipt of information clearly identifying that the protocol violation has occurred.

Major violations that will be considered are:

1. Conservative strategy patients with cardiac catheterization before achievement of an initial therapy end point.
2. The failure of Clinical Center staff to perform required procedures on invasive strategy patients and T3A patients.
3. The failure to ascertain the components of the primary end points for T3B including performance of the (a) Holter; (b) ETT prior to hospital discharge; (c) Thallium test prior to hospital discharge; (d) the six-week ETT and (e) the six-week ECG.
4. Assigning the wrong treatment kit to a patient.

III. Delinquencies of Forms and Study Materials

The third major area for monitoring Clinical Center performance will consider the number of delinquencies of forms or study materials and the number of procedures and tests performed outside of the designated time windows. Historical evidence from TIMI II shows that in-hospital forms and study materials were delinquent for 1% of the total number of forms and study materials that were submitted. Procedures and tests performed outside of the initial hospitalization have a higher delinquency rate associated with their submission. Based on TIMI II experience this delinquency rate should be no higher than 5%. Data Coordinating Center staff will establish reasonable

time windows by which forms and study materials should have been received. These time windows will be based upon the time of randomization reported on the Form 5D. If a form or study information is not received by the end of the designated time window it will be marked as delinquent. If the information is received, it will be removed from the delinquency list. Once a month, the Data Coordinating Center will send to the Clinical Centers a list of forms and information that are delinquent. Biannually, the DCC staff will tabulate the percentage of each form or other information that is delinquent as part of the Performance Report.

IV. Quality Control of Submitted Data to Core Laboratories

Data Coordinating Center staff will also monitor for the overall quality of study materials submitted to the Core Laboratories. As part of the biannual performance report, Data Coordinating Center staff will tabulate the number of acceptable procedures submitted to each Core Laboratory. Core Laboratories will also perform internal quality evaluations; Core Laboratory staff will contact Clinical Center staff concerning studies that cannot be interpreted or are of poor quality.

Summary of Clinical Center Performance Evaluation

Clinical Center performance will be evaluated based on performance on the first four categories in this proposal. The Operations Committee will be notified whenever a Clinical Center has poor performance in any two of these areas or marginal performance in three or more of these areas. Poor performance in two or more areas for two consecutive quarters, or any four quarters to date, may lead to probation or termination of patient recruitment.

15.6.2.3 Sampling Patient Records

The DCC staff propose to compare patient forms to patient records on Clinical Center site visits to select Clinical Centers. Information from the patient forms will also be compared with information on the T3 data base. Disagreements between these three different records will be noted, and forwarded to the Study Chairman's Office in the form of a Site Visit Report.

15.6.3 Data Coordinating Center

15.6.3.1 Introduction

Data Coordinating Center activities in T3 will be checked internally to enhance the quality of data and analyses. Persons (such as the Principal Investigator or Co-Investigators) not involved in the preparation of the data editing programs will fill out study forms, making deliberate errors. These forms will be keyed and processed through the data editing system to see if all of the errors are caught by the data management system. To detect problems with the data entry and with editing software, a sample of original data forms will be compared to the data base records for these forms.

Computer transformations will be tested by running a small subfile of 10 or 20 participants and independently producing the calculations manually from the original data. This procedure will verify that the correct variables have been selected from the analysis file, and have been defined properly.

15.6.3.2 Performance Reports

Performance of the DCC staff will be accomplished by monitoring the ratio of forms received versus forms keyed, and forms edited on a quarterly basis. In addition, the time from receipt of the form to the time the edit is completed will be control charted. If any of these quarterly measures are unusually large, the DCC staff will take corrective action to reduce the backlog.

Performance for individual data entry operators will be monitored by producing quarterly reports on: 1) the number of strokes per hour achieved by the operator and 2) the number of forms entered that failed to match a second operators entry of the same information. This information will be reported by form so that DCC staff can determine if performance is poor in general or just for a specific set of forms. Should performance of an operator be deemed low, the DCC staff will take corrective action.

15.6.3.3 Quality Control

A sample of patient forms will be selected for comparison with information contained on the T3 data base. The results will be compared as a measure of reliability of the data entry process. As an additional validity measure, the DCC staff propose to compare the adverse event summaries written by the Clinical Center staff to the forms and data base entries for that patient. The objective here will be to look for proper ordering of adverse events and general errors (such as recording the patient's age or sex, etc.) that have been made in the process of data collection. If an error is detected, the mistake will be corrected. Errors will be tabulated to determine the overall error rate of the standard data collection process.

15.6.4 Core Laboratories

15.6.4.1 Introduction

Collection of most information concerning angiograms, ventriculograms, ECG's, holter test, exercise thallium tests, and coagulation parameters for patients will flow directly from the Clinical Centers to Core Laboratories. However, the DCC staff will also collect information on performance and quality of Core Laboratory data collection by obtaining copies of forms sent to the Core Laboratories, and transmittal lists of materials sent to the Core Laboratories.

15.6.4.2 Performance Reports

The importance of complete ascertainment for the studies that comprise the primary end point cannot be understated. If the sustained incidence of absent studies for any study comprising part of the primary end point remains high, the use of that study as part of the primary end point could produce a serious bias. DCC staff will monitor monthly, the Clinical Center reports of procedures performed, and the amount of information processed at the Core Laboratories. If a procedure is missing in 10% of patients, the Study Chairman's Office will be notified.

15.6.4.3 Re-submission of Study Materials

Reliability studies will be performed by resubmitting a 10% sample of material received from the Core Laboratory.

Reliability will be assessed using Kappa Statistics for categorical data, Spearman's Rank Order Correlation Coefficient for ordinal data, and Pearson's or Spearman's Correlation Coefficient for continuous data.

15.7 References

1. Fleming TR, Harrington DP, O'Brien PC. Design for group sequential tests. Cont Clin Trials 1984;5:348.

T3 MANUAL OF OPERATIONS

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$$p(Y = 1 * \underset{\sim}{X}) = \frac{e^{"+\underset{\sim}{\$}'\underset{\sim}{X}}}{1+e^{"+\underset{\sim}{\$}'\underset{\sim}{X}}}$$

where Y equals one if the binary outcome of interest (e.g., a poor holter test between day 3 and 5) has occurred, X is a vector of baseline variables to be related to Y through β which is a vector of logarithms of odds ratios to be estimated. The vector X of baseline variables may include study drug group, age, race, cigarette smoking history, and cardiovascular disease history variables. The method of estimation will be maximum likelihood. Liang and Zeger (4) have extended this model to include repeated measures for binary variables and the use of time dependent covariables. This model will be used to model multivariate responses across time.

Adjustment of time-to-event data will be accomplished using the Cox proportional hazards model (5).

The form of the conventional Cox model is:

$$h(t|X,Z(t)) = h_0(t)\, e^{\beta_1' X + \beta_2' Z(t)},$$

where

$$h(t|X,Z(t)) = \lim_{\Delta \to 0} \frac{P(t < T < t+\Delta \mid X, Z(t))}{\Delta \cdot P(T > t \mid X, Z(t))},$$

T represents an individual's time to the outcome measure of interest, X is a vector of baseline covariables for that individual (variables indicating treatment will be included in this vector), $Z(t)$ represents a collection of time dependent covariates which can change in value over the course of the individual's follow-up, and β_1 and β_2 are vectors of logarithms of relative risks for X and $Z(t)$ which are to be estimated.

Continuous outcome measures collected at one point in time or as repeated measures will be analyzed using analysis of variance or analysis of covariance.