NIDDK Generic Data And Safety Monitoring Plan

For Clinical Trials *Not Requiring* A Data And Safety Monitoring Board (DSMB)

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INTRODUCTION

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), has identified the need to assist grantees conducting clinical trials by providing generic monitoring plans. Ongoing study monitoring of treatment outcomes is recognized as the ethical responsibility of study investigators to their participants (Friedman *et al*, 1996; Meinert, 1986; Weiss, 1996).

Safety monitoring is carried out to ensure and maintain the scientific integrity of human subjects research projects and to protect the safety of human subjects. Meinert (1986) defines safety monitoring as any process during a clinical trial that involves the review of accumulated outcome data for groups of patients to determine if any of the treatment procedures practiced should be altered or stopped. NIH Guidelines (1998) specify that all clinical trials should have in place a system for appropriate oversight and monitoring to ensure the safety of participants and the validity of the data.

Monitoring activities should be commensurate with the nature, size, and complexity of the trial. For a small, single center study, a statistician in conjunction with a Safety Officer usually performs the monitoring. However, for single site, high-risk trials, a monitoring committee called a Data and Safety Monitoring Board (DSMB) may be in order. For larger, single or multi-center, clinical trials, monitoring is usually performed by a DSMB. Ongoing review of the data by an independent individual or committee assures the investigators that the trial can continue without jeopardizing patient safety.

Data monitoring during an ongoing study focuses on several areas:

- *Performance* - to assess sites' performance with respect to subject recruitment, retention and follow-up, flow of data forms, protocol adherence and quality of data;
- *Safety* - to assess the magnitude of adverse events; and
- *Treatment* - to monitor and assess treatment effects.

In single-center studies, ***performance monitoring*** should be an ongoing activity performed by the study investigator and statistician, and reviewed by the Safety Officer.

The investigator and statistician also perform ongoing safety review of the data, and the Safety Officer reviews safety reports at regularly scheduled intervals.

Treatment monitoring or interim analyses by the statistician is a formal process that is specified in the protocol or by the Safety Officer. An interim analysis can result in early study termination if continuation will not produce benefit to patients or if the treatment outcome is known to have benefit. Meinert (1986) points out that ethical questions arise if studies continue beyond where the outcome is known and cites the Tuskegee Syphilis Study as an example. In this study, patients with syphilis were allowed to continue in the

study for years even though it was known that the treatment under study, penicillin, was beneficial. ***Stopping rules***, developed and implemented early in a study, specify the conditions under which a study may be stopped.

NIDDK recognizes that setting up the procedures for study monitoring and for developing reports for the Safety Officer can be a daunting task for investigators. This Guide provides a general approach to developing monitoring plans and incorporates the following:

- ***A list of issues*** to consider when developing a study safety monitoring plan that can form a checklist;
- ***A discussion of statistical issues and stopping rules*** along with examples and references; and
- ***An outline of Safety Officer data reports*** along with sample data presentations, their rationale and general data elements to be included.

CONSIDERATIONS IN DESIGNING A SAFETY MONITORING PLAN

There is no simple formula for how often data should be reviewed or how frequently relevant parties should meet. These decisions are usually set out in the protocol by the study statistician and are reviewed by the Safety Officer, who may develop a set of bylaws that govern these activities. To assist the study team and the Safety Officer in formulating the safety-monitoring plan, the following considerations should be reviewed.

Study Phase

For many Phase I and Phase II trials, an independent DSMB may not be necessary or appropriate when the intervention is low risk. Continuous, close monitoring by the study investigator in conjunction with a Safety Officer may be an adequate and appropriate format for monitoring, with prompt reporting of toxicity to the Institutional Review Board (IRB), Food and Drug Administration (FDA) and/or the NIH. In studies of small numbers of subjects, toxicity may more readily become apparent through close monitoring of individual patients, while in larger studies risk may better be assessed through statistical comparisons of treatment groups.

In situations involving potentially high risks or special populations, investigators must consider additional monitoring safeguards. For example, for studies involving children, investigators may consider the use of a consent monitor to ensure that informed consent or assent is properly administered. In addition, those trials with high risk (gene transfer, stem cell, etc.) will require a DSMB.

Grantee institutions with a large number of clinical trials may develop standard monitoring plans for Phase I and II trials. Thus, individual study investigators may include the IRB-approved monitoring plan in their submission to the NIH. However, such plans will always be evaluated for appropriateness to the particular investigation.
As studies progress through Phase II and III, a DSMB is required, as the intensity and frequency of safety monitoring increases as the number of subjects and sites increase, dosing levels are tested, and subjects are randomized to interventions. The need to document the safety profile of the drug, or likely adverse events (AE), and to insure data integrity requires more frequent and more rigorous views of the data.

Regulatory Considerations

There are additional administrative considerations if the clinical trial requires compliance with FDA regulations. Monitoring should conform to Good Clinical Practice (GCP) and International Committee on Harmonization (ICH) guidelines. Study phase (I-III) and plans for Investigational New Drug Application (IND) submission also influence the frequency and intensity of monitoring studies. Pivotal studies that will influence the outcome of an IND are generally subjected to rigorous monitoring. While it is often argued that the safety profile of a drug is known by the time a Phase III is conducted, early studies are generally conducted in small populations. Thus, adverse events may remain undetected. Further, other safety concerns such as futility of outcome, protocol adherence, site performance, and data quality need careful scrutiny.

Trial Design

The design of the trial is, in part, related to the study phase. As studies move from Phase I through Phases II and III, more subjects are required, and again, greater variability in both study implementation and subject population may occur. In addition, adverse events are more likely to emerge as more people are exposed to the intervention. In multi-center clinical trials, there is greater need to examine site-specific data collection and outcomes and inter-site differences.

Disease/Syndrome under Investigation

The nature of the disease being studied may influence the safety-monitoring plan. When the natural history of a disease is known, the investigators and the Safety Officer are more likely to anticipate the nature and frequency of adverse events. In addition, a monitoring plan should consider the nature of the intervention. The level of scrutiny will depend on the severity of the disease and may require frequently scheduled safety reviews. The same approach may be needed if the disease is serious and/or life threatening and endpoints are anticipated to occur frequently and/or early in the study.

Study Population

The nature of the disease and the trial design will influence the size and characteristics of the subject population. Phase I and II studies have smaller subject populations and

treatment studies for diseases are likely to include subjects of similar demographic and health statuses.

The diversity of a study population can be controlled, to some degree, by the inclusion/exclusion criteria which determine who is eligible to participate in a study. In some studies, eligibility criteria will increase the homogeneity of the patient population. Increased homogeneity may decrease the number of confounding variables that will be considered during analysis. However, stringent inclusion/exclusion criteria may also hinder subject recruitment and accrual to the study. It is therefore important to strike a balance between these two competing demands so that subjects can be recruited to a study in a timely and cost effective manner and that the study yields results that are of high quality and confirm the efficacy of the intervention. This consideration protects the subject's safety in that he/she is not committed to a study that is unduly extended over time or that shows no hope of successfully evaluating the intervention.

The safety plan should specify a review of the rate of subject accrual, adherence to inclusion/exclusion criteria and other protocol requirements, and the expected compliance rate of the subjects. Studies in which the study requirements are invasive, the intervention causes many adverse events, or the target population is very old, very young, or marginal (e.g., homeless, mentally ill, etc.) may have difficulty accruing and retaining subjects. Careful monitoring of the recruitment, enrollment and retention activities will help to protect the safety of study subjects, integrity of the study and the quality of the data.

If subject accrual is expected to occur quickly, then safety monitoring should take place early and may be tied to a percent of the total population to be accrued. For example, if 60 subjects are to be recruited in six months, safety review can take place after the first month of enrollment or after the first 10% of the subjects are enrolled, whichever comes first.

Study Intervention

The more that is known about the study treatment, the easier it is to plan for the monitoring of the study. As discussed, treatments that have been studied previously are more likely to have a known safety profile and the frequency and type of adverse events can be anticipated. However, the safety of a treatment is also related to the population being treated, the indication for its use, dosing level and frequency, the presence of co morbid diseases, and the subject's time on study drug. All of these factors need to be considered in deciding on the frequency and intensity of safety monitoring as well as the types of reports, e.g., number of adverse events per subject.

Endpoints/Outcome Variables

Endpoints that are well defined and immediate are easier to monitor. Acute illnesses are more likely to have these types of outcomes. For example, treatment of an acute infection with the study drug is likely to yield clear-cut results in a relatively short period of time. In contrast, outcomes from chronic illnesses such as diabetes and heart disease may

require a longer treatment intervention and follow-up period. Thus, the subject's time on study intervention and in the study from baseline through final follow-up will influence the type and frequency of safety monitoring.

DESIGNING THE SAFETY MONITORING PLAN

Once the study design and population are specified, the clinical investigators can design, with the study statistician, the study safety monitoring plan. The monitoring plan should specify the responsibilities of the Safety Officer, including frequency of data review, triggers for ad hoc reviews, and contents and format of the safety reports. In addition, specific instructions as to whom each report will be sent (e.g., Safety Officer, NIDDK, FDA), and what procedures, if any, the PI or recipient(s) should follow (e.g., Safety Officer will forward the report void of patient-specific information to NIDDK) to ensure that pertinent parties receive these documents.

Review Process

The monitoring plan should delineate the review process and the roles of the study coordinator, statistician, and the Safety Officer in relation to the content, format, and process of the review. Typically, the coordinator produces administrative reports that describe study progress including accrual, demographics, and subjects' status. Reports also describe adherence to inclusion/exclusion criteria and the study protocol. These reports are reviewed internally for ongoing quality control and then presented to the Safety Officer and NIDDK.

Safety Reports

Safety reports that list adverse events, serious adverse events, deaths, and disease or treatment specific events are required for Safety Officer review in order to ensure good clinical care and identify any potential trends. The statistician may review data routinely and will alert NIDDK and the Safety Officer if event rates are of statistical concern, occur in a disproportionate number in one of the treatment groups, or fall out of a pre-determined set of boundaries. The study statistician may distribute interim reports to the Safety Officer between meetings to allow for special sessions when necessary. ***The review plan should specify the process for reporting safety concerns among the IRB, the Safety Officer, NIDDK and, if appropriate, the FDA.***

Typically, the Safety Officer reviews the safety reports in aggregate fashion and by blinded treatment group. If there are a significant number of adverse events, the Safety Officer may request that the treatment groups be unblinded to ensure that there are not untoward treatment effects. ***The review plan should specify how data are to be presented and triggers for presenting safety data in an unblinded manner.***

Interim Analysis

The study coordinator also prepares the data for the study statistician to analyze in conformance with an interim analysis. The coordinator must have procedures in place for preparing the data for the analyses and for "freezing" the data set so that additional analyses may be performed or the analyses recreated, if necessary. The schedule for interim analyses can be a fixed time frame (e.g., every six months), after a certain number or percentage of subjects are enrolled (e.g., 25%, 50%, 75%, 100%), or in response to a specific number of occurrences of an event (e.g., *n* deaths).

Independence of Review

The Safety Officer should be separate and independent from the clinical staff or anyone responsible for patient care. The Safety Officer should not have scientific, financial, or other conflict of interest related to the trial. Current collaborators or associates of the PI (i.e., same institution) are not eligible. Clinicians should be blinded to the safety monitoring data, as exposure to emerging trends may influence enrollment and care, thus biasing the study.

Steps Emanating from Review

Statistical considerations, such as alpha spending and early stopping are discussed below in the section on statistical issues. The review may result in an amendment to the protocol, which must be approved by the IRB, NIDDK, Safety Officer, and/or FDA. If the review causes changes to the data collection plan or study forms, then there should be a set of procedures for documenting and implementing these changes since the study data sets and analyses may also be affected. The monitoring plan should also specify what steps will be taken as a result of the review and should consider the impact of the review on the study.

STATISTICAL CONSIDERATIONS

Statistical issues arise with ongoing data monitoring such as the "multiple testing" problem, spending the study "alpha", and powering the study for "multiple looks". These issues and associated methods are addressed in the monitoring plan and are briefly discussed. References provide more robust discussion of these issues.

"Multiple looks" at the data during interim analyses can reduce the power of a study. Thus, there is an inverse relationship between the number of interim analyses and the interim p-values for significance. Pocock (1977) recommends that the significance levels for all interim analyses be the same. For example, assuming five interim analyses, a significance level of 1.6% achieves an overall 5% significance. O'Brien and Fleming (1979) modify this rule so that the significance levels begin lower and end at the final analysis closer to the desired overall significance level. The adjustment of the analytic plan and significance level(s) for interim analysis is referred to as the 'alpha spending' function. The 'boundary conditions' described by the interim and final significance levels

are symmetrically 2-sided if it is important to measure both the potential positive and negative effects of a treatment vis-à-vis the placebo.

STOPPING RULES

A 'stopping rule' specifies the outcome differences detected between groups during an interim analysis that can stop a clinical trial. The stopping rules reflect one of the following conditions:

- There is clear evidence of harm or harmful side-effects of the treatment;
- There is no likelihood of demonstrating treatment benefit; or
- There is overwhelming evidence of the benefit of the treatment.

One of the benefits of stopping rules is that they can prevent over-reaction to random highs or lows in treatment response rates and adverse events since they generally require very low threshold p-values in interim analyses to indicate significance. However, stopping rules, also called 'discontinuation guidelines,' are not sufficient to justify stopping a trial for several reasons:

- ***New Information*** **-** There may be new information available such as the results of other trials, a change in the understanding of the underlying biology or outside evidence of unacceptable adverse effects.
- ***Limits of Assumptions*** **-** Assumptions in the trial design regarding sample size and power, subject recruitment, the adverse event profile, and anticipated treatment affect differences may prove to be false when the trial is underway.
- ***Limits of Rules*** **-** Rules cannot be developed for all potential study scenarios and contingencies.

Stopping a trial early, even if justified, has consequences. The scientific purpose behind clinical trials is to calculate with some assurance the size of the differences between treatment outcomes. With less than a full complement of events recorded, the confidence intervals associated with estimates of treatment effects are larger. Another consequence of early stopping is to bias the estimates of treatment effect upward. This bias occurs because random high values in treatment effect may be used to justify early stopping, but rarely would random low values be so used.

Stopping rules should be defined in the statistical plan or early in a study and require realistic estimates of sample size to be effective. Optimistic subject accrual projections often mean that the trial is unable to show the test effect with the necessary assurance.

Stopping rules are no more reliable than the data on which they are based. Thus, the quality of the data must be ascertained for the interim analyses.

Before employing stopping rules, there are a host of issues that should be considered, according to Friedman (1996):

- ***Group Differences*** - Possible differences in baseline characteristics and prognostic factors between the two groups should be explored and necessary adjustments made in the analysis.

- ***Response Variables*** - Potential bias in the assessment of response variables must be considered, especially when the trial is not double-blinded.

- ***Missing Data*** - Possible impact of missing data should be evaluated. For example, could the conclusions be reversed if the experience of participants with missing data form one group were different from the experience with missing data from the other group?

- ***Protocol Compliance*** - Different participant protocol compliance should be evaluated for possible impact.

- ***Side Effects*** - Potential side effects and outcomes of secondary response variables should be considered in addition to the outcome of the primary response variable.

- ***Subgroup Consistency*** - Internal consistency across subgroups and various outcome measures should be examined.

Relevant statistical methods used in monitoring include classical or group sequential methods, flexible group sequential procedures, applications of group sequential boundaries, asymmetric boundaries, curtailed sampling procedures, and other approaches. These methods are discussed in numerous statistical methods books for clinical trials, a few of which are included in the bibliography.

OUTLINE OF TYPICAL SAFETY REPORT

Appendix A contains an outline for a typical Monitoring Plan that utilizes a Safety Officer rather than a DSMB. The study's Data Management generally prepares a Safety Report. The report begins with a brief narrative section that describes the status of the study, progress or findings to-date, issues, and the procedures that produced the report (e.g., data obtained by a specific date). A study description along with a current organization chart, current timetable and study schedule should also be included.

Data are then presented that describe the administrative status of the study including recruitment and forms handling. Study data reports describe demographic and baseline clinical characteristics and provide a safety assessment. These tables are generally provided for the whole study population. The intent of the tables in this section is to provide a general scope of a typical Safety Officer report. The specifics of the study (i.e., the patient population, severity of the disease, and treatment) will guide the requirement for any tables necessary for routine Safety Officer reports and interim analyses. **Please note: Not all of the tables listed in Appendix A are appropriate for every study. Also, there may be additional tables not included in Appendix A that may better characterize the data. The tables in Appendix A are examples only and should be modified as appropriate to conform to study reporting requirements.**

After receipt and review of the Safety Report, the Safety Officer sends a brief evaluation, with recommendations as to whether or not the trial will continue, to NIDDK, and to the PI. The PI should then forward the Safety Officer's evaluation to the IRB. In some instances, the Safety Report is forwarded to the NIDDK Project Officer for review along with the Safety Officer.

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APPENDIX A: Sample Reports for Studies *Not Requiring* a DSMB

Table of Contents

Introduction

In general your monitoring plan should include the name and credentials of your Safety Officer (if approved prior to the writing of the plan) or what type of credentials your intended Officer will possess. The plan should list all information to be included in reports, with copies of the reports intended, and at what intervals throughout the trial the Safety Officer will receive trial updates. In addition, specific instructions as to whom each report will be sent [e.g., Safety Officer (only), NIDDK, FDA], and what procedures, if any, the PI or recipient(s) should follow (e.g., Safety Officer will forward the report void of patient-specific information to NIDDK) to ensure that pertinent parties receive these documents.

Safety Report Outline

The actual structure and content of the Safety Report will have to be adjusted to the type of study that is being performed. The following is an outline of the type of report the Safety Officer should receive:

I. Table of Contents
II. Narrative/ Trial Summary
    A. Summary of Main Findings
    B. Discussion of Issues or Problems
    C. Report Preparation Procedures
III. Study Description
    A. Project Organizational Chart, Personnel
    B. Brief Statement of Purpose of Trial
    C. Projected Timetable and Schedule
    D. List of any Resource Centers
IV. Study Administration
    A. Recruitment Status
        1. Enrollment by Year or Month
        2. Comparison of Targeted to Actual Enrollment
    B. Retention Status
        1. Overall Subject Status
        2. Individual Subject Status
V. Study Data Reports/Tables or Figures
    A. Generic Information
        1. Enrollment (Table 1, Figure 1)
        2. Status (Table 2 and 3)
        3. Demographics (Table 4 and 5)
    B. Safety Assessment
        1. Treatment Duration for All Subjects (Table 6)
        2. Treatment Duration for Subjects who Discontinue Treatment (Table 7)
        3. Adverse Events (Table 8)
        4. Serious Adverse Events (Table 9)

5. Deaths (Table 10)
6. Frequency of Specific Symptoms (Table 11)
7. Observed Adverse Events by Body System (Table 12)
8. Laboratory Data By Patient (Table 13)

Table 1. ENROLLMENT BY MONTH OF STUDY

Date: _____

Month	# Expected	# Screened	# Enrolled	# Withdrawn

FIGURE 1.
COMPARISON OF TARGET TO ACTUAL ENROLLMENT BY MONTH

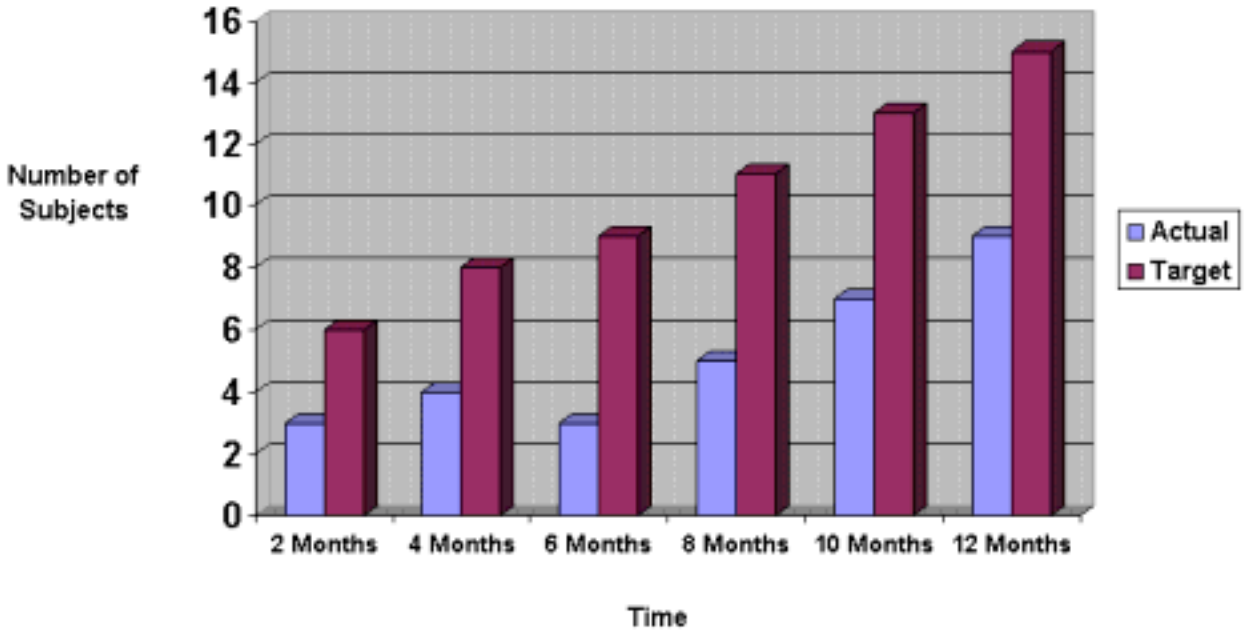

Table 2. OVERALL SUBJECT STATUS

Date: _____

	Pt. Identification	Screened	Date Enrolled	Date Completed	Active	Terminated/ Dropped Out (reason)
1						
2						
3						
4						
N Total						

Table 3. SUBJECT STATUS-DETAIL*

Date: _____

	Pt.	Active	Completed	Concurrent Illness	Drug Permanently Discontinued	Withdrawal of Consent	Adverse Event	Patient Stops Medication	Lost to Follow-Up
1									
2									
3									
4									
N Total									

***Note: It may be important to further capture information about patient withdrawal. Some suggested categories might be:**

1) Permanent drug discontinuation (serious adverse event), patient continues follow up
2) Permanent drug discontinuation (serious adverse event), patient refuses follow up
3) Patient stops drug (a specific reason e.g. side effects, inconvenience), patient continues follow up
4) Patient stops drug (a specific reason e.g. moves, side effects), but refuses further follow up
5) Patient lost to follow up (no explanation given)

Table 4. RACE/ETHNIC CHARACTERISTICS

Date: _____

TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date by Ethnicity and Race				
Ethnic Category	**Sex/Gender**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino				
Not Hispanic or Latino				
Unknown				
Ethnic Category: Total of All Subjects				
Racial Categories				
American Indian/Alaska Native				
Asian				
Native Hawaiian/Other Pacific Islander				
Black or African American				
White				
More than one race				
Unknown or unreported				
Racial Categories: Total All Subjects				
HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date				
Racial Categories				
American Indian/Alaska Native				
Asian				
Native Hawaiian/Other Pacific Islander				
Black or African American				
White				
More than one race				
Unknown or unreported				
Racial Categories: Total All Subjects				

Table 5. DEMOGRAPHIC AND KEY BASELINE CHARACTERISTICS BY GROUP

Date: _____

Characteristics	Group 1 N%	Group 2 N%	Total N%
Gender			
- Male			
- Female			
Ethnicity			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown			
Race			
- American Indian/Alaska Native			
- Asian			
- Native Hawaiian or Other Pacific Islander			
- Black or African American			
- White			
- More than one race			
- Unknown or not reported			
Age			
- Mean			
- Median			
- Minimum			
- Maximum			
Risk Factors			
Clinical Features			

Table 6. TREATMENT DURATION FOR ALL SUBJECTS

Date: _____

TIME IN STUDY	N	%	TOTAL
1 month or less			
2-5 months			
6-9 months			
10-11 months			
Completed study			

Table 7. TREATMENT DURATION FOR SUBJECTS WHO DISCONTINUED THERAPY

Date: _____

Time in Study	N	%	Total
1 month or less			
2-5 months			
6-9 months			
10-11 months			
Completed study			

Table 8. ADVERSE EVENTS

Date: _____

Subject	Adverse Event	Onset Date	Ending Date	*Severity	*Drug Related	*Action	*Outcome	Comments

CODES:

Severity:
1 = Mild
2 = Moderate
3 = Severe
4 = Life threatening**

Drug Relatedness:
0 = Definitely unrelated
1 = Unlikely
2 = Possibly Related
3 = Probably Related
4 = Definitely Related

Action (taken):
0 = None
1 = Dose modification
2 = Counteractive Medication (specify under comments)
3 = Medical/surgical intervention (specify under comments)
4 = Hospitalization**
5 = Drug permanently discontinued
6 = Other (specify under comments)

Outcome:
1 = Resolved
2 = Recovered with minor sequelae
3 = Recovered with major sequelae
4 = Condition still present and under treatment
5 = Condition continues to worsen
6 = Patient died**

****Event is serious and explained in detail on SAE form**

Table 9. SERIOUS ADVERSE EVENTS

Date: _____

Subject	Age	Treatment Date	Event	Onset Date	*Relationship	Description of Actions and Outcome (e.g., hospitalization concomitant meds, study, status, etc.)

***RELATIONSHIP**
0 = Definitely Unrelated
1 = Unlikely
2 = Possibly Related
3 = Probably Related
4 = Definitely Related

NOTE: Whether or not the event is "expected" might also be included in this table. "Expected" means the event is part of the natural course of the disease process or the event is a known consequence of the treatment as identified in the protocol or the investigator's brochure. This may be important information if this study is using an investigational or IND drug.

Table 10. DEATHS

Date: _____

Patient ID#	DOB	Date Enrolled	Treatment Duration	Cause of Death	Date of Death

Table 11. FREQUENCY OF SPECIFIC SYMPTOMS

Date: _____

Symptoms (depends on disease)	N%
Pain or Heaviness in Legs	
Swelling in Legs	
Pain or Heaviness in Chest	
Headaches	
Dizziness	
Nausea	
Abdominal Pain	
Weakness	
Fatigue	
Muscle Aches	
Urinary Frequency	
Total	

Table 12. OBSERVED ADVERSE EVENTS BY BODY SYSTEM

Date: _____

ADVERSE EVENT	SEVERITY		RELATIONSHIP TO DRUG			
	Mild/Mod	Severe	Related to Drug A Only	Related to Drug B Only	Related to Both	Not Related
Body System A:						
Event 1						
Body System B:						
Event 1						
Body System C:						
Event 1						

Table 13. LABORATORY DATA BY PATIENT: OUT OF RANGE VALUES

Date: _____

Pt. ID#	Visit #	HCT	WBC	PLT	Protein	Urine RBC	Creatinine	ALT	AST	Cholesterol	Amylase	BUN	CPK