6. SERIOUS ADVERSE EVENT REPORTING

6.1 Background

The purpose of this section is to inform site personnel regarding DCP requirements for identifying, documenting, and reporting SAEs for Phase I and II studies. In addition, this section provides orientation to the roles and responsibilities of the site staff, DCP personnel, and DCP contractors.

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. NOTE: For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting [Source: CDIS Glossary 12/06].

An AE becomes a SAE when it results in any one of the following outcomes:

- Death;
- Life-threatening event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- A congenital anomaly/birth defect; or
- An important medical event that may not result in death, be life threatening, or require hospitalization, though, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the previously identified outcomes.

The study protocol should state the version of the adverse event grading used. NCI Common Toxicity Criteria (CTC) Version 2.0 and Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 can be found at http://ctep.info.nih.gov/reporting/ctc.html.

The DCP Regulatory Contractor provides technical and regulatory support to the Division. The Regulatory Contractor assists DCP in assessing, tracking, and reporting SAEs.

6.2 Site Staff's Responsibility in Reporting SAEs to DCP

In the interest of participant safety in DCP studies, and to fulfill regulatory requirements, **all** SAEs, *whether related to the study agent or not*, will be reported to the sponsor (NCI/DCP) as follows:

- Contact the DCP Medical Monitor (as indicated in the protocol) by telephone or fax or as directed, within 24 hours of learning of the SAE. When calling or faxing, please include date, time, your name, phone number, affiliation, reason for calling/faxing, NCI contract number, and protocol number.

- Submit a written SAE report within 48 hours of learning of the event.

  - The written information shall be documented on the "NCI, Division of Cancer Prevention (DCP) Serious Adverse Event Form."

  - The SAE Form is available in Appendix E and at the DCP website: http://prevention.cancer.gov/files/clinical-trials/SAE_formAugust_9_2006.doc

  - Send the completed form to the DCP Medical Monitor as indicated in the protocol document.

  - Simultaneously submit the form to the DCP Regulatory Contractor:

    Safety Department
    CCS Associates, Inc.
    2005 Landing Drive
    Mountain View, CA 94043

    Telephone: 650-691-4400 (ask for the Safety Department)
    Fax: 650-691-4410

    Note: Do not delay sending the form. If all pertinent information is not available within the 48-hour window, send the form providing available information as soon as possible and update the form with the DCP Medical Monitor and the DCP Regulatory Contractor as additional information becomes available.

- All SAEs must be entered on the AE CRF.

- All SAEs are to be listed in the "Cumulative Adverse Event" section of the "Investigator Technical Progress Report"(ITPR), if applicable for your study; http://prevention.cancer.gov/files/clinical-trials/itpr-guidelines.pdf

- The PI must report all SAEs to the local IRB according to institutional guidelines.

6.3 DCP Processing and Reporting Responsibility to FDA

In its role as IND sponsor, NCI/DCP is required to review and analyze all SAE reports for impact on participant safety in the study. The DCP Medical Monitor immediately reviews all SAEs to determine attribution, expectedness, etc. The FDA requires the IND sponsor to submit the IND safety report to the FDA for an expedited SAE as soon as possible, but no later than 15 days after the event is reported. If the event is unexpected and fatal or life-threatening and associated with the use of the study agent, then the FDA must be notified as soon as possible but not later than 7 calendar days after the initial receipt of the information. An alert letter will be circulated to all investigators participating in trials using the study agent. The DCP Regulatory Contractor assists the Medical Monitor by ensuring that all required information is obtained from the site and performs as a liaison with the FDA. See Figure 6-1 for the SAE reporting process.

6.4 SAEs and Site Monitoring

- During a site visit, the CRA will ensure that site staff have:
  - Verifiable source documentation to support the SAE;
  - Appropriately filed the SAE documentation with DCP and the DCP Regulatory Contractor;
  - Recorded the SAE on the appropriate CRF; and
  - Notified the local IRB (if applicable).
- If the CRA identifies any unreported SAEs during a monitoring visit, the site staff will report and document the information in accordance with these guidelines (in the Study Site Monitoring Manual (SSMM) and with guidance from the CRA.

Figure 6-1. SAE Reporting Process