9. SITE MONITORING BY WESTAT/DCP MONITORING CONTRACTOR

NIH guidelines specify that all clinical trials should have a system in place for appropriate oversight and monitoring to ensure the safety of participants and the validity of the data. DCP places participant safety as the highest priority and the quality of the study is only as good as the quality of the data. Westat conducts a site initiation visit and annual/interim visit at the Lead Organization until patient followup is complete, and a close-out visit is made by Westat. The Lead Organization is responsible for the oversight and monitoring of the Participating Organizations.

9.1 Three Types of Site Visits

Westat Clinical Research Associates (CRAs) conduct three types of site visits to the Lead Organization: initiation, annual/interim, and close-out visits. Each of these will be discussed separately below. DCP representatives may choose to participate in each of these visits.

9.1.1 Initiation Visit

Purpose

The purpose of the initiation visit is to:

- Meet with key staff (Principal Investigator, study coordinator, pharmacist, lab technician, etc.) at the Lead Organization. If Participating Organizations are involved, it is expected that key staff from each of the Participating Organizations are present at the Lead Organization for the visit.
- Orient staff to all general aspects of the performance of the work.
- Discuss the roles and responsibilities of DCP, clinical site staff, and Westat Team staff.

Scheduling

The initiation visit is usually accomplished in one day and occurs when the site is ready to begin the study. Westat will coordinate timing of the visit with DCP and the Principal Investigator or study coordinator. Westat sends a confirmation letter and an agenda in advance of the initiation visit. DCP approves both the letter and the agenda.

Conduct of Visit

Topics discussed at an initiation visit include, but are not limited to, the following:

- Role of DCP staff;
- Role of the Lead Organization;
- Role of the Participating Organizations;
- Background and purpose of study;
- Study procedures;
- Participant enrollment;
- Participant recruitment and retention strategies;
- Adverse event reporting;
- Toxicity management;
- Study agent discontinuation;
- Data collection and data management;
- Source documentation/confidentiality;
- Policy and procedures manuals;
- Regulatory documentation and CCS Associate's role;
- Recordkeeping requirements;
- Laboratory procedures;

- Unblinding procedures;
- Pharmacy;
- Quality Assurance (QA) procedures;
- Communication;
- Handling protocol deviations;
- Site monitoring of Lead Organization; and
- Site monitoring of Participating Organization.

An initiation visit may include a tour of the physical facility.

Followup

At the conclusion of the visit, issues that require followup will be discussed. The CRA will complete the Initiation Visit report, which is reviewed by DCP. A copy of the report format is in Appendix F. Site personnel will receive a copy of this report 4-6 weeks after the visit.

9.1.2 Annual/Interim Visit

Purpose

An annual/interim visit at the Lead Organization can be scheduled at any time if the protocol is rapidly accruing or if deficiencies are discovered. The purpose of the annual/interim site visit is to determine that:

- Facilities used by the investigator are acceptable for study purposes;
- There is compliance with the study protocol or investigational plan;
- Changes to the protocol and/or consent document have been approved by the IRB and NCI;
- Changes to the consent document have been explained to participants and a revised consent document has been signed by participants;

- Source documentation is adequate and Case Report Forms are completed appropriately;
- Protocol deviations are recorded and reported according to DCP procedures;
- Participants have signed an informed consent document prior to the conduct of study visits and/or study procedures;
- There is accurate reporting of significant events such as adverse events (AEs) and serious adverse events (SAEs);
- Accurate, complete, and timely reports are being made to DCP and the IRB; and
- The investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.

Scheduling

An annual/interim monitoring visit is accomplished in 2 or 3 days at the Lead Organization. Westat will discuss plans to conduct the visit with DCP and the Principal Investigator or study coordinator at least 6 weeks in advance of the visit. If the Lead Organization has elected to have its Participating Organizations' charts reviewed at the annual visit, Westat will identify the charts that will be needed for review from those sites. Westat will send a letter confirming the visit to the Principal Investigator and study coordinator stating the purpose and objectives of the visit, the staff and documents to be made available, and the expected duration of the visit. At least 2 weeks prior to the visit, the CRA will notify the study coordinator of charts to be reviewed. At least two additional charts (not previously requested) from the Lead Organization will be reviewed at each annual/interim visit.

Requirements

The following must be available for the CRA upon arrival for a site visit:

- Site monitoring sign-in log;
- PID logbook;
- Case Report Forms notebooks;
- Binders containing copies of signed informed consents for all study participants;

- Source documentation, including clinic charts, shadow files, and hospital charts if relevant;
- Regulatory documents;
- Appointment to meet with the site pharmacist, if a pharmacy audit is being performed; and
- A quiet well-lit area for the CRA's use each day during the site visit.

In addition, the study coordinator or designated staff should be available each day to review findings and provide additional records that may be requested by the CRA. Time should be set aside at the conclusion of the visit for the study coordinator and Principal Investigator to meet with the CRA to discuss the findings, site performance parameters, and any outstanding issues.

Conduct of Visit

The CRA will review the following documents during the annual/interim visit at the Lead Organization:

- Confirm the following regulatory documents are on file:
  - NCI/IRB approval letters;
  - NCI/IRB letters of annual approval;
  - NCI/IRB-approved consents;
  - Form FDA 1572s;
  - Laboratory certificates;
  - Laboratory normal values;
  - Screening logs;
  - Safety reports and memos with appropriate IRB correspondence; and
  - Other IRB correspondence.
  - Human subjects protection training
- Ensure sensitive documents are stored appropriately

- Perform CRF and record review. The following data will be verified against source documents:
  - Signed and dated informed consent document, obtained prior to the pre-entry workup;
  - Inclusion/exclusion criteria;
  - Visit dates;
  - Clinical and laboratory evaluations;
  - Concomitant medications;
  - Adverse events;
  - Concurrent illness; and
  - Adherence to protocol.

The number of records that will be reviewed is dependent upon the number of participants enrolled in the study. Records will be selected from the Lead Organization and Participating Organizations when applicable.

The CRA will verify eligibility and perform chart reviews for a minimum of 7 charts or 25 percent (whichever is greater) of participant records per study at the Lead Organization. Informed consent documents will be reviewed for 100 percent of enrolled participants at the Lead Organization. The Westat CRA will also:

- Conduct pharmacy audit:
  - Review of pharmacy-related regulatory documentation;
  - Examine procedures for:
    1. Investigational agent storage
    2. Investigational agent distribution
    3. Investigational agent security
  - Compare shelf inventory (bottle count) versus the Drug Accountability Record Form (DARF);

- Audit participant records to compare investigational agent dispensed as recorded on the DARF versus that recorded as administered in the source document;

- Compare the DARF with the protocol registration listing to ensure that participants who received investigational agents were registered on the specified protocol;

- Verify accuracy of investigational agent preparation and calculation of dosage; and

- Authenticate that any unopened/unused or expired investigational agent containers are returned to DCP.

■ Assess site operations:

- Verify adequate resources (e.g., facilities, staffing database);

- Review internal QA activities;

- Review accrual of participants available/recruited for the study;

- Followup on problems previously identified;

■ Conduct a summary meeting with the Principal Investigator, pharmacist, and study staff to review the findings of the site visit. During this meeting the findings identified during the course of the site monitoring visit will be discussed, and recommendations for improvement will be made; and

■ Review the oversight of Participating Organizations by the Lead Organization.

Followup

At the conclusion of the visit, issues that require followup will be discussed. The CRA will complete the Annual Visit report, which is reviewed by DCP. A copy of the report format is in Appendix G. Site personnel will receive a copy of this report 4-6 weeks after the visit, once the report has been finalized and approved by DCP.

9.1.3 Close-out Visit

Purpose

A Westat CRA will typically conduct a close-out visit at the Lead Organization within 60 days of study termination. This is often done after the "draft final report" has been submitted to DCP, but before the final version of the report is submitted. The duration of the close-out visit is usually 1-2 days. The purpose of this visit is to:

- Formally bring closure to the study at the site;
- Ensure all data have been collected;
- Complete the final accounting and disposition of the study agent; and
- Verify that the investigator's files are complete.

The close-out visit for a particular protocol may be combined with elements of an annual site visit in specific situations. In these situations, the combined annual/close-out visit usually lasts 2-3 days.

Scheduling

A close-out visit will generally take one day, but may require more. Westat will discuss plans to conduct the visit with DCP and the Principal Investigator or study coordinator at least 6 weeks in advance of the visit. Westat will send a letter confirming the visit to the Principal Investigator and study coordinator stating the purpose and objectives of the visit, the staff and documents to be available at the Lead Organization, and the expected duration of the visit.

Requirements

The requirements for a close-out visit are the same as for an annual/interim visit (see page 9-4).

Conduct of Visit

During the close-out visit, the Westat CRA will perform the following:

- Ensure that all Case Report Forms for each participant has been completed;
  - Verify that all data have been keyed on-site or all forms have been submitted to the Lead Organization or the protocol-specified destination;
  - Ask to see the Quality Assurance (QA) Plan for keyed data;
  - If the data forms have not been completed, keyed, or submitted, the CRA will discuss with the investigator and study coordinator a timeline for accomplishing these tasks.
- Verify that a signed informed consent document is on file for each study participant;
- Review the status of all outstanding data edits, queries, or delinquent forms and timeline for their resolution;
- Confirm that the IRB/IEC has been informed of the study closure;
- Verify that all regulatory and other pertinent documents for the protocol (IRB approvals, consent documents, etc.) are up-to-date and on file;
- Verify that the investigator knows to submit a final report to DCP, and that a deadline for completion has been identified;
- Ensure that a progress note is included in each participant's medical record indicating that study participation has ended;
- Ensure that the Principal Investigator understands the requirements for reporting of adverse events for participants who have completed the study;
- Ensure that the Principal Investigator understands the requirements for retention of study records. (The investigator may refer to the award document which specifies the time for record retention);
- If applicable, determine the disposition of participant specimens obtained during the study and stored on-site. Ensure all specimens have been sent to the appropriate place/facility or that the Principal Investigator understands the plan for future shipment; and
- Meet with the site pharmacist to determine the disposition of remaining study agent and ensure that it has been returned to the repository. Ensure all required study agent accountability has been reconciled and forms have been completed appropriately. If a blinded study agent was used, confirm that the tear-off labels were not opened. For

any that were opened, documentation should be obtained noting the reason for unblinding.

Followup

At the conclusion of the visit, issues that require followup will be discussed. The CRA will complete the Close-Out visit report, which is reviewed by DCP. A copy of the report format is in Appendix H. Site personnel will receive a copy of this report 4-6 weeks after the visit, once the report has been finalized as approved by DCP.