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# **STUDY PROGRESS AND SAFETY MONITORING PLAN TEMPLATE**

(Intended primarily for use in monitoring of Phase III/IV trials)

**Final**

**December 20, 2006**

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## **1. PURPOSE OF THE TEMPLATE**

### **1.1 Purpose**

The purpose of this Study Progress and Safety Monitoring Plan Template is to assist Data Management Centers in the development of a Study Progress and Safety Monitoring Plan (SPSMP) and to describe the types, content, and schedules of distribution of study progress and safety monitoring reports required for Division of AIDS (DAIDS) funded and/or sponsored studies. If some types of information is available to DAIDS from other sources, its inclusion in the SPSMP may not be necessary.

### **1.2 Scope**

This Template may be utilized by Data Management Centers (which includes non-network study sites performing Data Management Center tasks) participating in DAIDS funded and/or sponsored clinical trials.

### **1.3 Introduction**

SPSMPs are required for DAIDS funded and/or sponsored clinical trials in order to:

- 1) Protect and ensure the safety of the subjects;
- 2) Ensure the validity and integrity of the data for DAIDS funded and/or sponsored clinical trials studies;
- 3) Ensure that the clinical trial is monitored appropriately;
- 4) Ensure that the data collected will be usable to monitor safety and address the protocol objectives; and
- 5) Ensure that the protocol team is aware of the schedule of monitoring for the clinical trial.

The SPSMP is usually prepared by the study Statistician(s) and the Data Manager(s), in conjunction with the Protocol Team, according to the requirements of the protocol and is approved by the DAIDS Clinical Representative. Once developed, the SPSMP will be periodically reviewed by the Protocol Team and modified as necessary.

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## 2. SUMMARY OF STUDY PROGRESS AND SAFETY MONITORING REPORT DISTRIBUTION

### 2.1 Phase III/IV Studies

Type of Report	Prep By*	Freq of Prep <sup>+</sup>	Distributed To			
			Protocol Team	Sites <sup>z</sup>	DAIDS Clinical Rep	DSMB <sup>&amp;</sup>
Accrual Update Report	DM	M	X	X		X
Progress Report (Open)	S	M	X			
Progress Report (Closed)	S	A				X
Delinquency Report by Site (List)	DM	M		X		
Delinquency Report (Summary)	DM	M	X		X	X
Periodic Summary Adverse Event Report (Open)	S	Q or SA	X			
Periodic Summary Adverse Event Report (Closed)	S	Q or SA			X**	X
Baseline Characteristics Report (Open)	S	SA	X			
Baseline Characteristics Report (Closed)	S	A				X
Data Completeness Report	DM	Q or A	X			X
HIV-1 Virology Data Quality Report	S DM LDC	Q	X**	X** †		
DSMB Outcomes Summary Report	S	A (not generated when Efficacy Report is prepared)				X
DSMB Efficacy Report	S	Per interim monitoring plan, e.g., after X subjects complete Y weeks of follow-up				X

\* Prep By: Prepared By:

DM: Data Manager      LDC: Laboratory Data Coordinator  
S: Statistician

<sup>+</sup> Freq of Prep:

Frequency of Preparation:

M: Monthly      SA: Semi-Annually  
Q: Quarterly      A: Annually

<sup>z</sup> Reports to Sites: Material is available for download for Network sites only.

<sup>&</sup> Reports to the DSMB are prepared annually, independent of preparation frequency of individual components.

\*\* If applicable to the study.

† Provided to Site Coordinator and/or Virology Laboratory only if there are problems with the report.

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## 2.2 Substudies (if applicable)

Type of Report	Prep By*	Freq of Prep <sup>+</sup>	Distributed To	
			Protocol Team	Sites <sup>z</sup>
Accrual Update Report	DM	M	X	X
Delinquency Report by Site (List)	DM	M		X

\* Prep By: Prepared By:  
DM: Data Manager

+ Freq of Prep: Frequency of Preparation:  
M: Monthly

<sup>z</sup> Reports to Sites: Material is available for download for Network sites only.

## 3. STUDY PROGRESS AND SAFETY MONITORING REPORTS AND CHARACTERISTICS

### 3.1 Accrual Update Report

#### 3.1.1 Purpose

The purpose of the Accrual Update Report is to monitor enrollment to ensure that accrual goals are met in a timely manner, to inform Sites of the number of subjects enrolled, and to notify Sites when the accrual goal is nearing completion.

#### 3.1.2 Responsibility for Preparation

It is the responsibility of the Data Manager to prepare the Accrual Update Report.

#### 3.1.3 Frequency of Preparation

The Accrual Update Report is prepared monthly.

#### 3.1.4 Distribution

The Accrual Update Report is distributed as follows:

- Protocol Team
- Site
- DSMB

#### 3.1.5 Contents

The contents of the Accrual Update Report are as follows:

- Total accrual by week or month

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- Accrual by step, if applicable
- Accrual by site by month
- Line listings by site of enrollment, including PID and randomization group as applicable

## 3.2 Progress Report

### 3.2.1 Purpose

The purpose of the Progress Report is to provide a summary of the enrollment and status of subjects for assessing progress on the study and to determine whether subjects are entering study/steps in a timely manner (if applicable).

### 3.2.2 Responsibility for Preparation

It is the responsibility of the Statistician to prepare the Progress Report.

### 3.2.3 Frequency of Preparation

The Progress Report is prepared as follows:

- Open Report: Monthly
- Closed Report: Annually

### 3.2.4 Distribution

The Progress Report is distributed as follows:

- Open Report: Protocol Team
- Closed Report: DSMB

### 3.2.5 Contents

The contents of the Progress Report are as follows:

#### **Open Report**

#### Results are combined over all study arms

- Number of subjects accrued/randomized to study/steps
- Number of subjects completing the study/steps
- Number of subjects off treatment/on-study
- Number of subjects off study
- Reasons off study
- Number of subjects lost to follow-up
- Inclusion/exclusion violations

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- Protocol violations

### **Closed Report**

#### Results listed separately by study arm

- Number of subjects accrued/randomized to study/steps
- Number of subjects completing the study/steps
- Number of subjects off treatment/on-study
- Number of subjects off study
- Reasons off study
- Number of subjects lost to follow-up
- Inclusion/exclusion violations
- Protocol violations
- Number of subjects completing the study
- Number of subjects off treatment/on-study
- Number of subjects off study
- Reasons for off study
- Number of subjects lost to follow-up

## **3.3 Delinquency Report**

### **3.3.1 Purpose**

The purpose of the Delinquency Report is to ensure a current database and to make Sites and Site Principal Investigators (PIs) aware of specific problems regarding missing clinical data for quick resolution.

### **3.3.2 Responsibility for Preparation**

It is the responsibility of the Data Manager to prepare the Delinquency Report.

### **3.3.3 Frequency of Preparation**

The Delinquency Report is prepared monthly.

### **3.3.4 Distribution**

The Delinquency Report is distributed as follows:

- Delinquency List: Site
- Delinquency Summary: Protocol Team, DAIDS Clinical Representative, and DSMB

### **3.3.5 Contents**

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The contents of the Delinquency Report are as follows:

### **Delinquency List**

- List of missing forms by PID

### **Delinquency Summary – Two Reports**

Report 1 lists the following information by site:

- Number of subjects
- Number of subjects with delinquent forms
- Number of forms delinquent as of the most current delinquency run
- Average number of delinquent forms per subject entry

Report 2 lists overdue forms by site as follows:

- 4 – 8 weeks overdue
- 9 – 12 weeks overdue
- > 12 weeks overdue

## **3.4 Periodic Summary Adverse Event Report**

### **3.4.1 Purpose**

The purpose of the Periodic Summary Adverse Event Report is to monitor toxicities, to evaluate unexpected toxicities, and to ensure that toxicity rates are acceptable.

### **3.4.2 Responsibility for Preparation**

It is the responsibility of the Statistician to prepare the Periodic Summary Adverse Event Report.

### **3.4.3 Frequency of Preparation**

The Periodic Summary Adverse Event Report is prepared as follows:

- Open Report: Quarterly or Semi-Annually
- Closed Report: Quarterly or Semi-Annually (if applicable)

### **3.4.4 Distribution**

The Periodic Summary Adverse Event Report is distributed as follows:

- Open Report: Protocol Team



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- Closed Report: DAIDS Clinical Representative (optional, depending upon study) and/or DSMB

#### 3.4.5 Contents

The contents of the Periodic Summary Adverse Event Report are as follows:

##### **Open Report**

###### Results are combined over all study arms

- Cumulative number of events and subjects that experienced the lowest Grade collected for the study on Case Report Forms (CRFs) through Grade 4 adverse events
- Cumulative number of events and subjects that experienced different grades of adverse events by body system or system organ class (SOC)
- Cumulative number of events and subjects that experienced different types of adverse events sorted body system or SOC
- All deaths
- Cumulative number of events and subjects since last report for all categories above
- Line listing of adverse events by PID with descriptions, if requested

##### **Closed Report**

###### Results listed separately by study arm

- Cumulative number of events and subjects that experienced the lowest Grade collected for the study on Case Report Forms (CRFs) through Grade 4 adverse events
- Cumulative number of events and subjects that experienced different grades of adverse events by body system or system organ class (SOC)
- Cumulative number of events and subjects that experienced different types of adverse events sorted body system or SOC
- All deaths
- Cumulative number of events and subjects since last report for all categories above
- Line listing of adverse events by PID with descriptions, if requested

### **3.5 Baseline Characteristics Report**

#### 3.5.1 Purpose

The purpose of the Baseline Characteristics Report is to provide a summary of subjects' baseline characteristics.

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### 3.5.2 Responsibility for Preparation

It is the responsibility of the Statistician to prepare the Baseline Characteristics Report.

### 3.5.3 Frequency of Preparation

The Baseline Characteristics Report is prepared as follows:

- Open Report: Semi-Annually
- Closed Report: Annually

### 3.5.4 Distribution

The Baseline Characteristics Report is distributed as follows:

- Open Report: Protocol Team
- Closed Report: DSMB

### 3.5.5 Contents

The contents of the Baseline Characteristics Report are as follows:

#### **Open Report**

##### Results are combined over all study arms

- Demographic information: gender, race/ethnicity, IV drug use, age, etc.
- Health status: Karnofsky performance score, CD4,  $\log_{10}$  HIV-1 RNA copy numbers, history of OIs, etc.
- Stratifications
- Other collected data

#### **Closed Report**

##### Results listed separately by study arm

- Demographic information: gender, race/ethnicity, IV drug use, age, etc.
- Health status: Karnofsky performance score, CD4,  $\log_{10}$  HIV-1 RNA copy numbers, history of OIs, etc.
- Stratifications
- Other collected data

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### 3.6 Data Completeness Report

#### 3.6.1 Purpose

The purpose of the Data Completeness Report is to monitor completeness of key forms at selected time points for analysis.

#### 3.6.2 Responsibility for Preparation

It is the responsibility of the Data Manager to prepare the Data Completeness Report.

#### 3.6.3 Frequency of Preparation

The Data Completeness Report is prepared quarterly or annually.

#### 3.6.4 Distribution

The Data Completeness Report is distributed as follows:

- Protocol Team: Quarterly
- DSMB: Annually

#### 3.6.5 Contents

The contents of the Data Completeness Report are data at selected time points (e.g., step entry, visit weeks, and final visit) compared to data expected and listed by study arm. For example:

- Diagnosis/endpoint record
- Study event tracking
- Subject visit
- Study regimen record
- Other treatment record (if appropriate)
- Other key endpoint data completeness (e.g., HIV-1 RNA results, CD4 lymphocytes)
- Endpoint evaluability
- Virology or other specimen tracking
- Other data as needed

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### 3.7 HIV-1 Virology Data Quality Report (only if applicable and appropriate)

#### 3.7.1 Purpose

The purpose of the HIV-1 Virology Data Quality Report is to examine plasma HIV-1 RNA data for inconsistencies and outliers.

#### 3.7.2 Responsibility for Preparation

It is the responsibility of the Statistician, Data Manager, and/or Laboratory Data Coordinator, as appropriate, to prepare the HIV-1 Virology Data Quality Report.

#### 3.7.3 Frequency of Preparation

The HIV-1 Virology Data Quality Report is prepared quarterly.

#### 3.7.4 Distribution

The HIV-1 Virology Data Quality Report is distributed as follows:

- Protocol Team
- Virology Laboratory (only if there are problems with the report)
- Site Coordinator (only if there are problems with the report)

#### 3.7.5 Contents

The contents of the HIV-1 Virology Data Quality Report are as follows:

Results are combined over all study arms

- Listing of inconsistencies in the laboratory virology database (i.e., date discrepancies, missing results, PID errors, etc.)
- Listing of inconsistencies between results on the form with those obtained directly from the laboratory virology database
- Listing of inconsistencies between specimen dates on the forms with those obtained directly from the laboratory virology database
- Listing of multiple RNA measurements with the same specimen date for one subject
- Listing of significant increases between study visit (i.e., 1 or more log<sub>10</sub> units)

### 3.8 DSMB Outcomes Summary Report

#### 3.8.1 Purpose

The purpose of the DSMB Outcomes Summary Report is to monitor the occurrence of primary (and key secondary) study endpoints, summarized over all study arms, to assess whether it is likely that the study will be able to reach conclusions at the end.

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### 3.8.2 Responsibility for Preparation

It is the responsibility of the Statistician to prepare the DSMB Outcomes Summary Report.

### 3.8.3 Frequency of Preparation

The DSMB Outcomes Summary Report is prepared annually.

If the DSMB Efficacy Report (see Section 4.9) is prepared, then the DSMB Outcomes Summary Report is **not** prepared.

### 3.8.4 Distribution

The DSMB Outcomes Summary Report is distributed to the DSMB.

### 3.8.5 Contents

The contents of the DSMB Outcomes Summary Report are as follows:

#### Results are combined over all study arms

- Distribution of primary and key secondary endpoints
- Frequency of component endpoints separately (if multiple) as individual yes/no variables
- Occurrences or reoccurrences of clinical events (if applicable)
  - ⇒ Number of new/recurrent clinical events, by disease, since last report
  - ⇒ Number of subjects that experienced one or more clinical event since last report
  - ⇒ Cumulative number of clinical events
  - ⇒ Cumulative number of subjects that experienced each clinical event
- Clinical outcomes of treatment for the presenting clinical events (if applicable) separately by type of event, including:
  - ⇒ Efficacy of treatment for enrollment event
  - ⇒ Additional treatments needed/treatment switches
  - ⇒ Duration to recovery from initial event

## 3.9 **DSMB Efficacy Report**

### 3.9.1 Purpose

The purpose of the DSMB Efficacy Report is to monitor through an interim analysis of the primary (and key secondary) objective endpoints at the time(s) of interim analysis specified in the DSMB interim monitoring plan in the protocol. The interim analysis boundary will be defined by a boundary, e.g., O'Brien-Fleming boundary,

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reflecting the actual information available at the analysis. Secondary analyses for outcomes may be done using the same boundary.

### 3.9.2 Responsibility for Preparation

It is the responsibility of the Statistician to prepare the DSMB Efficacy Report.

### 3.9.3 Frequency of Preparation

The DSMB Efficacy Report is prepared at the frequency determined in the DSMB interim monitoring plan.

### 3.9.4 Distribution

The DSMB Efficacy Report is distributed to the DSMB.

### 3.9.5 Contents

The contents of the DSMB Efficacy Report are as follows:

#### Results listed separately by study arm

- Distribution of primary and key secondary endpoints
- Frequency of component endpoints separately (if multiple) as individual yes/no variables
- Changes over time at X weeks after start of treatment in primary clinical endpoint events (if applicable)
  - ⇒ Occurrences or reoccurrences of a clinical event
  - ⇒ Number of new/recurrent clinical events, by disease, since last report
  - ⇒ Number of subjects that experienced one or more clinical event since last report
  - ⇒ Cumulative number of clinical events
  - ⇒ Cumulative number of subjects that experienced each clinical event
  - ⇒ Intolerance rates (if applicable)
- Clinical outcomes of treatment for the presenting clinical events (if applicable) separately by type of event, including:
  - ⇒ Efficacy of treatment for enrollment event
  - ⇒ Additional treatments needed for enrollment event
  - ⇒ Duration to recovery from initial event
  - ⇒ Intolerance rates (if applicable)

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### 3.10 Other Study-Specific Reports

The protocol may require study-specific reports other than those listed in this Template. Accordingly, the study Statistician(s) and Data Manager(s), in conjunction with the Protocol Team, will create reports as needed to meet protocol-specific requirements.