

**DIVISION OF AIDS (DAIDS)
REGULATORY COMPLIANCE CENTER (RCC)**

**SERIOUS ADVERSE EXPERIENCE (SAE)
REPORTING MANUAL**

for

**AIDS Clinical Trials Groups (AACTG & PACTG)
Community Programs for Clinical Research on AIDS (CPCRA)
Intramural Research Program (IRP)**

AUGUST 1, 1998

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RESPONSIBILITIES OF SPONSORS, INVESTIGATORS, AND CLINICAL SITES

In accordance with the Food and Drug Administration's (FDA) Code of Federal Regulations, the sponsor of a clinical trial and the investigators participating in a clinical trial are responsible for proper reporting of Serious Adverse Experiences (SAEs). The purpose of reporting SAEs is to better understand the toxicity and safety of investigational agents. Reporting and monitoring of SAEs is required to alert the FDA, sponsor, and clinical investigators of real and potential patient safety issues. The responsibilities of the sponsor and investigator described in the Code of Federal Regulations are enforceable by the FDA. Therefore, it is very important for investigators and study coordinators to be knowledgeable of the regulations. This manual will guide the investigator and study coordinator on procedures for reporting SAEs in accordance with FDA regulations.

As the sponsor of clinical trials, the Division of AIDS (DAIDS) has the responsibility of reviewing all information relevant to the safety of drugs. This includes the review of SAEs reported by the clinical sites. The DAIDS will carefully review the SAE Report and use this information to monitor the investigational drug's toxicity profile and patient safety. Those Adverse Experiences which are serious, unexpected, and related to the study drug must be reported by DAIDS to the FDA in the form of a written Safety Report. Safety Report submissions to the FDA must occur as soon as possible, but no later than 15 calendar days after the Serious Adverse Experience (SAE) Office is informed of the SAE.

Serious Adverse Experience data provides the FDA, DAIDS and investigators with an early toxicity profile of an investigational agent. The toxicity profile is an early warning system of potentially serious events which may occur with the use of an investigational agent. This information is also used during the New Drug Application (NDA) review to determine if a drug is safe for marketing. If a drug is approved, the safety information which was reported by the clinical sites during the clinical trial phase of drug development, will have contributed to the "Adverse Reaction" section of the Product Package Insert.

To ensure compliance with FDA regulations, the DAIDS requires that clinical sites report all SAEs which meet the reporting requirements set forth in this Manual. The Serious Adverse Experience (SAE) Form must be completed and sent to the DAIDS SAE Office as soon as possible after research staff becomes aware of the event. The SAE Office may need to contact the clinical site for additional information regarding the SAE. The SAE Office will maintain all SAE Reports on file and in a regulatory database. This will ensure that all SAEs occurring in DAIDS Therapeutic Treatment Trials are contained in a single, centralized regulatory database which will help the DAIDS better track and report patient safety.

I. GENERAL INFORMATION

A. DEFINITIONS:

1. **Adverse Experience:** Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.
2. **Serious Adverse Experience:** Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
3. **Study Treatment:** All therapeutics (drugs, biologics, or other therapeutic combinations) listed in the Study Treatment Section of the protocol document. These are considered study drug agents and are usually supplied by DAIDS. Agents being studied in a protocol can be either investigational products, licensed products, or a combination of both.

B. SERIOUS ADVERSE EXPERIENCE GRADING:

Toxicity grades (Grade 1, 2, 3, or 4) are assigned by the site to indicate the severity of Serious Adverse Experiences and to determine their reportability to the SAE Office. The DAIDS “Table for Grading Severity of Adverse Experiences” can be found in ACTG protocols as an Appendix. The CPCRA Toxicity Table can be found in the CPCRA Data Collection Handbook. These Toxicity Tables should be used by site clinicians to assign toxicity grades to all Adverse Experiences. For clinical events or laboratory abnormalities NOT identified in the Toxicity Table, refer to the “Guide for Estimating Severity Grade” within the Toxicity Table.

NOTE: The Toxicity Table in some DAIDS protocols may include toxicities which are only relevant to that particular protocol OR may have adjusted the grading criteria to meet the needs of study objectives. It is important to use the protocol specific toxicity table to ensure accurate grading of Adverse Experiences.

C. RELATIONSHIP ASSESSMENT:

Relationship between a Serious Adverse Experience and study treatment is determined by the site investigator or subinvestigator physician listed on the FDA Form 1572. In general, relationship is one of the main criteria used to determine the reportability of a Serious Adverse Experience to the SAE Office.

D. LEVELS OF REPORTING REQUIREMENTS:

DAIDS has designated three levels of reporting requirements for DAIDS research protocols. This designation is determined by the Protocol Team during protocol development and is indicated in the protocol document:

Neonate/Infants (N) - Events at ALL toxicity Grades (1-4)

Intensive (I) - Events at toxicity Grade 3 and 4

Standard (S) - Events at toxicity Grade 4

E. FOLLOW-UP INFORMATION:

If the site obtains additional information about a previously reported SAE which changes the site investigator's assessment of relationship, submit follow-up information to the SAE Office as soon as possible. For Serious Adverse Experiences which become FDA Safety Reports, the SAE Office may need to contact the site in the immediate period after reporting for important follow-up information. **Because the SAE Office must submit FDA Safety Reports within 15 days of SAE Report receipt, it is critical that this important follow-up information be obtained and communicated as soon as possible. If the updated information is not available within that 15 day time period, it should be obtained and forwarded as soon as possible so the SAE Office can submit a Follow-Up Safety Report to the FDA.**

Unless specifically requested, resolution/outcome of an SAE need **not** be reported to the SAE Office. When follow-up information is requested by the SAE Office, obtain and forward the requested information to the SAE Office as soon as possible.

F. MEANS OF REPORTING SERIOUS ADVERSE EXPERIENCES (SAEs):

Serious Adverse Experiences that meet reporting requirements must be reported on a DAIDS SERIOUS ADVERSE EXPERIENCE (SAE) FORM. Completed Forms should be submitted to the RCC Safety Office within 3 Working Days of unit/site awareness via phone, FAX, or U.S. Mail:

SAE Office Phone: 1-800-537-9979 or 301-897-1709

SAE Office FAX: 1-800-275-7619 or 301-897-1710

SAE Office E-Mail: RCCSafetyOffice@tech-res.com

**Mailing Address: REGULATORY COMPLIANCE CENTER
SERIOUS ADVERSE EXPERIENCE (SAE) OFFICE
TECHNICAL RESOURCES INTERNATIONAL
6500 ROCK SPRING DR., SUITE 650
ROCKVILLE, MD 20817**

NOTE: Reporting Serious Adverse Experiences on an SAE Form is not a substitute for completing Case Report Forms (CRFs).

Updated Contact Information 6 July 2004

II. NON-REPORTABLE ADVERSE EXPERIENCES

The following Adverse Experiences are NOT REPORTABLE on an SAE Form to the SAE Office at ANYTIME:

- 1) AIDS-Associated Diagnoses (See Pages 8-9)

These lists are to be used for SAE Reporting purposes only.

If a symptom can be definitively linked to an AIDS-Associated Diagnosis, and therefore assessed as NOT RELATED to study treatment, then the symptom need not be reported.

- 2) Diagnoses, illnesses and/or lab abnormalities assessed as “Not Related” to study treatment

Such events **MUST** have an alternative, definitive etiology documented in the patient’s medical record.

- 3) Permanent discontinuation of study treatment due to toxicities which do not meet SAE Reporting requirements

- 4) Overdoses:

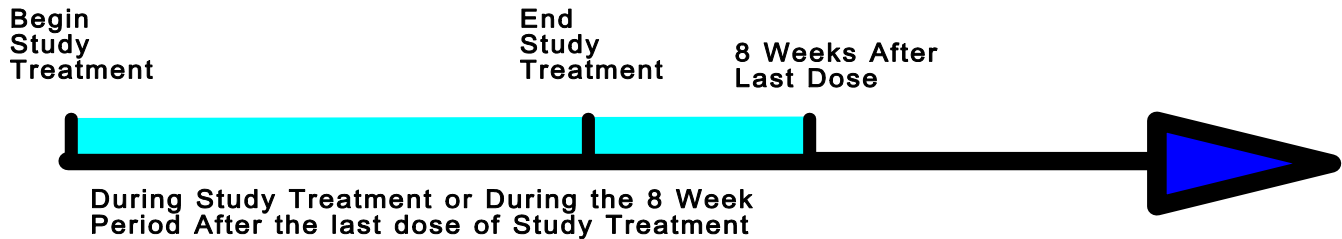
- a) with NO associated Adverse Experience, OR
- b) with an associated Grade 1 or 2 Adverse Experience

- 5) Recurrent events at the same toxicity grade level with etiology unchanged.

NOTE: Adverse Experiences listed above must still be reported on the appropriate Case Report Form(s).

III. REPORTABLE SERIOUS ADVERSE EXPERIENCES

A. OCCURRING DURING STUDY TREATMENT OR DURING THE 8 WEEK PERIOD AFTER THE LAST DOSE OF STUDY TREATMENT



A-1. REPORTABLE REGARDLESS OF RELATIONSHIP:

- DEATH
After submitting the SAE Form, submit pertinent follow-up information and autopsy reports to the SAE Office as soon as it becomes available if the report offers new information.
- CANCER OCCURRING ON STUDY
Exception: AIDS-Associated Malignancies (See AIDS-Associated Malignancies on Pages 8-9)
- CONGENITAL ANOMALY/BIRTH DEFECT
Congenital anomaly in a neonate or infant of a mother who has received Study Treatment
- PERMANENT DISABILITY/INCAPACITY
A permanent disability is defined as a persistent or significant disability or incapacity.
Exception: Disability/Incapacity caused by AIDS-Associated Diagnoses (See AIDS-Associated Diagnoses on Pages 8-9)

| Report if Event Occurs | Relationship Assessment | Reporting Time Frame* |
|---|--|--|
| During Study Treatment <u>OR</u> During the 8 Week Period After the last dose of Study Treatment | Definitely Possibly Unable to Judge Not Related | FAX or PHONE SAE Office within 24 Hours of unit/site awareness FOLLOWED BY Submit SAE Form within 3 Working Days of unit/site awareness to the SAE Office |

* See Section III-B on Page 7 for information about Death, Cancer, Congenital Anomaly/Birth Defect, and Permanent Disability/Incapacity occurring after 8 weeks OFF Study Treatment.

A. [CONTINUED]

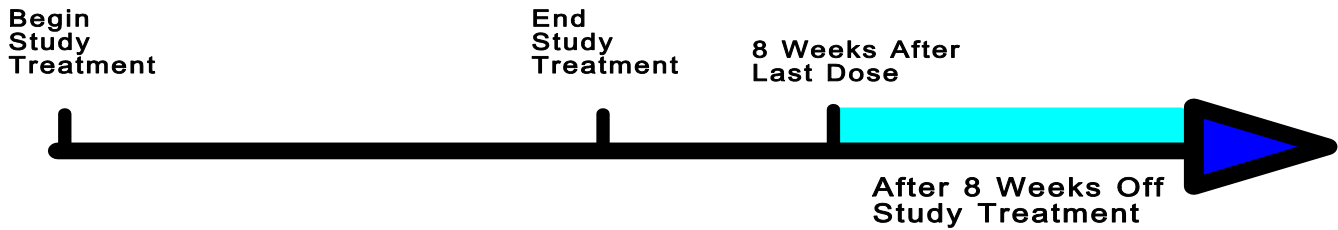
OCCURRING DURING STUDY TREATMENT OR DURING THE 8 WEEK PERIOD AFTER THE LAST DOSE OF STUDY TREATMENT

**A-2. REPORTABLE IF:
IS NOT AN AIDS-ASSOCIATED DIAGNOSIS, and
RELATIONSHIP IS ASSESSED AS DEFINITELY, POSSIBLY, or UNABLE TO JUDGE**

- GRADE 4 ADVERSE EXPERIENCES ON ALL PROTOCOLS
- GRADE 3 and 4 ADVERSE EXPERIENCES ON INTENSIVE PROTOCOLS
- GRADE 1 - 4 ADVERSE EXPERIENCES ON NEONATE/INFANT PROTOCOLS
Exception: Adverse Experiences or abnormalities which are considered normal for that age/stage of development, such as: physiologic jaundice, diaper rash, episodic upper respiratory infections, or otitis media
- GRADE 3 and 4 ADVERSE EXPERIENCES ASSOCIATED WITH AN OVERDOSE OF STUDY DRUG
- ADVERSE EXPERIENCES OF ANY TOXICITY GRADE (1 - 4) CONSIDERED SERIOUS BY THE SITE PHYSICIAN

| Report if Event Occurs | Relationship Assessment | Reporting Time Frame |
|---|---|--|
| During Study Treatment <u>OR</u> During the 8 Week Period After the last dose of Study Treatment | Definitely Possibly Unable to Judge | Submit SAE Form within 3 Working Days of unit/site awareness to the SAE Office |

B. OCCURRING AFTER 8 WEEKS OFF STUDY TREATMENT AND RELATIONSHIP ASSESSED AS DEFINITELY, POSSIBLY, or UNABLE TO JUDGE



- DEATH
After submitting the SAE Form, submit pertinent follow-up information and autopsy reports to the SAE Office as soon as it becomes available if the report offers new information.
- CANCER
Exception: AIDS-Associated Malignancies (See AIDS-Associated Malignancies on Pages 8-9)
- CONGENITAL ANOMALY/BIRTH DEFECT
Congenital anomaly in a neonate or infant of a mother who has received Study Treatment
- PERMANENT DISABILITY/INCAPACITY
A permanent disability is defined as a persistent or significant disability or incapacity.
Exception: Disability/Incapacity caused by AIDS-Associated Diagnoses
(See AIDS-Associated Diagnoses on Pages 8-9)

| Report if Event Occurs | Relationship Assessment | Reporting Time Frame |
|---|---|--|
| After 8 weeks OFF Study Treatment AND unit/site becomes aware | Definitely Possibly Unable to Judge | Submit SAE Form within 3 Working Days of unit/site awareness to the SAE Office |

AIDS-ASSOCIATED DIAGNOSES - ADOLESCENTS & ADULTS 1993*

OPPORTUNISTIC INFECTIONS:

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal, oropharyngeal, vaginal
- Coccidioidomycosis, disseminated or extra pulmonary
- Cryptococcosis, extra pulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis
- Herpes simplex: chronic ulcer(s), bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extra pulmonary
- Isosporiasis, chronic intestinal
- *Mycobacterium avium* complex or *M. Kansasii*, disseminated or extra pulmonary
- *Mycobacterium tuberculosis*, any site (pulmonary or extra pulmonary)
- *Mycobacterium*, other species or unidentified species, disseminated or extra pulmonary
- *Pneumocystis carinii* pneumonia
- Pneumonia, recurrent
- *Salmonella* septicemia
- Toxoplasmosis of brain

MALIGNANCIES:

- Cervical cancer, invasive
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain

OTHER:

- Encephalopathy, HIV-related
- Progressive multifocal leukoencephalopathy
- Wasting syndrome due to HIV

*Modified for use in SAE Reporting, from Morbidity and Mortality Weekly Report (MMWR) Volume 41

AIDS-ASSOCIATED DIAGNOSES - PEDIATRICS 1994 *

OPPORTUNISTIC INFECTIONS:

- Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than/in addition to lungs, or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis
- Cytomegalovirus disease with onset of symptoms at age > 1 months (at site other than liver, spleen, or lymph nodes)
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists >1 month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a child >1 month of age
- Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
- Histoplasmosis, disseminated (at a site other than or in addition to lungs, cervical, or hilar lymph nodes)
- Isosporidiosis
- *Mycobacterium tuberculosis*, disseminated or extra pulmonary
- *Mycobacterium*, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Pneumocystis carinii* pneumonia
- Salmonella (nontyphoid) septicemia
- Toxoplasmosis of the brain with onset at > 1 month of age
- Varicella, disseminated (complicated chickenpox)

MALIGNANCIES:

- Kaposi's sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype

OTHER:

- Encephalopathy [at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings: a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children < 2 years of age); c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance]
- Lymphoid Interstitial Pneumonia
- Progressive multifocal leukoencephalopathy
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: a) persistent weight loss > 10% of baseline OR b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child ≥ 1 year of age OR c) < 5th percentile on weight-for-height chart on two consecutive measurements, ≥ 30 days apart PLUS a) chronic diarrhea (i.e., at least two loose stools per day for ≥ 30 days OR b) documented fever (for ≥ 30 days, intermittent or constant)

* Modified for use in SAE Reporting, from Morbidity and Mortality Weekly Report (MMWR) Volume 43

SAE REPORTING FLOW CHART

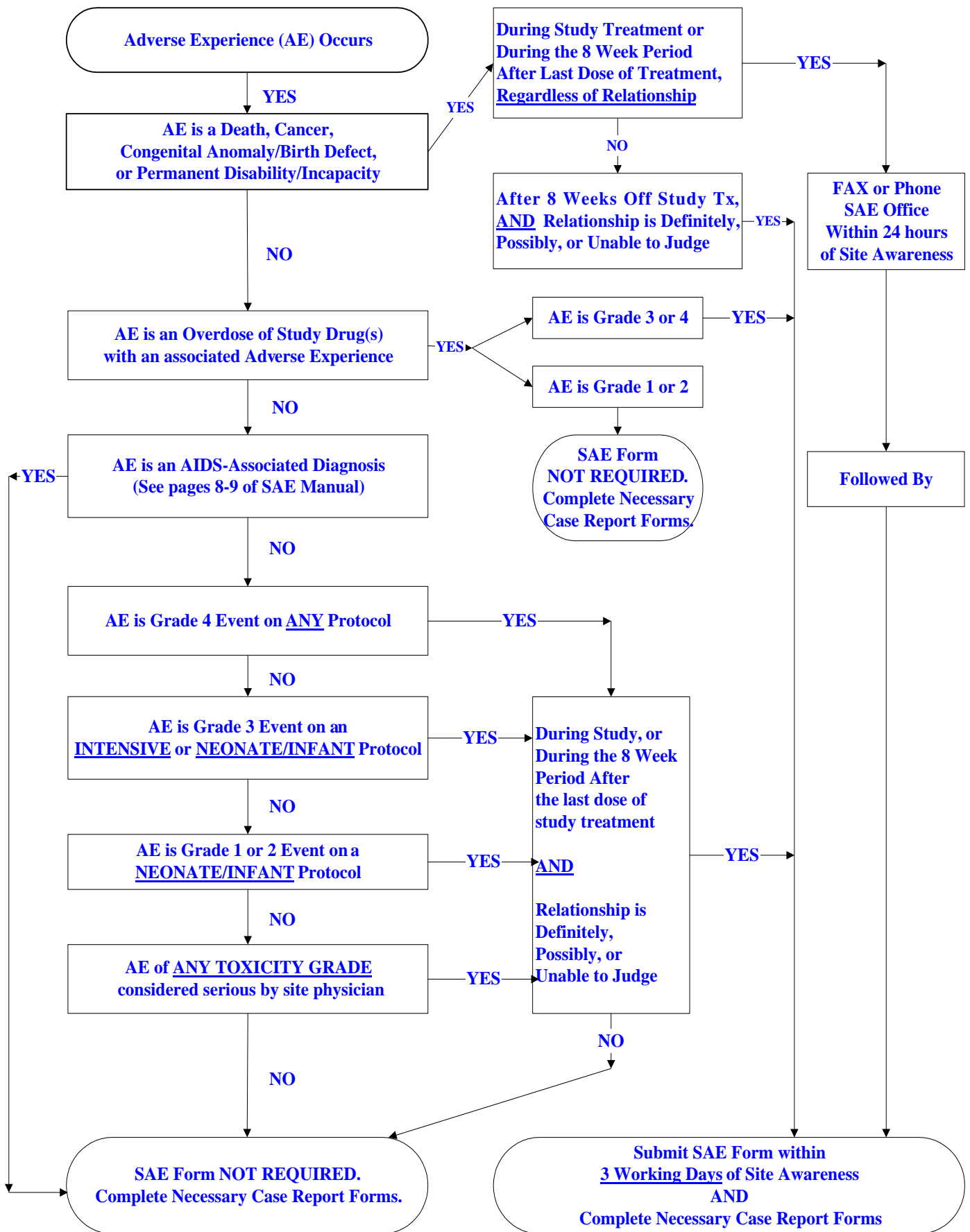


TABLE OF REPORTABLE SAEs

General Reporting Guidelines:

- Check the protocol document for the level of SAE Reporting Requirements: Neonate/Infant (N), Intensive (I), Standard (S)
- AIDS-Associated Diagnoses are NOT REPORTABLE to the SAE Office

| N | I | S | CATEGORIES OF REPORTABILITY | REPORTING Time Frame |
|---|---|---|--|--|
| √ | √ | √ | <p>A. REPORTABLE DURING STUDY TREATMENT OR DURING THE 8 WEEK PERIOD AFTER LAST DOSE OF STUDY TREATMENT</p> <p>1. Regardless of Relationship</p> <ul style="list-style-type: none"> • Death • Cancer - except AIDS-Associated Malignancies* • Congenital Anomaly/Birth Defect • Permanent Disability/Incapacity - except disability/incapacity caused by AIDS-Associated Diagnoses* | <p>FAX or PHONE the SAE Office within <u>24 Hours</u> of unit/site awareness</p> <p>FOLLOWED BY</p> <p>Submit SAE Form within <u>3 Working Days</u> of unit/site awareness</p> |
| √ | √ | √ | <p>2. Reportable If: IS NOT an AIDS-Associated Diagnosis and Relationship assessed as Definitely, Possibly, or Unable to Judge</p> <ul style="list-style-type: none"> • Grade 4 Adverse Experiences • Grade 3 Adverse Experiences • Grade 3 or 4 Adverse Experience associated with an Overdose of study drug • Grade 1 or 2 Adverse Experiences • Adverse Experiences of <u>any toxicity grade</u> considered serious by site physician | |
| √ | √ | √ | <p>B. REPORTABLE AFTER 8 WEEKS OFF STUDY TREATMENT AND RELATIONSHIP ASSESSED AS DEFINITELY, POSSIBLY RELATED OR UNABLE TO JUDGE</p> <ul style="list-style-type: none"> • Death • Cancer - except AIDS-Associated Malignancies* • Congenital Anomaly/Birth Defect • Permanent Disability/Incapacity - except disability/incapacity caused by AIDS-Associated Diagnoses* | <p>Submit SAE Form within <u>3 Working Days</u> of unit/site awareness</p> |

KEY: = Serious Adverse Experiences which must be reported on a Division of AIDS SAE Form

* = See Pages 8-9 for AIDS-Associated Diagnoses

EXAMPLES OF REPORTABLE & NON-REPORTABLE SAEs

EXAMPLES OF DEATHS:

- Reportable:** A patient who dies of PCP during study assessed as not related to study treatment.
- Non-Reportable:** A patient who dies of PCP 3 months after study treatment was discontinued.
- Non-Reportable:** A patient who dies of head injuries from a motor vehicle accident 3 months after the last dose of study treatment.

EXAMPLES OF CANCERS:

- Reportable:** A 54 year old male with a prior history of Basal Cell Carcinoma 5 years ago before starting on study treatment. Current history of non-healing lesion for two months. Biopsy done and diagnosed with Basal Cell Carcinoma while on study treatment.
- Non-Reportable:** A 10 year old child diagnosed with Kaposi's Sarcoma (KS) 2 weeks after the last dose of study treatment.

EXAMPLES OF CONGENITAL ANOMALIES:

- Reportable:** A mother completes study treatment in her first trimester of pregnancy. She delivers a baby at term with polydactyly and relationship is assessed as unable to judge.

EXAMPLES OF PERMANENT DISABILITIES:

- Reportable:** A patient on week 7 of study treatment develops hearing loss which the PMD determines to be irreversible.
- Non-Reportable:** A patient diagnosed with CMV retinitis whose disease progresses to blindness.

EXAMPLES OF AEs AT ANY TOXICITY GRADE CONSIDERED SERIOUS:

- Reportable:** An adult patient, with no cardiac history or opportunistic infections, experiences chest pain with palpitations during week 1 of study treatment. Although this was assigned a toxicity Grade 2 and no cardiac drugs were initiated, this was assessed by the site physician to be a serious event.
- Non-Reportable:** An adult patient with a history of peptic ulcer disease develops a Grade 3 GI bleed. This is considered serious for this patient by the site physician but assessed as not related to study treatment.

EXAMPLES OF GRADE 4 EVENTS:

Reportable: A patient on week 8 of study develops a Grade 4 creatinine.

Non-Reportable: A patient who develops Grade 4 diarrhea on study and is diagnosed with Cryptosporidium.

EXAMPLES OF GRADE 3 AND 4 EVENTS ON INTENSIVE PROTOCOLS:

Reportable: A patient on an Intensive study develops a Grade 3 paresthesia.

Non-Reportable: A patient last took study drug 3 months ago. Laboratory tests done at a follow-up visit revealed Grade 3 liver function tests.

EXAMPLES OF GRADE 1 - 4 EVENTS ON NEONATE/INFANT PROTOCOLS:

Reportable: An infant at week 3 of study develops a Grade 2 full body rash.

Non-Reportable: A newborn with Grade 2 hyperbilirubinemia and physiologic jaundice.

PID # | | | | | | | | | | | | | | | |

Report Date | | | | | | | | | | | | | | | |
M M D D Y Y

**DIVISION OF AIDS
REGULATORY COMPLIANCE CENTER
SERIOUS ADVERSE EXPERIENCE (SAE) FORM
TREATMENT TRIALS PROGRAMS - ACTG, CPCRA & IRP**

SAE OFFICE PHONE: 1-800-537-9979

SAE OFFICE FAX: 1-800-275-7619

or

1-301-897-1709

E-MAIL: RCCSafetyOffice@tech-res.com

or

1-301-897-1710

| | | |
|---------------------|---|--|
| SAE OFFICE USE ONLY | SAE NUMBER | PROTOCOL NUMBER |
| _____ | _____ | _____ |
| Received Date Stamp | Report Received by: Initial Report [] | Mail [] FAX [] Follow-up Report [] |

I CONFIRM THAT THE DATA PROVIDED ON THIS FORM IS ACCURATE AND COMPLETE.

Physician Signature: _____

Physician Name Printed: _____

Site Report Date: | | | | | | | | | | | | | | | |
M M D D Y Y

Site Awareness Date: | | | | | | | | | | | | | | | |
M M D D Y Y

Site Name: _____

Site Number: _____

Completed by: _____
(Print Name, Title)

Phone Number: () _____

E-Mail: _____

Patient ID # : | | | | | | | | | | | | | | | |

ACTG ACTG ACTG
 CPCRA CPCRA CPCRA
 Protocol #s: _____ IRP _____ IRP _____ IRP

Days
 Months Male lb in
 Age: _____ Years Sex Female Weight: _____ kg Height: _____ cm

1. Check MAIN reason SAE is being reported:

- _____ Death
- _____ Cancer diagnosed after receiving study treatment (except AIDS-Associated Malignancies)
- _____ Congenital anomaly/Birth defect
- _____ Development of permanent disability/Incapacity
- _____ SAE meets reporting requirements, but is NOT any category above
- _____ SAE is considered serious for this patient by the site physician, but is NOT at a reportable level

PID # | | | | | | | | | | | | | | | |

Report Date | | | | | | | | | | | | | | | |
M M D D Y Y

2. Patient required hospitalization in the immediate period after SAE onset:

Yes No Already Hospitalized Unknown

3. Study Treatment Data

Complete the Table below. List ALL DAIDS protocols in which the patient is enrolled, and include information about ALL Study Drugs used in each protocol.

| Protocol Number | Study Drug Name (List 1 Study Drug Per Line) | Dose, Route, Schedule of Study Drug (s) at SAE Onset | Date Study Drug First Started (mm/dd/yy) | Date Study Drug Last Taken (mm/dd/yy) | ◆Drug Mgmt | Date of Drug Mgmt (mm/dd/yy) |
|-----------------|--|--|--|---------------------------------------|------------|------------------------------|
| | 1. | | | | | |
| | 2. | | | | | |
| | 3. | | | | | |
| | 4. | | | | | |
| | 5. | | | | | |
| | 6. | | | | | |

◆**Drug Management as a result of SAE:**
C = Drug Continued Without Change in Dose or Schedule
R = Drug Dose or Schedule Reduced
T = Drug Temporarily Held due to SAE
D = Drug Permanently Discontinued due to SAE
O = Drug Course Completed or Patient Off Drug at SAE Onset

4. Serious Adverse Experience Data

| Serious Adverse Experience (Key Word, Diagnosis, or Cause of Death) | ★Toxicity Grade of SAE | Onset Date (mm/dd/yy) | Study Week or CPCRA Study Month | ▽Relationship to Study Drugs Listed in Item 3 | | | | | |
|---|------------------------|-----------------------|---------------------------------|---|--------|--------|--------|--------|--------|
| | | | | Drug 1 | Drug 2 | Drug 3 | Drug 4 | Drug 5 | Drug 6 |
| 1. | | | | | | | | | |
| 2. | | | | | | | | | |
| 3. | | | | | | | | | |

★**Toxicity Grading Scale**
 1 - Mild
 2 - Moderate
 3 - Severe
 4 - Life-Threatening
 5 - Death

▽**Relationship**
 1 - Definitely Related
 2 - Possibly Related
 3 - Not Related
 8 - Unable to Judge Relationship

PID # | | | | | | | | | | | | | | | |

Report Date | | | | | | | | | | | | | | | |
M M D D Y Y

5. Laboratory Tests

List Abnormal Lab Results in the Table below OR attach copies of Lab Reports.

Abnormal Laboratory Results

| Test | Collection Date | Abnormal Result | Site Normal Range | Lab Value Previous to this SAE | Collection Date |
|------|-----------------|-----------------|-------------------|--------------------------------|-----------------|
| 1. | | | | | |
| 2. | | | | | |
| 3. | | | | | |
| 4. | | | | | |
| 5. | | | | | |
| 6. | | | | | |

6. Diagnostic Tests (Example: MRI, CT Scan, Ultrasound)

List Abnormal Diagnostic Tests in the Table below OR attach copies of the Diagnostic Tests.

| Test | Date Performed | Results/Comments |
|------|----------------|------------------|
| 1. | | |
| 2. | | |
| 3. | | |

Additional Diagnostic Tests planned: _____

7. Concomitant Medications

List concomitant medications being taken at SAE onset OR attach a copy of the current medication profile. DO NOT list medications used to treat the SAE.

| Drug Name | Approximate Duration of Use |
|-----------|-----------------------------|
| 1. | |
| 2. | |
| 3. | |
| 4. | |
| 5. | |
| 6. | |
| 7. | |
| 8. | |

Instructions for Completing the ACTG, CPCRA & IRP Serious Adverse Experience (SAE) Form

HEADER INFORMATION:

Shaded Box: Do Not Write in this Box. This is for SAE Office use only.

Physician Signature: Signature of an Investigator or Subinvestigator Physician listed on the FDA Form 1572, who has reviewed and verified the data on the SAE Form for accuracy and completeness.

Site Report Date: The date the SAE form was completed by the Site.

Site Awareness Date: The date the Site first became aware OR was first notified of the SAE.

Site Name: Print the name of the clinical site.

Site Number: Enter the Site Number that was assigned to your clinical site.

Completed by: Name and Title of the person filling out the SAE Form.

Phone #: Enter the telephone number where the person who filled out the form can be reached for questions concerning the SAE.

Patient ID #: Starting with the first box, use as many boxes as needed. Do not use dashes.

Protocol #s: Write the protocol number(s) on the lines provided and check the box which indicates the appropriate Division of AIDS treatment trials program. List ALL DAIDS protocols for which this SAE is reportable to the SAE Office. This may include protocols in which the patient is currently enrolled or was previously enrolled, depending on the time period of SAE occurrence on study and the relationship of SAE to study treatment.

Age: Write the patient's age on the line provided and check the appropriate box.

Sex, Weight, Height: Fill out each category completely.

ITEM 1: Check the **ONE MAIN REASON** this SAE is being reported.

ITEM 2: Check the box that applies.

ITEM 3: Complete the Study Treatment Data Table.

Protocol Number: Repeat the DAIDS protocol number(s) listed in the Header Section on Page 1.

Study Drug Name: Study Drugs being used in each protocol, even if the patient was not taking a Study Drug at the time of the SAE. List one Study Drug per line.

Dose, Route, Schedule of Study Drug at SAE Onset: Next to each Study Drug listed, enter the dose, route and schedule that was administered at the time of the SAE.

Date Study Drug First Started: Enter the Initial Date that the patient began taking that Study Drug. For cyclic drugs, enter the Initial Date that the patient received the first dose of study drug for the protocol.

Date Study Drug Last Taken: Enter the Last Date that the patient took that Study Drug. If the patient is being Continued on Study Drug in response to the SAE, this date field should be left blank.

Drug Management at SAE Onset: Using the Key provided below the Table, enter the Drug Management code that represents how the Study Drug was managed as a result of the SAE.

Date of Drug Management: Enter the Date when the Study Drug Management became effective. This field should be left blank when "O" is entered as the Drug Management code.

ITEM 4: Complete the Serious Adverse Experience Data Table. The Table allows for the reporting of up to 3 Serious Adverse Experiences, if needed. List one reportable SAE per line.

Serious Adverse Experience: List the SAE using a Key Word, Diagnosis, or Cause of Death.

Toxicity Grade: Using the Toxicity Grading Scale provided below the Table as a guide, enter a Toxicity Grade to indicate the severity of the SAE. (Toxicity Grade assignment should be made using the DAIDS Toxicity Table.)

Onset Date: For each reportable SAE, enter the date when the SAE first occurred at this Toxicity Grade level. (For SAEs which are Lab Abnormalities, use the specimen collection date).

Study Week or Study Month: For ACTG and IRP protocols, enter the Study Week that the SAE occurred. For CPCRA protocols, enter the Study Month that the SAE occurred.

Relationship to Study Drugs: Using the Relationship Key below the Table, enter the numeric code that reflects

the Site Investigator Physician's assessment of relationship between the SAE and the protocol Study Drugs. The Study Drug numbers 1 - 6 in this Table should directly correspond to Study Drugs 1 - 6 entered in Item 3.

ITEM 5:

If the SAE being reported is a **Lab Abnormality**, complete the Table provided OR attach copies of Laboratory Reports. If attaching copies of Laboratory Reports, remember to remove patient identifiers from source documents and attach a PID label or write the PID on the lab reports.

ITEM 6:

Complete the Diagnostic Tests Table OR attach copies of Diagnostic Tests Results, if applicable. If attaching copies of Test Results, remember to remove patient identifiers from source documents and attach a PID label or write the PID on the copy. List any additional Diagnostic Tests that are planned.

ITEM 7: Complete the Concomitant Medications Table. List Concomitant Medications being taken at SAE onset and the approximate number of days, weeks, or years that the patient was taking each drug. Concomitant Medications are defined as drugs other than the ACTG, CPCRA or IRP Study Treatment(s) listed on page 2. If attaching a copy of the medication profile, remember to remove patient identifiers and attach a PID label or write the PID on the copy.

ITEM 8: In this narrative section, provide a brief summary of the Serious Adverse Experience. Include all relevant information and details surrounding the event. If attaching copies of source documentation (i.e. Progress Notes, Discharge Summary, ER Notes), remember to remove patient identifiers and attach a PID label or write the PID on the copy.