9. SITE MONITORING BY THE DCP MONITORING CONTRACTOR

NIH guidelines specify that all clinical trials have a process in place for appropriate oversight and monitoring to ensure the safety of participants and the validity of the data. The CRAs conduct a site initiation visit, annual and interim visits at the MAH lead organization until participant follow-up is complete, and they conduct a close-out visit at the lead organization at the completion of the trial. For other funding mechanisms within DCP, the Monitoring Contractor also conducts quality audit visits. The lead organization is responsible for the oversight and monitoring of the participating organizations.

9.1 Types of Site Visits

The CRAs conduct four types of site visits at the MAH lead organizations: initiation, annual and interim, and close-out visits. Each visit type is discussed below. DCP representatives may choose to participate in each of these visits.

9.1.1 Initiation Visit

Purpose

The purposes of the initiation visit are to:

- Meet with key staff (PI, Study Coordinator, pharmacist, lab technician, etc.) at the lead organization. If participating organizations are involved, key staff from each organization may attend the visit at the lead organization;
- Review and discuss aspects of the protocol and study procedures as outlined;
- Answer questions by research study staff as they relate to trial operations;
- Identify key site staff and discuss specific study responsibilities;
- Discuss and identify outstanding issues that require resolution before study participants are enrolled;
- Tour facilities to determine that they are adequate for study purposes;

- Orient staff to all general aspects of the conduct of the clinical trial to ensure successful performance;
- Discuss the roles and responsibilities of DCP, clinical site staff, and the DCP Monitoring Contractor; and
- Ensure that all regulatory requirements are in order.

Scheduling

The initiation visit is usually accomplished in one day on site and occurs when the site is ready to begin the study. Criteria for site initiation visit readiness include DCP and local IRB approval of the protocol, IND readiness (as appropriate), availability of the investigational agent to be shipped upon request after final study approval by DCP and the availability of qualified site staff. The DCP Monitoring Contractor coordinates the timing of the visit with DCP and the PI or Study Coordinator. The DCP Monitoring Contractor sends a confirmation email and an agenda in advance of the initiation visit. The DCP Medical Monitor or Scientific Monitor approves the agenda before it is sent to the site.

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 (if applicable);
- Background and purpose of study;
- Study procedures;
- Protocol activation and participant enrollment;
- Participant recruitment and retention strategies;
- AE and SAE reporting and management;
- Study agent discontinuation and dosing modifications (if applicable);
- Study endpoints;
- Data collection and data management;

- Source documentation/confidentiality;
- Policy and procedures manuals and other resources;
- Maintenance of regulatory documents and role of the Regulatory Contractor;
- Recordkeeping requirements, including secure storage;
- Laboratory procedures;
- Collection and handling of specimens;
- Unblinding procedures (if applicable);
- Pharmacy procedures;
- Quality Assurance (QA) procedures;
- Communication with DCP, the DCP Regulatory Contractor, and the DCP Monitoring Contractor;
- Recording and reporting protocol deviations;
- Protocol amendment submission to the DCP PIO;
- Frequency of site monitoring of lead organization; and
- Site monitoring responsibilities of lead organization for any participating organization(s).

The end of an initiation visit typically includes a tour of the physical facility, which includes the laboratories, pharmacy, and clinical examination rooms to be utilized for the trial. The tour may also include the office of the Study Coordinator or Research Nurse to view the secure area where the research records will be kept.

Follow-up

At the conclusion of the visit, issues that require follow-up will be discussed. The CRA will complete the Initiation Visit Report including a list of the action items identified during the visit. The action item list will be reviewed by the DCP Medical or Scientific Monitor and Nurse Specialist. A copy of the report template is in Appendix F.

Site personnel will receive a copy of this DCP-approved site visit report approximately 4 weeks (calendar days) after the visit. If the report includes action items for the site, the PI and/or Study

Coordinator must submit a follow-up letter outlining the institution's plan to resolve any action items including the action to be taken, the person responsible for the action, and the timeframe for completion. The follow-up letter, which may be transmitted by email, is sent to the CRA and copied to the DCP Medical Monitor and/or Nurse Specialist within 30 calendar days of receipt of the site visit report. The CRA tracks site responses to action item follow-up.

9.1.2 Annual and Interim Visits

Purpose

Monitoring visits are conducted annually at the lead organization until participant follow-up is complete. In addition, an interim visit at the lead organization can be scheduled at any time if the protocol is accruing rapidly or if deficiencies are suspected. The purpose of the annual site visit is to determine that:

- There is compliance with applicable regulations, guidelines, and the study protocol or investigational plan;
- Changes to the protocol and/or consent document have been approved by DCP and the IRB;
- Changes to the consent document have been explained to participants and, where applicable, participants who are still on study have been re-consented on the revised document;
- Source documentation is adequate and CRFs are completed appropriately;
- CRF data have been entered into the database of record;
- Protocol deviations are recorded and reported according to DCP procedures;
- Participants have signed the most recently approved informed consent document prior to the conduct of study visits and/or study procedures;
- There is accurate reporting of significant events such as AEs and 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.

An interim visit is scheduled within 6-8 months after an annual visit if specific deficiencies are identified or at the request of DCP. The areas of concentration for the interim visit will depend on

deficiencies identified in the review of participant charts, regulatory documents, and pharmacy audit findings.

Scheduling

Each annual or interim monitoring visit is generally accomplished in 2.5 days at the lead organization. The CRA will discuss plans to conduct the visit with DCP and the PI or Study Coordinator at least 6 weeks in advance of the visit. The CRA will send a visit confirmation letter to the PI 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 and the DCP principals of charts to be reviewed. Additional charts (not previously requested) from the lead organization may be reviewed at each annual/interim visit.

Requirements

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

- Site monitoring visit log;
- Participant identification logbook (if applicable);
- CRF notebooks or folders;
- 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, when 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. The PI, Study Coordinator, and other key study staff should set aside time at the conclusion of the visit to meet with the CRA and a DCP representative to discuss the findings, site performance metrics, and any outstanding issues.

Conduct of Visit

The CRA will perform the following tasks during the annual/interim visit at the lead organization:

- Confirm that the following regulatory documents are on file:
  - DCP/IRB-approved protocol and any amendments, informed consent forms, and CRFs;
  - DCP/IRB approval letters for the protocol and any amendments, informed consent forms, and CRFs;
  - IRB-approved educational and advertising materials;
  - IRB letters of annual approval;
  - Current Federal Wide Assurance (FWA) documentation;
  - Form FDA 1572, with signed and dated curriculum vitae (CVs) and copies of appropriate professional licenses for investigators listed;
  - Human subjects protection training for investigators listed on the Form FDA 1572 and any other relevant staff;
  - Financial disclosure forms for investigators listed on the Form FDA 1572;
  - Laboratory certifications;
  - Laboratory normal values;
  - Screening logs;
  - Investigator Brochure (all versions);
  - Safety reports and memos with appropriate IRB correspondence;
  - Other IRB correspondence;
  - Relevant DCP correspondence;
  - Site signature/delegation log;
  - Site monitoring log (to be updated during the visit);
  - Previous site monitoring visit reports and the confirmation letter for the current visit;
  - Participant Identifier (PID)/screening log;

- Notes to file regarding study procedures; and
- Protocol deviation submissions and DCP responses.

- Ensure that confidential documents are stored appropriately.
- Perform CRF and record review. The following data will be verified against source documents to determine adherence to the protocol:
  - Signed and dated informed consent document, obtained prior to the pre-entry workup and in accordance with Federal regulations;
  - Inclusion/exclusion criteria;
  - Visit dates;
  - Clinical and laboratory evaluations;
  - Concomitant medications;
  - Adverse Events and Serious Adverse Events; and
  - Concurrent illness.

The number of records that will be reviewed is dependent upon the number of participants enrolled in the study. For studies funded under the MAH mechanism, records for review will be selected from the lead organization only.

The CRA will verify eligibility and perform chart reviews on all charts with an SAE (as time allows). In addition, the CRA will verify eligibility and perform chart reviews for a minimum of seven 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 CRA will also:

- Review a sample of completed CRFs against entries in the database of record;
- Conduct a pharmacy audit:
  - Review of pharmacy-related regulatory documentation;
  - Examine procedures for:
    1. Investigational agent storage;
    2. Investigational agent distribution; and
    3. Investigational agent security.

- Compare shelf inventory (bottle count) against the balance as stated on the NCI 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; and

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

■ Assess site operations:

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

- Review internal QA activities;

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

- Inquire about and note if a database is used for study-specific procedures; and

- Follow up on problems previously identified.

- Assess security of agent, agent dispensing and blinding procedures

The CRA will conduct a summary meeting with the PI and study staff to review the findings of the site visit. The DCP Medical Monitor, Scientific Monitor, and/or Nurse Specialist often attend this summary meeting, either in person or via teleconference. 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

■ The oversight of participating organizations by the lead organization will be reviewed based on the processes implemented at the site.

The CRA must immediately notify the DCP Medical/Scientific Monitor and Nurse Specialist of any findings suggestive of intentional misrepresentation of data and or disregard for regulatory safeguards for any of the components of the monitoring visit. This initial notification will be done by phone to permit clarification of the issues. Documentation of intentional misrepresentation of data and or the disregard of regulatory safeguards by site staff should be included in the site visit report.

Follow-up

At the conclusion of the visit, issues that require follow-up will be discussed. Within 1 business day of completion of the annual or interim visit, the CRA will send a preliminary report to DCP that lists an overall rating for items reviewed based on the presence or absence of deficiencies found. A copy of the report format is in Appendix G. The CRA will then complete the full Annual Visit Report including a list of the action items identified during the visit, and the Pharmacy Audit Report, which are reviewed by DCP. A copy of the Annual Visit Report format may be found in Appendix G; a copy of the Pharmacy Audit Report is in Appendix I. Site personnel will receive a copy of the reports approximately 4 weeks (calendar days) after the visit, once they have been finalized and approved by DCP. The PI and/or Study Coordinator must submit a follow-up letter outlining the institution's plan to resolve any action items including the action to be taken, the person responsible for the action, and the timeframe for completion. The follow-up letter is sent to the CRA and copied to the DCP Medical Monitor and/or Nurse Specialist within 30 calendar days of receipt of the site visit report. The follow-up letter should be sent via email.

9.1.3 Close-out Visit

Purpose

The CRA will typically conduct a close-out visit at the lead organization after the draft final report of the study has been submitted to DCP, but before the final version of the report is submitted. The duration of the visit is usually 1 day on-site. The purpose of this visit is to:

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

If a close-out visit for a particular protocol and an annual site visit are scheduled around the same timeframe, the two visits may be combined. To prepare for these visits, the site staff will be informed of the criteria used for evaluation. The combined annual/close-out visit would usually last 2-3 days.

Scheduling

A close-out visit will generally take 1 day on-site, but may require more. The CRA will discuss plans to conduct the visit with DCP and the PI or Study Coordinator at least 6 weeks in advance of the visit. The CRA will send a letter confirming the visit to the PI 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 regarding preparation for the CRA for a close-out visit are the same as for an annual/interim visit (see Section 9.1.2).

Conduct of Visit

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

- Ensure that all CRFs for each participant have been completed:
  - Verify that all data have been keyed into a database or all forms have been submitted to the lead organization or the protocol-specified destination;
  - If data from the forms have not been completed, entered into the database, or submitted, the CRA will discuss a timeline for accomplishing these tasks with the PI and Study Coordinator;
- 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 current and on file;
- Verify that the PI is aware of the process and timeline for submitting a final report to DCP;

- Ensure that a progress note is included in each participant's study record indicating that study participation has ended;

- Ensure that the PI understands the requirements for including AEs in the final report for participants who have been accrued to the study;

- Ensure that the PI 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 that all specimens have been sent to the appropriate place/facility or that the PI understands the plan for future shipment including handling of the specimens; 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 that 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.

Follow-up

At the conclusion of the visit, issues that require follow-up will be discussed. The CRA will complete the Close-out Visit Report including a list of the action items identified during the visit. The close-out visit report and list of action items will be reviewed by the DCP Medical Monitor, Scientific Monitor or Nurse Specialist. A copy of the report format is in Appendix H. Once the report has been finalized and approved by DCP, site personnel will receive a copy of this report approximately 4 weeks (calendar days) after the visit has occurred. The PI and/or Study Coordinator must submit a follow-up letter outlining the institution's plan to resolve any action items including the action to be taken, the person responsible for the action, and the timeframe for completion. The follow-up letter is sent to the CRA and copied to the DCP Medical Monitor and/or Nurse Specialist within 30 calendar days of receipt of the site visit report. The follow-up letter should be sent via email.