Division of Cancer Prevention (DCP)

Study Site Monitoring Manual

Master Agreement Holder (MAH) Phase I and II Studies

June 2008

Study Site Monitoring Manual
DIVISION OF CANCER PREVENTION (DCP)

SUMMARY OF CHANGES

DCP Version Date: June 2008

Chapter	Title	Modifications
Table of Contents	Table of Contents	▪ Added *New in 2008* note to Chapter 7 and Appendix D
7	PROTOCOL DEVIATION REPORTING	▪ The Procedure Section and DCP Protocol Deviation form were amended due to a change in DCP policy. ▪ The DCP Protocol Deviation form will now be emailed (instead of faxed) by the Site Coordinator or designated staff member to the DCP Medical Monitor.
Appendix D	PROTOCOL DEVIATION NOTIFICATION	▪ The Procedure Section and DCP Protocol Deviation form were amended due to a change in DCP policy. ▪ Signature lines were removed and fax lines were removed. ▪ The DCP Protocol Deviation form will now be emailed (instead of faxed) by the Site Coordinator or designated staff member to the DCP Medical Monitor. ▪ The Principal Investigator (PI) must review the completed DCP Protocol Deviation Notification form before the form is submitted to DCP for review. The designated staff member who completes the form should check box #20 to acknowledge that the PI has reviewed the completed form.

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1. INTRODUCTION

1.1 Purpose of Site Monitoring

Clinical trials site monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirements. The Food and Drug Administration (FDA) requires that clinical investigations involving human subjects are periodically monitored (21 CFR 312.56, Review of Ongoing Investigations). In order to fulfill this regulatory requirement, the Division of Cancer Prevention (DCP) has contracted with a Contract Research Organization to provide qualified Clinical Research Associates (CRAs) to periodically visit the Protocol Lead Organization to verify that:

- The rights and well-being of human subjects are protected;
- The study data are of the highest quality and integrity; and
- The study is in compliance with the currently approved protocol/amendments, GCP, and other regulatory requirements.

1.2 Purpose of this Manual

Staff at DCP created the *Study Site Monitoring Manual (SSMM)* (hereafter referred to as the Manual) initially for Master Agreement Holder (MAH) institutions conducting DCP-sponsored Phase I and II chemoprevention studies to provide clinical study site staff with reference information about monitoring clinical research studies. Currently, there are other DCP constituencies who will refer to this Manual as well.

The user of this Manual should have a basic understanding of the clinical research process. The Manual does not replace protocol-specific instructions or procedures. This Manual will be posted to the Clinical Trials Management section (http://prevention.cancer.gov/clinicaltrials/management) of the DCP website and will be updated regularly.

The Manual provides general information about DCP's mission and organization and the following:

- Study staff roles and responsibilities are described;
- Participant enrollment and study record maintenance are outlined;
- Serious Adverse Events (SAEs) procedures are reviewed;
- Protocol deviation procedures are reviewed;
- Participant status changes are reviewed;
- The types of monitoring visits are delineated;
- The process for conducting the visits is explained; and
- A list of staff, key to the management of clinical trials, is provided.

1.2.1 Manual Feedback

Feedback about the Manual content and organization can be directed to the DCP Help Desk at nci-dcpmonitoring@westat.com.

2. DCP ORGANIZATIONAL OVERVIEW, DESCRIPTION OF PREVENTION TRIALS, AND SUMMARY OF CONTRACTOR RESPONSIBILITIES

2.1 Overview

The National Cancer Institute (NCI) coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer, rehabilitation from cancer, and the continuing care of cancer patients and the families of cancer patients (http://www.cancer.gov/aboutnci/overview/mission). The Institute has six divisions, each specializing in a different aspect of cancer research. DCP is the primary unit of the NCI devoted to cancer prevention research. The mission of DCP is to plan, direct, implement, and monitor cancer research and training that is focused on early detection, cancer risk, chemoprevention, and supportive care. More information about the work of DCP is available at the following website: http://prevention.cancer.gov/about/mission.

2.2 Prevention Trials

Projects within DCP address the need to identify where a person is in the process of carcinogenesis, and to determine ways to actively intervene to stop it from becoming invasive cancer. Varied approaches are supported, from pre-clinical discovery and development of biomarkers and chemoprevention agents, including pharmaceuticals and micronutrients, to Phase III clinical testing. Programs are harmonized with other NCI divisions, NIH institutes, and federal and state agencies (http://prevention.cancer.gov/about/mission).

There are three types of prevention trials: screening, control, and intervention.

- **Screening Trials:** The goals of screening trials are to develop tools for detecting cancer or precancers before an individual becomes symptomatic and to see if early detection and treatment of disease improves the outcome. Screening can include:
  - Imaging tests (e.g., x-rays) that produce images of internal organs and tissues in the body;
  - Biological tests of the blood, urine, other bodily fluids, and tissues to find indicators of disease processes; and
  - Genetic tests that look for inherited genetic markers linked to certain types of cancers (e.g., BRCA1 gene mutation).

- **Control Trials:** A cancer-control trial assesses the effect of an intervention on cancer symptoms, side effects of cancer treatment, or the participant's quality of life. As with other clinical trials supported by DCP, the intervention can be pharmaceutical, nutriceutical, dietary, or behavioral.

- **Intervention trials:** These trials generally take one of two forms. Behavioral studies focus on finding out whether actions people take, such as exercise or smoking cessation, can prevent cancer. Agent studies focus on examining whether taking certain medicines, vitamins, minerals, or food supplements (or a combination of them), can prevent cancer.

- **Chemoprevention Trials:** Chemoprevention trials are a type of intervention trial. They may be Phase I, II, or III studies.

  - Phase I chemoprevention trials are the first studies in participants that evaluate how new agents should be given (i.e., by mouth, applied to the skin), how often, and what dose is safe. A Phase I trial usually enrolls only a small number of participants.

  - Phase II chemoprevention trials are conducted in larger groups of participants who are at high risk for certain cancers. While these trials continue to study the safety of the agent, they also evaluate the efficacy of the new agent usually by measuring the effect of the agent on biomarkers thus interrupting the process of carcinogenesis. Phase II studies usually focus on a particular type of cancer. Frequently these trials are conducted using a placebo-controlled group.

  - Phase III chemoprevention trials are conducted either in populations at high risk for specific cancers or in participants from the general population. These studies test new agents, a combination of agents, or a new surgical procedure in comparison to the current standard or to a placebo. A participant is usually randomly assigned to one of the groups defined in the protocol, which could include an investigational intervention, a standard intervention, or placebo. Phase III trials often enroll large numbers of participants to provide the sample size needed to address the research question and may require 5 to 10 years to complete. Phase III trials may be conducted at a variety of clinical settings nationwide such as physicians' offices, clinics, hospitals, or cancer centers.

2.3 DCP Organization

Peter Greenwald, M.D., Dr. PH is the Director of DCP. Leslie Ford, M.D., is the Acting Deputy Director and Associate Director for Clinical Research. DCP is organized into a number of specific groups and project teams. The DCP Protocol Information Office (PIO) is the coordinating office for cancer prevention studies. All protocol activity from protocol development to final report submission is

coordinated through the PIO. The PIO works closely with the Organ System Research Groups, the Chemopreventive Agent Development Research Group (CADRG), and the Community Oncology and Prevention Trials Research Group (COPTRG) to facilitate the research process for Principal Investigators conducting cancer prevention trials. A list of names, email addresses, and telephone numbers of DCP staff is available in Appendix A and also through the DCP website (http://prevention.cancer.gov/about/staff).

2.4 Prevention Protocol Management

There are three primary areas of protocol management:

- Protocol Development;
- Regulatory Affairs; and
- Study Site Monitoring.

DCP has enlisted the support of several contractors to assist with these activities. The DCP Regulatory Contractor assists with protocol development and regulatory affairs. The DCP Monitoring Contractor manages the study site monitoring, data management, and informatics activities.

The DCP Regulatory Contractor is responsible for assisting the PIO, Research Group personnel, and study site staff with protocol development and management of regulatory issues during the conduct of a study. The DCP Regulatory Contractor also provides technical assistance with drafting, revising, and managing investigational new drug (IND) packages, and DCP-sponsored New Drug Application (NDA) documents. Regulatory documents are described in Chapter 5, Study Record Maintenance.

The DCP Monitoring Contractor consists of staff with clinical trials monitoring experience, data management, education and training experience, and clinical trials database informatics experience. Through their existing contract, the DCP Monitoring Contractor will:

- Enhance the existing database, DCP Enterprise System Knowledgebase (DESK), and develop software applications to collect, analyze, and report the study data;
- Standardize site monitoring processes; and
- Provide consistent education and training to site staff about the conduct and management of clinical research trials.

A glossary of terms in Appendix B is provided to assist site staff and other readers with definitions of DCP prevention terminology.

3. DCP STUDY STAFF ROLES AND RESPONSIBILITIES

The study site research team usually includes the following members: Principal Investigator (PI), Study Coordinator or Research Nurse, and Pharmacist. Members of the research team at DCP include the Medical Monitor and/or Scientific Monitor, Organ System Research Group Nurse Specialist, PIO staff, Contracting Officer, and Contracting Specialist.

The National Institutes of Health (NIH) mandates education on human subject protection for all investigators and research team members who apply for or receive NIH funds for research involving human subjects. Each research team member must document completion of training in human subject protection and this documentation must be maintained at the site. This documentation must also be submitted to DCP prior to initiating a clinical trial. An online continuing education program is utilized by the NCI to fulfill this requirement. The educational program, Human Participant Protections Education for Research Teams, is available online at the following website: http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp. This online educational link may be used by sites that do not have a local training program.

The following sections describe the roles of various research team members and tasks that are often performed by them or delegated to them. Though select tasks are delegated to the Study Coordinator, Research Nurse, or pharmacist, the PI is ultimately responsible for the research conducted at the site.

3.1 Principal Investigator

The PI is responsible for the overall conduct of research activities at the site. The PI is expected to comply with the Code of Federal Regulations (CFR) and the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH/GCP). By signing the Form FDA 1572, the PI agrees to:

- Conduct the study(ies) in accordance with the relevant, current protocol(s) and will make changes in a protocol only after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects;
- Personally conduct or supervise the described investigation(s);

- Inform any participants, or any persons used as controls, that the agents are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met;

- Report to the sponsor any adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64;

- Read and understand the information in the investigator's brochure, including the potential risks and side effects of the agent;

- Ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments;

- Maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68;

- Ensure that the IRB complies with the requirements of 21 CFR Part 56 and will be responsible for the initial and continuing review and approval of the clinical investigation;

- Promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others;

- Make no changes in the research protocol without obtaining prior DCP and IRB approval except in extenuating circumstances to minimize immediate threats to the safety of human subjects; and

- Agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

NOTE: Refer to Section 9 of Form FDA 1572 for complete information on investigator responsibilities. The instructions for completing the form are located at this link: http://www.fda.gov/cder/forms/1571-1572-help.html. The form can be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html. See Appendix C for a sample of the form.

3.2 Study Coordinator or Research Nurse

A well-implemented protocol is often attributable to an organized, responsible Study Coordinator or Research Nurse. The PI may delegate some or all of the following tasks to the Study Coordinator or Research Nurse. Under the PI's guidance, this person may:

- Submit protocol and amendments, informed consent, protocol submission worksheet, Data Safety Monitoring Plan, and Case Report Forms (CRFs) to the DCP PIO for review;
- Prepare regulatory documentation;
- Ensure the study is conducted in compliance with protocol requirements;
- Maintain IRB correspondence and regulatory documentation;
- Recruit potentially eligible participants for clinical trials enrollment;
- Meet with study participants to review the details of study enrollment;
- Evaluate study participants for protocol eligibility;
- Ensure that informed consent has been obtained from the participants before initiating research-related activities;
- Instruct and educate participants regarding study interventions and anticipated side effects and their management;
- Develop strategies to retain study participants in a clinical trial;
- Schedule tests and appointments for participants within timeframes required by the protocol;
- Identify abnormal laboratory results and obtain repeat evaluations as required by the protocol;
- Send the investigator-signed prescriptions for study agent to the pharmacist;
- Provide guidance to the PI, pharmacist, and participant on dose adjustments based on protocol dose modification section;
- Inform the pharmacist about any dose changes (as prescribed by the study investigator(s));
- Collect returned study agent;
- Monitor participant dosing compliance;

- Maintain source documentation for each study participant in accordance with the protocol;
- Complete CRFs accurately and retain a copy in the CRF notebook or folder;
- Perform quality assurance on aspects of data collection that were completed by other study staff;
- Identify and document Adverse Events (AEs) and SAEs;
- Initiate SAEs and obtain the PI's signature within the proper timeframes, notify appropriate individuals stated in the protocol, and submit reports according to DCP procedures;
- Identify, document, and submit protocol deviations in accordance with DCP procedures;
- Enter study data from paper CRFs to electronic systems (if available);
- Respond to data queries in a timely manner;
- Monitor study progress at participating organizations (as designated by NCI/DCP);
- Conduct monitoring visits at participating sites;
- Prepare for site monitoring visits by sponsor-designated clinical research associates or auditors;
- Contact the appropriate DCP Organ System Nurse Specialist with questions regarding study implementation; and
- Update the PI on study status.

3.3 Pharmacist

The pharmacist or designated qualified staff member is accountable for:

- Study agent supply, receipt, storage, preparation, dispensation, and disposal or return;
- Accountability of records and record security, including retention of:
  - Instructions for ordering study agent;
  - Shipping receipts and return records;
  - NCI Drug Accountability Record Forms (DARFs); and
  - Transfer forms;

- Agent administration record;
- Maintenance of blinded study integrity; and
- Instruction to the care provider on the proper method of agent administration.

  NOTE: All study agents and records in the investigational pharmacy must be accessible only to specified pharmacy staff.

3.4 DCP Medical Monitor

The Medical Monitor is a physician or other licensed clinician who is a member of the DCP staff who belongs to one of the Research Groups within DCP. The Medical Monitor's responsibilities include:

- Managing scientific portfolios of grants, contracts, and other long-term projects in a distinct area of cancer prevention science;
- Reviewing protocols;
- Ensuring the quality and scientific integrity of protocol design, implementation, and data;
- Ensuring that the protocol is conducted safely and according to GCP and regulatory requirements;
- Reviewing SAE reports, deviations, and all clinical data; and
- Serving as a resource to study PIs and site staff for protocol-specific clarification.

3.5 Organ System Research Group Nurse Specialist

The Organ System Research Group Nurse Specialist is a registered nurse with advanced knowledge in the conduct of clinical research studies. The Nurse Specialist's responsibilities include:

- Serving as a resource and liaison to site staff conducting cancer prevention research;
- Participating in the management of cancer prevention research protocols;
- Participating in and leading DCP project teams and work groups; and
- Updating the DCP Medical Monitor on study status.

3.6 Contracting Officer

The Contracting Officer is a staff member who is responsible for the performance of pre-award and post-award contracting functions with NCI. The Contracting Officer is the only representative authorized by the United States Government to enter into contracts (i.e., commit Federal funds) and administer them. The Contracting Officer's acts are binding and responsibilities include the following:

- Providing guidance and technical assistance to program personnel who are involved in the planning and development of specifications, descriptions, and statements of work;
- Reviewing and evaluating requests for acquisitions, recommending and/or making revisions, analyzing requirements, and determining adequacy and completeness of requests;
- Recommending or deciding on the types of contracts;
- Coordinating the establishment of a peer review of proposals;
- Analyzing proposals through evaluating technical, cost/price data, proposal feasibility, and other factors; and
- Working with DCP officials to develop negotiation strategies.

3.7 Clinical Research Associate (CRA)

The CRA is qualified by training and experience, and is responsible for ensuring that clinical trials are conducted according to the CFR and the ICH/GCP. The CRA is an employee of the DCP Monitoring Contractor and represents DCP in the monitoring process. The CRA is responsible for verifying/assuring the following:

- The acceptability and accuracy of the investigator's and site staff's qualifications;
- The acceptability of the agent storage facilities;
- The initial and ongoing acceptability of the investigational site facilities;
- Investigational agents are supplied only to participants who are eligible to receive them, and in accordance with the dosing specified in the protocol;
- Participants are given the necessary instructions on properly using, handling, storing, and returning the study agent;
- The receipt, use, and return of the investigational agents at the sites are controlled and documented accurately;

- The study site research team complies with the protocol, applicable regulatory requirements, GCPs, and DCP policies;
- Informed consent was obtained prior to each participant's involvement in the trial;
- Study site staff are adequately informed and receive all trial documents and supplies to enable them to properly conduct the trial;
- The PI has appropriately delegated his or her authority;
- The PI is randomizing only eligible participants;
- Accurate reporting of the enrollment rate for the protocol;
- Accurate, complete, and current source documents and trial records are maintained;
- The PI provides all the required reports, notifications, applications, and IRB submissions, and that these documents are accurate, complete, timely, legible, and dated;
- The accuracy and completeness of the CRF relative to the source;
- Appropriate reporting of AEs and SAEs;
- Protocol changes/deviations are documented and reported to DCP and the IRB;
- Protocol deviations are reported to the PI, and the site has taken appropriate action to prevent the recurrence of the identified deviations;
- Data are entered appropriately and in a timely manner in a research database; and
- Data queries are addressed as appropriate to the coordinating center or as defined by the research database operations.

3.8 Protocol Information Office (PIO)

The DCP PIO is the central office for all protocol-related information management for DCP sponsored trials. The mission of the PIO is to coordinate all administrative aspects related to clinical trial development to assure that quality protocols are developed in the most expeditious and efficient manner possible. PIO personnel work closely with DCP and site staff assigned to this protocol to facilitate the research process for the Principal Investigator(s). The DCP PIO is responsible for the following:

- Coordinating all protocol activity form protocol development to final report submission; and

Collecting, processing, and tracking all protocol-related information between DCP, the study staff, the DCP Monitoring Contractor, and the DCP Regulatory Contractor.

4. PARTICIPANT ENROLLMENT

4.1 Initiation of a New Study

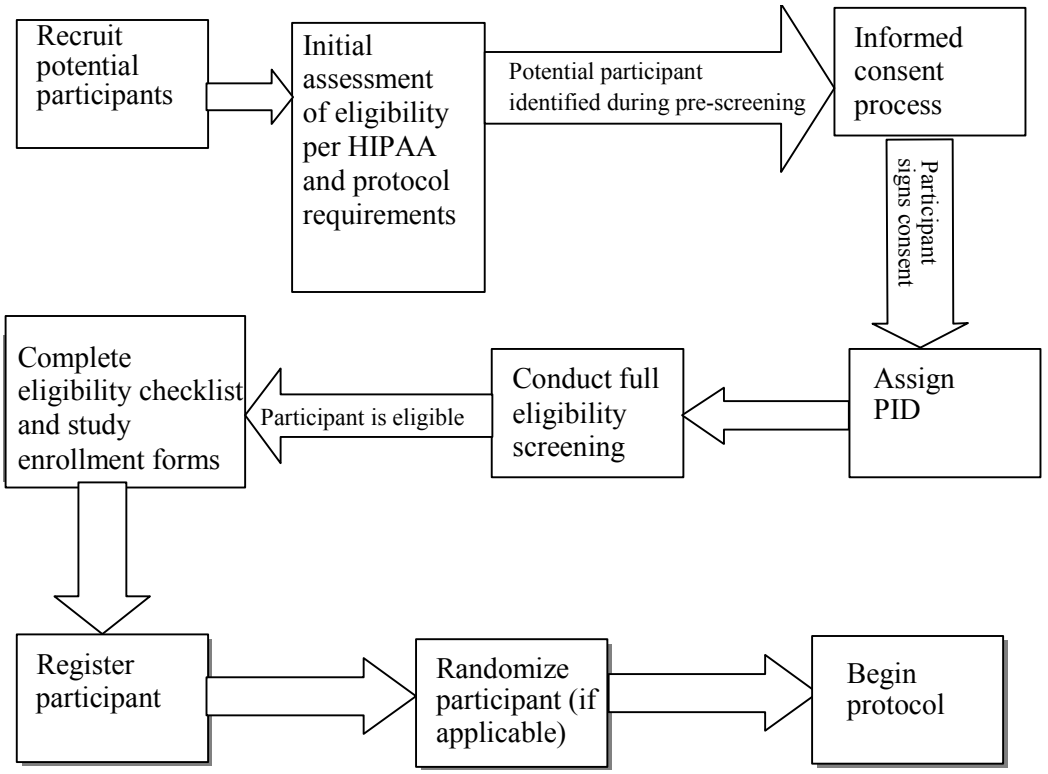
Prior to initiating a new Phase I or II study, qualified site staff are responsible for the implementation of a number of tasks that will contribute to a successful completion of a clinical trial. The PI, Study Coordinator, and other research staff will work within existing systems within the institution in order to accomplish a successful launch of a new study. The following is a list of key items necessary for study staff to implement at the beginning of each study protocol:

- Obtain DCP approval of clinical protocol, informed consent, CRF, Biomarker Methods Validation Report (if applicable), and Data and Safety Monitoring Plan;
- Submit all required regulatory documents and other requested documents to DCP;
- Assure that for all DCP-sponsored IND trials: 30-day waiting period following FDA submission of IND with no clinical holds placed by the FDA;
- Receive IRB approval and send letter/documentation to DCP and the DCP Regulatory Contractor;
- Obtain an executable contract with the lead organization;
- Receive adequate study agent supply on site;
- Have approved CRFs present and available for use;
- Determine whether a site initiation visit by the CRA from the DCP Monitoring Contractor, DCP staff, and involved study site staff (as required by DCP) will be conducted prior to the beginning of study approval;
- Prepare a Site Personnel Signature/Delegation Log;
- Have available copies of the DCP/IRB-approved informed consent forms and recruitment materials for the research team to provide to potential participants;
- Develop procedures for CRF completion, data entry, and a mechanism to prepare study progress reports;
- Record procedures for the collection, shipping, and processing of laboratory specimens required by the protocol; and
- Develop a Participant Identifier (PID) logbook and screening log.

4.2 The Enrollment Process

When required by DCP, the enrollment process may begin once the initiation visit has taken place and the site is prepared logistically to conduct the study (see Figure 4-1). The initiation visit can take place when DCP has given final study approval and the appropriate IRB has granted approval. Enrollment refers to the tasks that each site undertakes to initiate participant accrual beginning with recruitment and followed by a review of potentially eligible participants.

FIGURE 4-1. Participant Enrollment Process



4.2.1 Participant Recruitment

Recruitment for DCP chemoprevention trials will occur in different ways depending upon the particular study, research site, and creativity of assigned recruitment staff. Some potential participants may be recruited through primary care and specialty practices such as dermatology or urology. Other potential participants may be reached through oncology clinics. General media or specific outreach methods can be used to recruit members of the public. Each site is responsible for developing a

recruitment plan, recruitment materials, and methods to retain study participants as necessary. All participant recruitment materials must be approved by DCP and the IRB prior to their use.

In developing site-specific recruitment strategies, it is important that site staff be sensitive to the culture, personal beliefs, and current life circumstances of potential participants that could influence their decision to participate on a chemoprevention clinical trial. For example, potential participants may want to take a more active role in their health care and/or receive regular medical attention, or they may want to assist in the gathering of medical knowledge. They may also worry about perceived and/or real side effects, payment issues, and being viewed as "guinea pigs." The process of informed consent begins with the recruitment phase of a study.

4.2.2 Initial Evaluation of Participant's Eligibility Using the Inclusion/Exclusion Criteria

A general assessment of the participant's potential eligibility should be made to determine if further eligibility screening is warranted. Tests and procedures to confirm eligibility can be done only after the participant has signed the informed consent form.

4.2.3 Obtaining Informed Consent

Every effort must be made to protect the rights of the study participants. An investigator may not involve a participant in research (including tests to evaluate eligibility) unless the investigator or his or her representative has obtained a signed DCP and IRB-approved informed consent document. An investigator should obtain informed consent only under circumstances that provide the prospective participant sufficient opportunity to consider whether or not to participate.

NOTE: Participants who are minors or who cannot make their own health care decisions will need a legal representative to provide consent. Assent requirements may also apply. For further information on assent requirements, consult your local institution and/or state regulations.

Obtaining informed consent is more than obtaining a signature on a form. It is a process designed to:

- Provide the participant with current and ongoing information about the study;

- Ensure that the participant understands the information that has been presented and has an opportunity to ask questions;
- Discuss the participant's rights as outlined in the consent form;
- Grant the participant the opportunity to agree or disagree to take part in the study;
- Allow the participant the opportunity to freely withdraw from the study in the future; and
- Permit the participant the opportunity to allow or refuse to have his or her biologic samples stored and used for future research.

NOTE: During a site monitoring visit, the CRA will check the date the participant or legal representative signed the informed consent, as well as whether that signature was obtained on or before the date(s) that any screening or other study-related procedures were conducted. The CRA will also review the date an informed consent form was approved by the IRB and will determine whether a participant's signature was obtained only IRB approval.

4.3 Assigning a Participant Identification Number

Once a participant has been identified as potentially eligible for enrollment in the study and has signed an informed consent document, the participant will be assigned a unique identifier sometimes referred to as a Participant Identifier (PID). Depending on the funding mechanism of the clinical center, the staff, will develop a strategy for providing this PID, or it will be provided by DCP. Once a participant has been assigned a PID number, that number never changes. If the participant is enrolled in future stages of the study, he or she will retain that PID number. If the participant does not enroll, that PID number will not be reassigned. The PID logbook that contains the participants' names and their assigned PID numbers must be kept in a locked, secure place with access limited to appropriate study personnel.

NOTE: DCP will comply with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule in order to protect the privacy of research participants. Please refer to the following website for more information: http://www.hhs.gov/ocr/hipaa/.

4.4 Determining Eligibility

Once a participant is identified as a potential candidate for a study and has signed the informed consent document, the screening (or pre-entry) assessment to fully evaluate and confirm eligibility begins. This eligibility evaluation may include laboratory and/or clinical tests. The results of

the tests help determine whether the participant satisfies the inclusion/exclusion criteria of the protocol. All screening evaluations are performed prior to the participant's registration.

All participants who undergo screening for a study must be recorded in a study-specific screening log. If a participant is found to be ineligible or otherwise does not enroll in the study, the reason for this must be stated in the log.

Participants who sign the informed consent document, but who are not eligible for the study due to the inclusion or exclusion criteria, must be told why they cannot participate in the clinical trial. This explanation is often provided by the Research Nurse or Study Coordinator. The reason(s) for ineligibility must be recorded in the participant's study chart and should include a note indicating the participant understood the rationale for exclusion.

After eligibility has been determined, the protocol-specific eligibility checklist must be completed to document that the participant fulfills the inclusion/exclusion criteria of the protocol. If the participant meets the criteria of the protocol, the study enrollment form will be completed and the participant will be ready for registration.

NOTE: During a site monitoring visit, the CRA will check the Eligibility Checklist CRF against the source documentation. The CRA may also ask to review the screening log while on site.

4.5 Registering/Randomizing Participants

The mechanism for officially registering and randomizing participants onto a DCP study will vary depending upon the protocol. The person responsible for randomizing participants and study staff to be blinded to study agent also will differ with each protocol. Details for registering/randomizing participants should be found in the protocol. For example, if a pharmaceutical company is involved in the study and is assigned randomization responsibilities, site staff may be required to call or fax the eligibility and enrollment forms to that company. Likewise, if several sites are involved in the study and the statisticians at the lead organization are responsible for randomization, all sites will send eligibility and enrollment information to the lead organization's statisticians. In other instances, the research pharmacist at the site may be responsible for implementing the randomization process. DCP does not perform the function of registering and randomizing participants. Therefore, it is critical that site staff assess eligibility criteria carefully, as eligibility may be checked only at the time of the annual site monitor visit. During

site monitoring visits, participant eligibility will be one of the main items assessed by the CRA or by other designated monitoring staff.

5. STUDY RECORD MAINTENANCE

One of the primary responsibilities of the CRA during a site visit is to review the study records and ensure that they are complete and that any information transcribed from one source to a protocol-specific form has been done so accurately. This chapter describes the different types of study records and lists the documents the CRA will review during a site visit.

5.1 Regulatory Binder

The Regulatory Binder contains all study-specific information and regulatory documentation. This Binder does not include completed CRFs or signed informed consent forms. While the site must keep all original informed consents that have been signed by participants, it is recommended that these be maintained in a separate binder or as directed by the policies of the clinical site. The terms Study Binder, Investigator Binder, Administrative Binder, Regulatory Files, and Investigator's Study Files are used synonymously to describe the Regulatory Binder. The Regulatory Binder may take the form of file folders, one or more three-ring binders, a filing system, or a combination of these organizational methods.

Typically, the Regulatory Binder contains the elements described in the Regulatory Binder checklist. The order and organization of the documents may vary from site to site. During a site visit, the CRA will review the Regulatory Binder to ensure its completeness.

5.1.1 Regulatory Binder Checklist

The following documents should be found in the Regulatory Binder and in a number of folders within a specified series of files as organized by the Research Nurse or Study Coordinator. The order may vary by site:

- Protocol and amendments (all approved versions);
- Investigator Brochure (all versions);
- CRFs (blank set that can be duplicated, all versions);
- Completed Form FDA 1572s (current, as well as those outdated);

- Curriculum vitae (CV) and copies of professional licenses for all investigators (from time of study initiation to date) for relevant site staff;
- Human subject protection training documentation (from time of study initiation to date);
- Financial disclosure forms (which should be kept in a locked, secure location); for anyone listed on the 1572, if applicable
- Confirmation of current Federal Wide Assurance; required for all institutions receiving funding for Department of Health and Human Services (DHHS) supported studies;
- IRB approval documentation for:
  - The protocol (all versions);
  - Protocol amendments (all versions);
  - Informed consent form document (original and all versions);
  - Other written (educational) materials provided to the participants;
  - Continuation of the study (based on annual or periodic reviews); and
  - Study advertising;
- IRB correspondence:
  - Notification of new safety information and the IRB's recommendations pertaining to this information; and
  - IRB roster and credentials of IRB members;
- NCI-DCP approval documentation for:
  - The protocol (all versions);
  - Protocol amendments (all versions);
  - Informed consent form document (original and all versions);
  - Other written (educational) materials provided to the participants; and
  - Pertinent recruitment and retention materials;
- NCI-DCP correspondence;
- Informed consent:
  - Original copies of IRB-approved versions; and

- Original copies of NCI-approved versions;

NOTE: Original, signed informed consents are usually kept in the participant's medical records or research records and not in the Regulatory Binder.

- SAEs and IND safety reports;
- Signature and delegation log (site personnel signature sheet);

NOTE: This is a comprehensive list of all research staff involved in the conduct of the study. The log includes signatures, initials, delegated tasks, and effective dates.

- Site monitoring log;
- Site visit reports and confirmation letter;
- Participant Identification/screening log;

NOTE: This log documents the chronological screening/enrollment of participants. This log is kept in a secure location separate from the Regulatory Binder.

- Clinical laboratory certification (if required) and normal ranges (from time of study initiation to date);
- Study agent documentation:
  - Agent shipment and receipt records/forms;
  - Accountability logs;
  - NCI Drug Accountability Record Form (DARF); and
  - DCP Agent Return Form (if applicable);

NOTE: Study agent documentation is often kept in the pharmacy, and not in the Regulatory Binder.

- Notes to file regarding study procedures;
- Accurate and consistent records of study operations including electronic and or paper communications with the IRB, study sponsor, Regulatory Contractor, Monitoring Contractor and other study- related organizations;
- Protocol deviations filed with the study sponsor; and
- Study close-out information.

5.2 Source Documentation

Source documents are the original signed and dated records of participant information (e.g., the medical record, shadow chart) which may include electronic documents containing all the information related to a participant's protocol participation. Source documents are used to verify the integrity of the study data, to verify participant eligibility, and to verify that mandatory protocol procedures were followed. An investigator and other designated staff are required to prepare and maintain adequate and accurate documentation that records all observations and other data pertinent to the investigation for each individual participating in the study. All data recorded in the research record (including data recorded on CRFs) must originate in the participant's medical record, study record, or other official document sources.

5.2.1 List of Source Documents

Source documents, which may be either paper or electronic, may include but are not limited to the following items.

- Institutional, research, hospital, clinic, or office records containing:
  - Inpatient and outpatient medical records;
  - Progress notes;
  - Consults;
  - Nursing notes;
  - Pathology reports;
  - Radiology reports;
  - Imaging study(ies) reports;
  - Medicine/radiation administration records;
  - Surgical reports;
  - Laboratory results;
  - Admission forms;
  - Flow sheets and study-specific checklists that are signed and dated;
  - Discharge summaries;

- Protocol or study road maps;
- Appointment books; and
- Participant diaries/calendars.

- Relevant participant-specific written communication from non-study health care providers, including comments related to past medical history, entry criteria, or other referral or follow-up information;
- Participant-specific correspondence, such as documented telephone calls, email messages, and faxes; and
- Obituaries, autopsy reports, and death certificates.

5.2.2 Source Documentation Guidelines

Source documents substantiate CRF information. All participant case records (e.g., flow sheets, clinical records, physician notes, correspondence) must adhere to the following standards:

- Clearly labeled in accordance with HIPAA practices so that they can be associated with a particular participant or PID;
- Legibly written in ink;
- Signed and dated in a real time basis by health care practitioner evaluating or treating the participant; and
- Correction liquid or tape must not be used in source documents or on CRFs. Corrections are made by drawing a single line through the error. Do not obliterate the original entry. Insert the correct information, initial, and date the entry.

All laboratory reports, pathology reports, x-rays, imaging study and scans must have:

- Complete identifying information (name and address of the organization performing, analyzing, and/or reporting the results of the test); and
- Range of normal values for each result listed.

5.3 Case Report Forms

Participant information that relates to a clinical study is abstracted from the source documents to the appropriate data fields on CRFs. The PI or designee for each DCP study typically

develops the CRFs for use in a particular study. However, DCP does provide sample CRF templates that can be used for Phase I and II DCP chemoprevention trials. These templates contain recommended content and formats and may be downloaded from the DCP PIO website area (http://prevention.cancer.gov/clinicaltrials/management/pio/instructions), and modified to address study-specific information for each trial.

NOTE: CRFs consist of single or triplicate paper forms (such as when a study is sponsored by a pharmaceutical company) that an authorized person completes by hand by transferring data from the source documents. Increasingly, the authorized staff person may transfer data directly from the source into an electronic database, essentially creating an electronic CRF. These electronic records may be printed and filed in the participants' CRF notebook for monitoring purposes. An alternative mechanism that allows appropriate access to electronic CRF information may be used for monitoring purposes.

The CRA will review participant CRFs to ensure that they are completed or accurately entered into a database if applicable. The CRA will verify that all data entered on the CRFs can be validated by information in the source documents. The CRA will also review the source documents to ensure that the correct and pertinent information is included on the CRFs.

5.3.1 Completing a CRF

- Any assigned member of the study staff who has signed the Signature Log in the Regulatory Binder may complete a CRF;
- CRFs should be completed within one week after the relevant information becomes available (i.e., the participant completes the visit or the laboratory results have been received);
- The information documented on the CRF must be identical to the information found in the source document (i.e., participant charts, laboratory result printouts);

  NOTE: All source documents and CRFs must be available for verification by the CRA during site monitoring visits.
- If the source information is **missing**, write or enter "ND" (no data) in the boxes/space. If the information is **unknown**, write or enter "UNK" in the boxes/space. Entries of "Missing" or "Unknown" information must be explained in the source document (i.e., nurse's or clinic notes) for future verification;
- Enter information on a paper CRF with an ink (preferably black) pen only. Do not use pencil;

- When check boxes are provided for a response and CRFs are completed by hand, be sure to clearly mark the box to be selected with a ✓ or —. Make sure the mark is clear and unambiguous;

- For CRFs completed manually, corrections should be made in ink by crossing out the incorrect entry with a single horizontal line, placing the correct information next to the error, and providing an initial and date next to the correction. Do not backdate. Do not use any type of correction fluid to mask previous entry or erase any entries on the forms;

  NOTE: Corrections to electronically-created CRFs must be made within the same database that was used to create them—that is, not simply crossed out on the paper printout. If the site uses an electronic system to create CRFs, then it should also have a method in place to track data edits, including who made the edit and when.

- Do not write in the margins of the CRFs. Provide any relevant additional information in the appropriate "comments" section;

- Avoid the use of abbreviations other than those that have been recommended;

- CRFs are required for the following participants:

  - All participants who had a procedure required by protocol after signing informed consent; and

  - All participants who have been randomized.

  NOTE: CRFs are not required for potential study participants found to be ineligible for study enrollment; however, these participants should be tracked in a screening log.

5.4 CRF Notebook

CRFs contain participant information related only to the study. Each participant has a CRF notebook or folder, or another system is used to organize the participant's CRFs. Hard-copy and/or electronic CRFs should be kept in a locked and secure area and/or a protected access system at all times.

The CRFs notebook is arranged in a protocol-specific logical order. The forms in each section may be arranged chronologically or in reverse chronological order. In either case, there must be consistency throughout the designated notebook.

Each CRF should be identified by PID, study visit, and visit date. Each notebook or folder should be organized into the following sections (as appropriate):

1. Demographic information;

2. Pretreatment section:

   - Eligibility checklist;
   - Registration/randomization forms;
   - Confirmation of registration;
   - On study form;
   - Copy of signed informed consent and specimen banking consent (if applicable); and
   - All other required forms to be completed and/or submitted prior to treatment.

3. Intervention section (arranged by cycle, study week, or other time point):

   - Procedure forms and/or flow sheet;
   - Concomitant medications;
   - AE and SAE reports (if applicable); and
   - Lab data.

4. Tumor evaluation/response to intervention (if applicable):

   - Radiology forms;
   - Cytology report;
   - Pathology results;
   - Bone marrow aspiration results;
   - Tumor measurements; and
   - Imaging study results.

5. SAEs (as needed):

   - Copy of supporting and follow-up documentation.

6. Off study:

   - Off study forms.

7. Followup Forms:

   - Death report form (if appropriate);
   - Late AE documentation; and

- Correspondence relating to participant status (relapse, additional treatment, etc.).

5.5 Record Retention

The U.S. Department of Health and Human Services (DHHS) and the FDA have regulations related to retention of protocol records.

- DHHS Regulations (45 CFR 46.115) apply to all research conducted or supported by any Federal department or agency. This regulation states that IRB records relating to research conducted shall be retained for at least 3 years after completion of the research. The Food and Drug Administration (FDA) regulation (21 CFR 56.115) is virtually identical; it also states that IRB records must be retained for at least 3 years after completion of the research;

- Trials with a FDA IND must additionally comply with 21 CFR 312.57 and 21 CFR 312.62. These regulations apply to investigational agent records, investigator financial interest records, and patient case histories. Both of these regulations require that the sponsor retain records and reports for 2 years after a marketing application is approved for the agent. If an application is not approved for the agent, the sponsor retains records and reports until 2 years after shipment and delivery of the agent for investigational use is discontinued and FDA has been so notified; and

- The contract awarded for each study should state how long records are to be retained for that study. These statements should be as stringent as the Federal regulations. This information should be specified in the study protocol.

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.

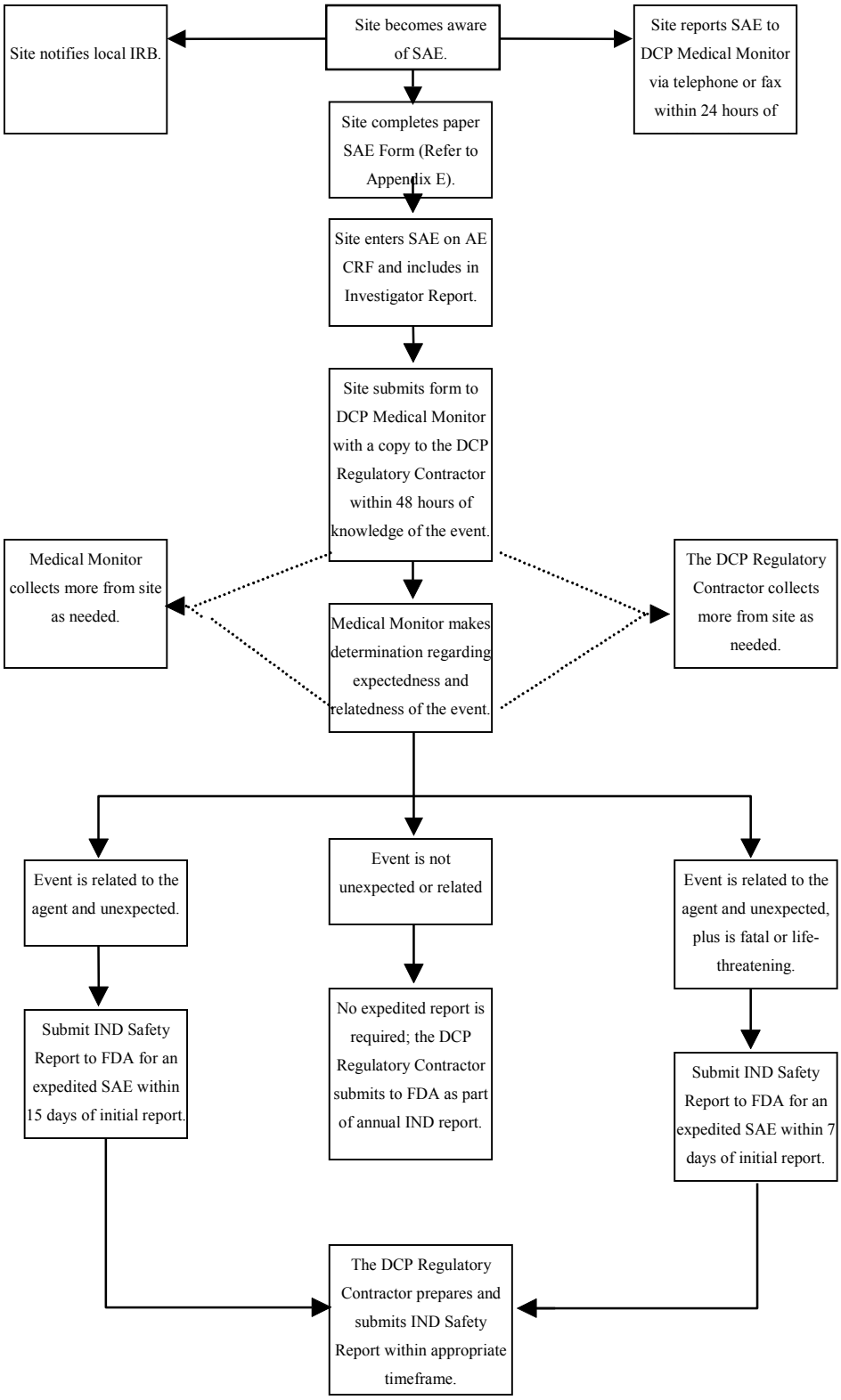
6.3 DCP Processing and Reporting Responsibility to FDA

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



7. PROTOCOL DEVIATION REPORTING

7.1 Purpose

The purpose of this section is to provide a definition of a protocol deviation and the process for reporting these deviations to DCP.

A deviation is any noncompliance with the DCP and Institutional Review Board (IRB) approved protocol and may result from actions by the study participant, the investigators, or the clinical staff conducting the study. A deviation may not always be construed as a deficiency although it may be discovered and reported during an on-site monitoring visit. Deviations from the protocol may be inadvertent, and cannot always be used as a measure of site performance. Proper documentation and reporting of protocol deviations as they occur is helpful for investigators and study sponsors, as these data can be used to determine the need for amendments to the protocol and/or the related documents. The monitoring of the frequency and nature of protocol deviations can also be used as a quality assurance measure for the site.

A deviation or noncompliance with the study protocol should be reported as soon as it is identified. This is consistent with Good Clinical Practices (GCPs). It is the PI and Site Coordinator's responsibility to report the deviation to the Medical Monitor at the time the deviation is noted.

7.2 Procedure

Site staff should record a single deviation from the protocol on the DCP Protocol Deviation Notification form (version 5/2/08). Instructions for completing each field of this form are included in the form (See Appendix D). The DCP Protocol Deviation Notification form is available on the DCP website at http://dcp.cancer.gov/files/clinical-trials/ProtocolDeviationNotification.doc.

The Site Coordinator must determine which site staff are authorized to complete this form. Using the Instructions for Completion as a guide, fields one through twenty-one should be completed by site staff.

The PI must review the completed DCP Protocol Deviation Notification form before the form is submitted to DCP for review. The designated staff member who completes the form should check

box twenty to acknowledge that the PI has reviewed the completed form. The designated staff member should email the completed DCP Protocol Deviation Notification form to the appropriate DCP Medical Monitor (See Appendix A for the email addresses of the DCP Medical Monitors by Research Group).

The DCP Medical Monitor or designee will review the DCP Protocol Deviation Notification form. Once any queries have been resolved, the Medical Monitor or designee will complete fields twenty-two through twenty-five. This form is then submitted via email to the DCP Monitoring Contractor via the DCP Help Desk (nci-dcpmonitoring@westat.com).

Site staff should expect to receive the completed form, with comments from the DCP Medical Monitor (or designee), via email from the DCP Monitoring Contractor, within seven calendar days of receipt from DCP. Site staff should file the completed form in the specific study participant's record and/or protocol specific record, and should follow recommendations, as directed, by the DCP Medical Monitor (or designee).

7.3 Documentation

Site staff will use the DCP Protocol Deviation Notification form (version 5/2/08) to document protocol deviations. An example of the DCP Protocol Deviation Notification form can be found in Appendix D. The Protocol Deviation Notification form must be completed by electronically typing into the fillable form. Site staff may access the form from the DCP website (http://prevention.cancer.gov/) specifically at http://dcp.cancer.gov/files/clinical-trials/ProtocolDeviationNotification.doc. Completed copies of the form should be filed with study documentation.

8. CHANGE IN PARTICIPANT STATUS

8.1 Off Study Agent

Some protocols document a difference in procedure for when a participant is temporarily off the study drug/agent. The criteria are similar to those for being 'off study.' There are two events that define an "Off Study Agent" event. The first is that a study participant may discontinue use of a study agent but continue to be followed in a study. In this case, the participant's status is identified as "Off Study Agent," and the participant continues to be followed as specified by the protocol. The second event is that a participant who completes the protocol interventions and any protocol-specified follow-up period or evaluations may also be considered as "Off Study Agent." This applies to specific protocols written to include this distinction. Reasons that participants may stop a study agent include:

- Any AEs or SAEs as reported on the completed AE/SAE Form;
- Noncompliant participant (includes refused study agent and/or assessments);
- Concomitant medication contraindicated by protocol;
- Medical contraindication (e.g., pregnancy);
- The discretion of the investigator; or
- Other (which should be described in the source document and noted on the case report form).

When a participant has permanently discontinued the study agent, the final study visit and clinical/laboratory evaluations must be obtained as specified in the protocol (when applicable). All study agents or supplies need to be returned to the site staff.

8.1.1 Required Follow-up for Off Study Agent Status

The study forms required at the time of permanent discontinuation of a study agent are specified in the "Off Study Agent" section in the protocol. The procedures and/or clinical evaluations completed for "Off Study Agent" are specified in the protocol and should be consistent with the end points described in the objectives and statistical analysis sections of the protocol.

8.1.2 Off Study

Participants who are considered to be "Off Study" are those who are permanently discontinued from the study agent or who do not wish to participate in the study any longer. This includes those participants who have completed all study visits and the protocol-specified evaluations. The following are some reasons a participant can go off study:

- Completed (completed protocol intervention and any protocol-specified follow-up period or evaluations);
- Any AEs or SAEs as reported on the completed AE/SAE Form;
- Noncompliant participant (includes refused study agent, assessments);
- Concomitant medication contraindicated by protocol;
- Medical contraindication (e.g., pregnancy);
- The discretion of the investigator;
- Lost to follow-up;
- Withdrew consent;
- Death (complete Death CRF); or
- Other (which should be described in the source document and noted on the case report form).

NOTE: Any participant who is withdrawn for AEs must be followed until resolution of the event or until the PI considers it unnecessary to continue follow-up. Documentation of this reason to discontinue follow-up must be noted and maintained in the participant's study chart. Relevant information should be abstracted into the "Continuing AE" section of the Off Study Form.

8.2 Death

All known deaths of participants enrolled in DCP-funded clinical studies are to be reported as an SAE regardless of the relatedness or attribution to the study agent. The SAE report is forwarded to the DCP Medical Monitor for review. The SAE procedures in Chapter 6 of this Manual include instructions on completing an SAE form and details about submission timeframes. In general, the following information should be submitted on the SAE form at the time the death is reported:

- Name and phone number of the reporter;
- Participant's study identification number;
- Date of death;
- Primary cause of death (if known);
- Name of study agent(s);
- Date study agent(s) last given;
- Assessment of whether death was related to study agent; and
- Brief history leading to death. (Submit autopsy report if available.)

Deaths are to be reported using the protocol-specific death form usually located with the protocol-specific CRFs. A Death CRF is to be completed for each protocol in which the participant was enrolled. The purpose of this form is to gather information regarding the participant's death and when it occurred during the study. If the exact date and time of the death are unknown despite attempts to obtain this information, an estimate based on known facts is allowed.

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.

Appendix A

Division of Cancer Prevention, DCP Monitoring Contractor, and DCP Regulatory Contractor Staff List

June 2008

APPENDIX A

DIVISION OF CANCER PREVENTION, DCP MONITORING CONTRACTOR, AND DCP REGULATORY CONTRACTOR STAFF LIST

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DCP Monitoring Contractor Address:	Westat 1441 West Montgomery Avenue Rockville, MD 20850-2062 T: 301-738-3653 F: 301-738-8379	
DCP Regulatory Contractor Address:	CCS Associates, Inc. 2005 Landing Drive Mountain View, CA 94043 T: 650-691-4400 F: 650-691-4410	
DCP Help Desk:	1-888-662-8354 or email NCI-DCPmonitoring@westat.com	
	Business hours are between 8:00 a.m. and 4:00 p.m. (ET) Monday through Friday. The caller is asked to leave a detailed voice or email message outlining the information needed. The DCP Monitoring Contractor staff check the Help Desk voice mail box every hour and the Help Desk email box every hour during business hours. Calls and/or emails will be triaged to the appropriate individual for follow-up. A response to the call or email will be sent as soon as possible. If there is an immediate need, please contact the DCP Help Desk at ncidcpmonitoring@westat.com or 1-888-662-8354.	
DCP Staff: **Acting Deputy Director, Associate Director for Clinical Research**	Leslie Ford, MD T: 301-496-0265 F: 301-435-3541 E: ford1@mail.nih.gov	
Protocol Information Office: **For protocol development, review, amendment approval**	**Protocol Information Office:**	6130 Executive Boulevard MSC #7323 Executive Plaza North, Rm. 2050 Bethesda, MD 20892 T: 301-496-0090 F: 301-480-1342 E: nci_dcp_pio@mail.nih.gov

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Appendix B

Glossary of Terms

Acronym	Term	Definition
AE	Adverse Event	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 adverse event (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. "[Modified from ICH E2A]" *Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience.* [Source: CDISC 12/06]
	Agent	A pharmaceutical, nutraceutical or other agent used individually or in combination with others that is being tested in a cancer prevention trial.
	Amendment	A written description of a change(s) to, or formal clarification of, a protocol. [Source: CDISC 12/06]
	Audit	A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s). [ICH E6 Glossary] [Source: CDISC 12/06]
	Audit Task Manager	An appropriately qualified DCP Monitoring Contractor employee, by training and experience, whose responsibilities include, but are not limited to, DCP project goal planning for on-site monitoring, supervision of staff, assignment of protocol(s) and sites to monitor, assuring compliance with specific SOPs, and assuring that on-site monitoring visits are conducted and site visit reports are recorded appropriately.
	Balanced Study	Trial in which a particular type of subject is equally represented in each study group. [Source: CDISC 12/06]
	Biomarker	A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. [Biomarker definitions working group] [Source: CDISC 12/06]
BGCRG	Breast and Gynecological Cancer Research Group	This group conducts and supports research on the prevention and early detection of breast, cervix, endometrial, and ovarian cancers. Clinical trials and the evaluation of new agents, surrogate biomarkers, and new technologies to identify premalignant lesions are developed and supported. [Source: http://prevention.cancer.gov/programs-resources/groups/bgcrg]

Acronym	Term	Definition
caBIG	Cancer Bioinformatics Grid	An initiative of the NCI to accelerate research discoveries and improve patient outcomes by linking researchers, physicians, and patients throughout the cancer community. caBIG™ serves as the cornerstone of NCI's biomedical informatics efforts to transform cancer research into a more collaborative, efficient, and effective endeavor. [Source: https://cabig.nci.nih.gov/overview]
CB	Cancer Biomarkers Research Group	This group promotes and supports research to identify, develop, and validate biological markers for earlier cancer detection and risk assessment. The group integrates basic and clinical science studies along with computational, statistical and epidemiologic approaches for a comprehensive understanding of biomarkers. It coordinates the Early Detection Research Network. [Source: http://prevention.cancer.gov/programs-resources/groups/cb]
CRF	Case Report Form	1. A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor for each trial subject. 2. A record of clinical study observations and other information that a study protocol designates must be completed for each subject. NOTE: In common usage, CRF can refer to either a CRF page, which denotes a group of one or more data items linked together for collection and display, or a casebook, which includes the entire group of CRF pages on which a set of clinical study observations and other information can be or have been collected, or the information actually collected by completion of such CRF pages for a subject in a clinical study [ICH E6 Glossary] *See also CRF (paper).* [Source: CDISC 12/06]
CCSA	CCS Associates	The DCP Regulatory Contractor who is responsible for assisting the PIO, Organ Site Research Group personnel and study staff with protocol development and management of regulatory issues.
CADRG	Chemopreventive Agent Development Research Group	This group supports scientific and administrative oversight for preclinical chemoprevention agent development up to early phase I chemopreventive agent research using physiological endpoints in healthy volunteers. Research focuses on identifying and developing agents with the potential to block, reverse, or delay early stages of cancer, using a battery of preclinical pharmacology, toxicology, and efficacy tests, and conducting phase 1 pharmacokinetic and safety studies. [Source: http://prevention.cancer.gov/programs-resources/groups/cad]
	Clinical Investigation	*See clinical trial.* [Source: CDISC 12/06]
CRA	Clinical Research Associate	Person employed by a sponsor, or by a contract research organization acting on a sponsor's behalf, who monitors the progress of investigator sites participating in a clinical study. At some sites (primarily in academic settings), clinical research coordinators are called CRAs. [Source: CDISC 12/06]

Acronym	Term	Definition
CRC	Clinical Research Coordinator	Person who handles most of the administrative responsibilities of a clinical trial on behalf of a site investigator, acts as liaison between investigative site and sponsor, and reviews all data and records before a monitor's visit. *Synonyms: trial coordinator, study coordinator, research coordinator, clinical coordinator, research nurse, protocol nurse.* [Source: CDISC 12/06]
	Clinical Trial	Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one of more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s), and/or to study absorption, distribution, metabolism and excretion of one of more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy. [Directive 2001/20/EC; Modified from ICH E6 Glossary] [Source: CDISC 12/06]
CFR	Code of Federal Regulations	The Code of Federal Regulations (CFR) is the codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the Federal Government. It is divided into 50 titles that represent broad areas subject to Federal regulation. Each volume of the CFR is updated once each calendar year and is issued on a quarterly basis. [Source: http://www.gpoaccess.gov/cfr/index.html]
	Commercial Agent	Any agent not supplied under an IND but instead, obtained from a commercial source.
CDE	Common Data Elements	Metadata descriptors used for forms and applications which were developed to promote interoperability among systems developed for NCI-sponsored research.
CTC v.2.0 and CTCAE v.3.0	Common Toxicity Criteria/ Common Terminology Criteria for Adverse Events	The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term. [Source: http://ctep.cancer.gov/forms/CTCAEv3.pdf]
	Confidentiality	Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity. [ICH E6 Glossary] [Source: CDISC 12/06]

Acronym	Term	Definition
CF	Consent Form	Document used during the informed consent process that is the basis for explaining to potential subjects the risks and potential benefits of a study and the rights and responsibilities of the parties involved. NOTE: The informed consent document provides a summary of a clinical trial (including its purpose, the treatment procedures and schedule, potential risks and benefits, alternatives to participation, etc.) and explains an individual's rights as a subject. It is designed to begin the informed consent process, which consists of conversations between the subject and the research team. If the individual then decides to enter the trial, s/he gives her/his official consent by signing the document. *Synonym: informed consent form; see also informed consent.* [Source: CDISC 12/06]
CRO	Contract Research Organization	A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions. [ICH E6 Glossary] [Source: CDISC 12/06]
	Control Group	The group of subjects in a controlled study that receives no treatment, a standard treatment, or a placebo. [21 CFR 314.126] *See also controls.* [Source: CDISC 12/06]
	Controls	Comparator against which the study treatment is evaluated [e.g., concurrent (placebo, no treatment, dose-response, active), and external (historical, published literature)] 2. Computer: processes or operations intended to ensure authenticity, integrity, and confidentiality of electronic records. NOTE: The protocol incorporates scientific rationale for selection of comparator and describes how the comparator serves as a reference point for the evaluation. [1. After ICH E10. 2. After 21 CFR Part 11; CSUCT] [Source: CDISC 12/06]
CV	Curriculum Vitae	Document that outlines a person's educational and professional history. [Source: CDISC 12/06]
	Data Acquisition	Capture of data into a structured computerized format without a human-computer interface (from another automated or computerized source). Contrast with data entry, electronic data capture. [Source: CDISC 12/06]
	Database Administrator	A systems professional, trained in database administration techniques, who is responsible for utilizing these techniques to manage security and performance of an Oracle database. These responsibilities include: creating and removing user accounts, developing appropriate access roles and profiles, controlling and monitoring user access, identification of security violations, backup and recovery of the database, and monitoring and optimizing performance. There will be a primary and secondary project database administrator for Oracle Clinical databases on the DCP project. A corporate database administrator is responsible for establishing policies and procedures for all Oracle databases at offices of the DCP Monitoring Contractor.

Acronym	Term	Definition
	Data Entry	Human input of data into a structured, computerized format using an interface such as a keyboard, pen-based tablet, or voice recognition. Contrast with data acquisition, electronic data capture. [Source: CDISC 12/06]
	Data Management	Tasks associated with the entry, transfer and/or preparation of source data and derived items for entry into a clinical trial database. NOTE: Data management could include database creation, data entry, review, coding, data editing, data QC, locking, or archiving; it typically does not include source data capture. [Source: CDISC 12/06]
	Data Monitoring	Process by which clinical data are examined for completeness, consistency, and accuracy. [Source: CDISC 12/06]
DMC/ DSMB	Data Monitoring Committee/ Data and Safety Monitoring Board	Group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical trial. The DMC advises the sponsor regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial. NOTE: A DMC can stop a trial if it finds toxicities or if treatment is proved beneficial. [After FDA guidance on establishment and operation of clinical trial data monitoring committees] [Source: CDISC 12/06]
DESK	DCP Enterprise System Knowledgebase	The DCP Enterprise System Knowledgebase (DESK) supports the NCI Division of Cancer Prevention (DCP) data such as agents and address modules. [Source: http://ncicb.nci.nih.gov/tools/tools_introduction]
	Discontinuation	The act of concluding participation, prior to completion of all protocol-required elements, in a trial by an enrolled subject NOTE: Four categories of discontinuation are distinguished: a) dropout: Active discontinuation by a subject (also a noun referring to such a discontinued subject); b) investigator initiated discontinuation (e.g., for cause); c) loss to follow-up: cessation of participation without notice or action by the subject; d) sponsor initiated discontinuation. Note that subject discontinuation does not necessarily imply exclusion of subject data from analysis. "Termination" has a history of synonymous use, but is now considered non-standard. *See also withdrawal.* [Source: CDISC 12/06]
DCP	Division of Cancer Prevention	The Division of Cancer Prevention (DCP) is the primary unit of the National Cancer Institute devoted to cancer prevention research. DCP provides funding and administrative support to clinical and laboratory researchers, multidisciplinary teams, and collaborative, research-based networks. [Source: http://prevention.cancer.gov/about]
	Drug Accountability	Maintaining current and accurate records showing the quantities of drug received, dispensed, stored at the site, and returned to the sponsor.

Acronym	Term	Definition
DARF	Drug Accountability Report Form	The NCI Drug Accountability Report Form that is used by the site pharmacists to record study agent disposition (receipt, transfer, dispensing and return).
	Effectiveness	The desired measure of a drug's influence on a disease or condition as demonstrated by substantial evidence from adequate and well-controlled investigations. [Source: CDISC 12/06]
	Efficacy	The capacity of a drug or treatment to produce beneficial effects on the course or duration of a disease at the dose tested and against the illness (and patient population) for which it is designed. [Source: CDISC 12/06]
eCRF	Electronic Case Report Form	1. Auditable electronic record designed to capture information required by the clinical trial protocol to be reported to the sponsor on each trial subject. 2. A CRF in which related data items and their associated comments, notes, and signatures are linked electronically. NOTE: eCRFs may include special display elements, electronic edit checks, and other special properties or functions and are used for both capture and display of the linked data. [FDA CSUCT] [Source: CDISC 12/06]
EDC	Electronic Data Capture	The process of collecting clinical trial data into a permanent electronic form. NOTE: "Permanent" in the context of these definitions implies that any changes made to the electronic data are recorded via an audit trail. *Synonym: remote data capture; see also data entry, data acquisition.* [Source: CDISC 12/06]
EC	Ethics Committee	*See institutional review board, independent ethics committee.* [Source: CDISC 12/06]
	Evaluable (for Efficacy and Safety)	Pertains to data or subjects that meet Statistical Analysis Plan criteria for inclusion in Efficacy/Safety datasets. [Source: CDISC 12/06]
	Financial Disclosure Form	Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860), an applicant is required to submit to FDA a list of clinical investigators who conducted covered clinical studies and certify and/or disclose certain financial arrangements as follows: 1. Certification that no financial arrangements with an investigator have been made where study outcome could affect compensation; that the investigator has no proprietary interest in the tested product; that the investigator does not have a significant equity interest in the sponsor of the covered study; and that the investigator has not received significant payments of other sorts; and/or 2. Disclosure of specified financial arrangements and any steps taken to minimize the potential for bias. [Source: http://www.fda.gov/oc/guidance/financialdis.html]

Acronym	Term	Definition
FDA	Food and Drug Administration	The United States regulatory authority charged with, among other responsibilities, granting IND and NDA approvals. [Source: CDISC 12/06]
	Form FDA 1572	Statement of the investigator that outlines the responsibilities that the investigator agrees to assume in order to conduct the clinical trial.
GOCRG	Gastrointestinal and Other Cancers Research Group	This group conducts and supports research on the prevention and early detection of colorectal, esophageal, liver, pancreatic, skin, and hematolymphoid cancers. Clinical trials and the evaluation of new agents, surrogate biomarkers, and new technologies to identify premalignant lesions are developed and supported. [Source: http://prevention.cancer.gov/programs-resources/groups/gocrg]
	Global Librarian	A person assigned the responsibility of internal administration and change management of the Global Library in an Oracle Clinical database. This person is also assigned the responsibility of granting and revoking access for individual users to specific protocols.
GCP	Good Clinical Practice	A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. NOTE: For Guidance on Good Clinical Practice see COMP/ICH/135/95; Declaration of Helsinki; 21 CFR 50, 21 CFR 54, 21 CFR 56, and 21 CFR 312. [ICH] [Source: CDISC 12/06]
HIPAA	Health Insurance Portability and Accountability Act	A federal law that created national standards to protect the privacy of personal health information.
	Human Subject	Individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. [21 CFR 50.3]. *Synonym: subject/trial subject.* [Source: CDISC 12/06]
HTML	Hyper Text Markup Language	A specification of the W3C that provides markup of documents for display in a Web browser. [HL7] *Contrast to XML.* [Source: CDISC 12/06]
HTTP	Hyper Text Transfer Protocol	A standard through which a client browser talks to a server to load the requested document.
	Informatics	The design and implementation of complex hardware and software systems for the extraction of knowledge from large databases.

Acronym	Term	Definition
IC	Informed Consent	An ongoing process that provides the subject with explanations that will help in making educated decisions about whether to begin or continue participating in a trial. Informed consent is an ongoing, interactive process, rather than a onetime information session. NOTE: Under 21 CFR 50.20, no informed consent form may include any "language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence." [ICH] *See also consent form.* [Source: CDISC 12/06]
	Initiation Visit	A type of site visit conducted to verify that all regulatory and other requirements are in place prior to implementing a study.
IRB	Institutional Review Board	An independent body constituted of medical, scientific, and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects. *Synonyms: independent review board, independent ethics committee, committee for the protection of human subjects.* [Source: CDISC 12/06]
ICH	International Conference on Harmonisation	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. [Source: http://www.ich.org/cache/compo/276-254-1.html]
	Investigational Agent	An agent sponsored under an Investigational New Drug Application (IND).
IND	Investigational New Drug Application	An Investigational New Drug Application (IND) is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application. [Source: http://www.fda.gov/cber/ind/ind.htm]

Acronym	Term	Definition
	Investigator	1. A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. 2. The individual "under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team". [1. ICH E6 1.35. 2. from 21CFR 50.3] *See also sponsor-investigator.* [Source: CDISC 12/06]
IB	Investigator's Brochure	A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects. [Source: CDISC 12/06]
	JavaScript	Lightweight scripting language used at client web browsers to perform basic web page validation and processes.
KA	Knowledge Acquisition	The formalized process of collecting information about business organizational processes necessary for developing requirements.
	Lead Organization	The MAH institution holding the funding agreement with the NCI. This is the institution of the Principal Investigator.
LUACG	Lung and Upper Aerodigestive Cancer Group,	This group conducts and supports research on the prevention and early detection of head and neck and lung cancers. Clinical trials and the evaluation of new agents, surrogate biomarkers, and new technologies to identify premalignant lesions are developed and supported. [Source: http://prevention.cancer.gov/programs-resources/groups/luacrg]
	Marketing Application	An application for a new drug submitted under section 505(b) of the act of biologics license application for a biological product submitted under the Public Health Service Act.
	Medical Monitor	A sponsor representative who has medical authority for the evaluation of the safety aspects of a clinical trial. [Source: CDISC 12/06]
	Monitor	Person employed by the sponsor or CRO who is responsible for determining that a trial is being conducted in accordance with the protocol and GCP guidance. NOTE: A monitor's duties may include, but are not limited to, helping to plan and initiate a trial, assessing the conduct of trials, and assisting in data analysis, interpretation, and extrapolation. Monitors work with the clinical research coordinator to check all data and documentation from the trial. [from ICH E6, 5.18] *See also clinical research associate.* [Source: CDISC 12/06]
	Monitoring	The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s). [ICH E6 Glossary] [Source: CDISC 12/06]

Acronym	Term	Definition
NCICBIT	National Cancer Institute Center for Bioinformatics and Information Technology	A center within NCI which provides the interoperable biomedical informatics infrastructure, tools, and data that biomedical communities need for cancer research, prevention and care. [Source: http://ncicb.nci.nih.gov/NCICB/about]
	Oracle® Clinical	A software product of the Oracle® Corporation designed to meet the data management needs of the clinical trials industry.
	Organ System Group	The Organ Systems research groups design, develop, implement, and monitor the breadth of cancer prevention research efforts in four major organ sites: Breast and Gynecological, Gastrointestinal, Lung, Head and Neck, and Prostate and Urological. [Source: http://prevention.cancer.gov/programs-resources/groups]
	Participating Organization	Institutions who by arrangement with the NCI/DCP and the lead organization participate in a clinical trial by accruing patients.
PK	Pharmacokinetics	Study of the processes of bodily absorption, distribution, metabolism, and excretion (ADME) of medicinal products. [Source: CDISC 12/06]
	Placebo	A pharmaceutical preparation that does not contain the investigational agent. In blinded studies, it is generally prepared to be physically indistinguishable from the preparation containing the investigational product. [Source: CDISC 12/06]
PI	Principal Investigator	The individual responsible for the conduct of the study at the clinical center and for ensuring the safety of study participants enrolled at that site (i.e., under whose immediate direction the test agent is administered or dispensed to the study participant). If a team of individuals conducts a trial, the principal investigator is the responsible leader of the team.
PUCRG	Prostate and Urologic Cancer Research Group	This group conducts and supports research on the prevention and early detection of prostate and bladder cancer. Clinical trials and the evaluation of new agents, surrogate biomarkers, and new technologies to identify premalignant lesions are developed and supported. [Source: http://prevention.cancer.gov/programs-resources/groups/pucrg]
	Project Director	An appropriately qualified DCP Monitoring Contractor employee, by training and experience, whose responsibilities include, but are not limited to: monitoring project budgets; allocating staff resources; complying with project goals and objectives; evaluating whether the scope of work is being met; serving as official contact for the client, collaborators, and contractors; preparing project progress reports to deliver to the client on a routine basis; and assuming final responsibility for assuring that all project work is completed accurately, on time, and within budget.

Acronym	Term	Definition
	Project Manager	An appropriately qualified DCP Monitoring Contractor employee, by training or experience, whose responsibilities include, but are not limited to: project goal planning, supervision of staff, and evaluation and assessment of project activities. The project manager's responsibilities may also include conducting on-site monitoring visits.
	Protocol	A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments. NOTE: Present usage can refer to any of three distinct entities: 1) the plan (i.e., content) of a protocol, 2) the protocol document and 3) a series of tests or treatments (as in oncology). [ICH E6 Glossary] [Source: CDISC 12/06]
PIMS	Protocol Information Management System	A component of the DCP Enterprise Knowledgebase System (DESK).
PIO	Protocol Information Office	The central office for all protocol-related information management for DCP sponsored trials. The mission of the PIO is to coordinate all administrative aspects related to clinical trial development to assure that quality protocols are developed in the most expeditious and efficient manner possible. Towards that end, the PIO collects, processes, tracks, and monitors all protocol-related information between DCP, the study site staff, DCP Monitoring Contractor, and the DCP Regulatory Contractor.
QA	Quality Assurance	All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with good clinical practice (GCP) and the applicable regulatory requirement(s). [ICH] [Source: CDISC 12/06]
QOL	Quality of Life	A broad ranging concept that incorporates an individual's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationships to salient features of the environment. NOTE: Quality of Life is one way to measure the benefits or negative impacts of an "improvement" measured in terms of a physiological or psychological symptom. QOL research seeks to quantify what an intervention means to a patient's sense that their life has changed. [WHO Group, 1994] [Source: CDISC 12/06]

Acronym	Term	Definition
	Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias. NOTE: Unequal randomization is used to allocate subjects into groups at a differential rate; for example, three subjects may be assigned to a treatment group for every one assigned to the control group. [ICH E6 1.48] *See also balanced study.* [Source: CDISC 12/06]
	Regulatory Binder	The Regulatory Binder contains all study-specific information and regulatory documentation. This Binder (or series of files) does not include completed CRFs or signed informed consent forms. While the site must keep all original informed consents that have been signed by participants, it is recommended that these be maintained in separate binders or files as directed by the policies of the clinical site. The Regulatory Binder may take the form of file folders, one or more three-ring binders, a filing system, or a combination of these organizational methods. *Synonyms: Study Binder, Investigator Binder, Administrative Binder, Regulatory Files, and Investigator's Study Files*
RDC/RDE	Remote Data Capture/Remote Data Entry	*See electronic data capture.*
SAE/ Serious ADR	Serious Adverse Event/ Serious Adverse Drug Reaction	Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. [ICH] See also adverse experience. [Source: CDISC 12/06]
SAE	Serious Adverse Experience	Any experience that suggests a significant hazard, contra-indication, side effect or precaution. *See also serious adverse event.* [Source: CDISC 12/06]
	Site Coordinator	The responsible person at the clinical site who is the primary contact and ensures that the studies are conducted appropriately. Also called Study Coordinator.
	Sponsor	1. An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial. 2. A corporation or agency whose employees conduct the investigation is considered a sponsor and the employees are considered investigators. [1. ICH. 2. 21 CFR 50.3] [Source: CDISC 12/06]
	Sponsor-investigator	An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. NOTE: The term does not include any person other than an individual (i.e., it does not include a corporation or an agency). The obligations of a sponsor investigator include both those of a sponsor and those of an investigator. [21 CFR 50.3f] [ICH] [Source: CDISC 12/06]

Acronym	Term	Definition
SOPs	Standard Operating Procedures	Detailed, written instructions to achieve uniformity of the performance of a specific function. [ICH] [Source: CDISC 12/06]
	Study Coordinator	*See clinical research coordinator.* [Source: CDISC 12/06]
	Sub-investigator	Any member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows) [ICH] *See also investigator.* [Source: CDISC 12/06]
URL	Uniform Resource Locator	Address of a Web page, actmagazine.com, for example. [Source: CDISC 12/06]
	Visit	A clinical encounter that encompasses planned and unplanned trial interventions, procedures and assessments that may be performed on a subject. A visit has a start and an end, each described with a rule. NOTE: For many domains each visit results in one record per visit. [SDTM, Trial Design Model] [Source: CDISC 12/06]
	Withdrawal	The act of reducing the degree of participation by a subject in a clinical trial. Subjects may withdraw permission for Sponsor use of data derived from study participation, privacy waivers, informed consent, or they may withdraw from the active treatment component of a clinical trial but continue to be observed. Withdrawal from participation in a study is called discontinuation. *See also discontinuation.* [Source: CDISC 12/06]

Appendix C

Form FDA 1572

APPENDIX C. FORM FDA 1572

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)
(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014.
Expiration Date: May 31, 2009.
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

☐ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

FORM FDA 1572 (5/06) PREVIOUS EDITION IS OBSOLETE. **PAGE 1 OF 2**

PSC Graphics (301) 443-1090 EF

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

10. SIGNATURE OF INVESTIGATOR	11. DATE

(**WARNING:** A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-143)
Central Document Room
5901-B Ammendale Road
Beltsville, MD 207052-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address.

FORM FDA 1572 (5/06) **PAGE 2 OF 2**

Appendix D

Protocol Deviation Notification

ATTACHMENT 1
DIVISION OF CANCER PREVENTION
PROTOCOL DEVIATION NOTIFICATION

(REFER TO PAGE 2 FOR SPECIFIC COMPLETION INSTRUCTIONS)

1. Date Protocol Deviation Occurred: __/__/____ (MM/DD/YYYY)	**2. Reported to IRB:** ☐ Yes ☐ No ☐ Not Required	**3. Date DCP Notified:** __/__/____ (MM/DD/YYYY)
4. Participant ID:	**5. Local Protocol No.:**	**6. DCP Protocol #:**
7. Agent(s) Name:	**8. Site Name:**	**9. NCI Institution No.:** (if applicable)
10. Protocol Deviation Description:		
11. Relevant Protocol Section No.: (describe below) **12. Relevant Protocol Section Description:**		
13. Action Taken:		
14. Completed By: _____		**15. Email Address:**
16. Date: __/__/____ (MM/DD/YYYY)		**17. Phone No.:**
18. Principal Investigator:		**19. Principal Investigator Email Address:**
20. By Checking this Box, I Confirm that the Principal Investigator has Reviewed this Form. ☐		**21. Date Principal Investigator Reviewed Form:** __/__/____ (MM/DD/YYYY)
For Medical Monitor Use Only	**22. Protocol Deviation Grade*:**	
	23. Medical Monitor (or designee) Review:	
	24. Medical Monitor (or designee) Name: _____ **25. Date:** __/__/____ (MM/DD/YYYY)	

Revised May 2, 2008

***Protocol Deviation Grade**

0 (Not a deviation) = Mistakenly reported as a deviation

1 (Minor) = No meaningful effect on data integrity and no meaningful risk to participant safety

2 (Moderate) = Potential to affect data integrity or jeopardize participant safety

3 (Major) = Will affect major endpoint data integrity or will have a major impact on participant safety or ethical concerns

DIVISION OF CANCER PREVENTION
PROTOCOL DEVIATION NOTIFICATION INSTRUCTIONS FOR COMPLETION

NOTE: This must be completed by electronically typing into the fillable form. Once completed, save this to your desktop/files.

Question numbers 1-21 are to be completed by the clinical site reporting the deviation.

1.	Date Protocol Deviation Occurred	Record the date the deviation occurred using the MM/DD/YYYY format.
2.	Reported to IRB	Indicate if the Local IRB was alerted of this protocol deviation by checking the Yes or No box. If notification to the IRB for protocol deviations is not a requirement at your institution, check 'Not Required.'
3.	Date DCP Notified	Record the date the Protocol Deviation Notification form was faxed to DCP using the MM/DD/YYYY format.
4.	Participant ID	Record the unique identification number assigned to the participant. This is the number that is used to report the participant's CRF data within the RDC database.
5.	Local Protocol No.	Record the institution-specific protocol number assigned by your institution to identify this protocol.
6.	DCP Protocol #	Record the protocol number assigned by DCP for this specific study. For example: UWI03-1-01
7.	Agent(s) Name	Record the name of the study agent(s) for the specific protocol.
8.	Site Name	Record the name of the institution where the protocol deviation occurred.
9.	NCI Institution No. (if applicable)	Record the NCI institution code, if applicable, for the site at which the deviation occurred. If the NCI institution code is unknown, this field may be left blank.
10.	Protocol Deviation Description	Record a description of the deviation which includes reasons and contributing factors.
11.	Relevant Protocol Section No.	Record the specific section number from the protocol that is related to the deviation.
12.	Relevant Protocol Section Description	Describe the relevant protocol section (referenced in number 11) that has been deviated. This description can be copied verbatim from the protocol document or a brief description can be written that summarizes the appropriate section of the protocol.
13.	Action Taken	Describe the action taken to minimize harm to the participant, maintain data integrity and prevent reoccurrence.
14.	Completed By	Record the name of the staff member completing this form at the site.
15.	Email Address	Include a current email address.
16.	Date	Record the date the form was completed using the MM/DD/YYYY format.
17.	Phone No.	Include a current phone number.
18.	Principal Investigator	Record the name of the Principal Investigator at the clinical site where the deviation occurred.
19.	PI Email Address	Include the Principal Investigator's current email address.
20.	By Checking this Box, I Confirm that the Principal Investigator has Reviewed this Form.	Record confirmation that the Principal Investigator has reviewed the protocol deviation before it is provided to DCP.
21.	Date Principal Investigator Reviewed Form	Include the date of the Principal Investigator review using the MM/DD/YYYY format.

Question numbers 22-25 are to be completed by the DCP Medical Monitor (or designee).

22.	Protocol Deviation Grade	Assign a protocol deviation grade (0-3) using the following scale: 0 (Not a deviation) = Mistakenly reported as a deviation 1 (Minor) = No meaningful effect on data integrity and no meaningful risk to participant safety 2 (Moderate) = Potential to affect data integrity or jeopardize participant safety 3 (Major) = Will affect major endpoint data integrity or will have a major impact on participant safety or ethical concerns
23.	Medical Monitor (or designee) Review	Review the action plan to determine if appropriate action has been taken or has been planned to minimize participant harm, maintain data integrity and prevent reoccurrence. Record any additional comments, instructions or suggestions.
24.	Medical Monitor (or designee) Name	Record the name of the Medical Monitor (or designee).
25.	Date	Record the date using the MM/DD/YYYY format.

Appendix E

Serious Adverse Event Form

NCI Contract/Grant No._____
IRB Protocol No. _____

NCI, DIVISION OF CANCER PREVENTION (DCP)
SERIOUS ADVERSE EVENT FORM

REQUIRED FIELDS ON ALL REPORTS

Today's Date:	Sponsor: NCI, DCP	Study (Indication):
Drug(s) under Investigation:	IND No.:	

A. Study Subject Information

1. Study Participant # or PID #	2. Year of Birth: _____	3. Weight at Time of Event: _____ [ ] kg [ ] lbs. [ ] not available	4. Height at Time of Event: _____ [ ] cm [ ] ft [ ] not available

B. Event Information

[ ] Initial Event Report [ ] Follow-up	Gender: (circle one) M F	Dose at Event:
Event Onset Date: (Month/Day/Year)	Primary Event (diagnosis):	
Event Approx. Time: (Indicate A.M./P.M.)		
Event Occurred at:		
Duration of Drug Exposure at Event:	Primary Treatment Approx. Time (A.M./P.M.): Primary Treatment of Event:	
Attending Physician (Name): Phone/FAX No.: Hospital/Clinic: Address:		
Describe Event (if applicable, include dates of hospitalization for event):		
Form Completed by: (Print Name) _____ Title_____ Investigator Signature _____ Date _____ Phone No. _____ (Month/Day/Year)		

SAE Form Revised: 8/09/2006

ALL FIELDS APPEARING IN THE FOLLOWING PAGES (C-F) MUST BE COMPLETED FOR THE INITIAL REPORT; THEREAFTER, FILL IN ONLY SECTIONS THAT PROVIDE ADDITIONAL/ CORRECTIVE INFORMATION.

C. Site information

1. Investigator Name

2. Address

D. Suspect Medication(s)

1. Study Design: [ ] Blind [ ] Open/Unblind

Possible Dose (*e.g.,* 300 mg) _____ Frequency (*e.g.,* qd) _____ Route (*e.g.*, po)_____

2. Study Drug

Formulation (*e.g.,* tablet, solution)

Lot No. (If known)

3. Start Date of Study Drug (Month/Day/Year):

4. Was blind broken due to event? [ ] No [ ] Yes [ ] NA

5. Was Study Drug stopped/interrupted/reduced in response to event? [ ] No [ ] Yes

>> If yes, complete a-e:

a. If stopped, specify date study drug last taken: _____ [ ] NA
(Month/Day/Year)

b. If reduced, specify: New dose _____ Date reduced _____ [ ] NA
(Month/Day/Year)

c. If interrupted, specify total number of days not given: _____ [ ] NA

d. Did event abate after study drug was stopped or dose reduced? [ ] NA [ ] Yes [ ] No

e. Did event reappear after study drug was reintroduced? [ ] NA [ ] Yes [ ] No

6. Was patient taking any other medications concomitantly at the time of the event?[ ] No [ ] Yes >> If yes, complete below.
(DO NOT LIST DRUGS USED TO TREAT EVENT)

Drug Name Doses (units, frequency, route, indication for use)	Start Date			Stop Date or mark (X) if continuing			
	Month	Day	Year	Month	Day	Year	(X)

(continue on a separate sheet if necessary)

SAE Form Revised: 8/09/2006

E. Adverse Event

1. Relevant Laboratory/Diagnostic Tests [ ] No tests performed

Date	Test	Results	
		Actual Value	Normal Range
Month Day Year			

(continue on a separate sheet if necessary)

2. Relevant Medical History, including preexisting conditions (*e.g.,* allergies, pregnancy, smoking & alcohol use, hepatic/renal dysfunction, medical/surgical history, *etc.*)

Date (if known)	Diseases/Surgeries/Treatment

(continue on a separate sheet if necessary)

3. **NCI Toxicity GRADE of the Event** (use NCI Common Toxicity Criteria): [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5
   If not gradable by NCI CTC, check one of the following: [ ] Mild [ ] Moderate [ ] Severe [ ] Life-threatening [ ] Fatal

4. Why Serious?
   [ ] Results in death [ ] Is life-threatening [ ] Requires inpatient hospitalization or prolongation of existing hospitalization
   [ ] Results in persistent or significant disability/incapacity [ ] Is a congenital anomaly/birth defect
   [ ] Other, specify:_____

5. Outcome of Event (at time of report)

   [ ] Resolved-date: _____ [ ] Improved [ ] Unchanged [ ] Worse [ ] Not available
   (Month/Day/Year)
   [ ] Fatal-date of death: _____ Autopsy performed? Y N
   (Month/Day/Year) (circle one)
   Cause of death: _____ (please attach death certificate and autopsy report, if applicable)

6. Investigator's opinion of the relationship between the event and the study drug (If more than one event is being reported, list secondary events and corresponding relationship to study drug in the comments section below.) Check applicable box:

   [ ] Not related [ ] Unlikely [ ] Possible [ ] Probable [ ] Definite

7. Was this event reported by the Investigator to (check all that apply): [ ] IRB [ ] Manufacturer/Distributor
   [ ] Other Investigators participating in this study, if checked, please list names and institutions

_____
_____
_____
_____

SAE Form Revised: 8/09/2006

NCI Contract/Grant No._____
IRB Protocol No. _____

F. Comments/Clarifications:

FOR NCI USE ONLY
1. Date NCI notified of event (Month/Day/Year): _____
2. Medical Monitor Review: Medical Assessment of Event (including drug relationship and expectancy): Is this an FDA reportable (7 calendar days) event? [ ] Yes [ ] No Is this an FDA reportable (15 calendar days) event? [ ] Yes [ ] No >> If No, specify reason:_____ Is more information expected? [ ] Yes [ ] No >> If Yes, specify:_____ Is this event to be communicated to other NCI contractors using this investigational drug? [ ] Yes [ ] No >> If Yes, how? By telephone (attach a TC Form): [ ] Yes, attached TC Form [ ] No Other (FAX, mail, e-mail, *etc.*): [ ] Yes, attached a copy of the correspondence [ ] No Medical Monitor: Print name _____ Signature _____ Date _____

SAE Form Revised: 8/09/2006

Appendix F

Initiation Visit Report Form

DCP PROJECT
CLINICAL INITIATION VISIT REPORT

I. SITE INFORMATION

Instructions: Please provide the requested information for each of the items listed below. Provide comments whenever necessary or helpful.

Name of Clinical Site:

Protocol Name:

NCI Protocol Number:

Date(s) of Visit:

Conducted by:

DCP Representative(s) Present:

Clinical Site Personnel Present at the Visit:

NAME	TITLE	ORGANIZATION	PRESENT AT MEETING
	Principal Investigator		
	Site Coordinator		
	Pharmacist		
	Other		

Additional Comments:

CLINICAL INITIATION VISIT CHECKLIST

ITEMS VERIFIED and/or DISCUSSED	Y	N	NA	COMMENTS
Background and Purpose of Study				
Study Objectives and Design				
Study Procedures				
Clinical Evaluations				

ITEMS VERIFIED and/or DISCUSSED	Y	N	NA	COMMENTS
Laboratory Evaluations				
Schedule of Evaluations				
Implications of Missed Evaluations				
Protocol Deviations/Violations				
Toxicity Management				
Protocol Initiation and Enrollment				
Informed Consent Process				
Screening/Pre-Entry Period				
Exemptions				
Registration/Randomization				
Recruitment/Retention				
Anticipated Start of Enrollment				
Staff Roles and Responsibilities				
Source Documentation				
Study Drug Prescriptions				
Agent Dispensing Procedures				
Informed Consent				
CRF Completion				
Specimen Storage				
Registration/Randomization				
Regulatory Update				
Blinding Procedures				
Quarterly Report Preparation				
DCP OC-RDC Data Entry and Management (Consortia trials only)				
Agent Information and SAE Reporting				
Procedures and Forms				
Receipt, Review, and Filing of Investigator's Brochure				
Receipt, Review, and Filing of Package Insert				
Receipt, Review, and Filing of any Safety Reports				
Off-Treatment and Study Endpoints				
Evaluations for Treatment/Study Discontinuation				
Study Endpoints				
Data Collection				
Procedures				
CRF Completion Guidelines				
Common Errors Noted in Data Collection				
Corrections				
Form Update Procedures				

ITEMS VERIFIED and/or DISCUSSED	Y	N	NA	COMMENTS
Plans for Missed Visits				
Disposition of Forms				
NCI CTC Version				
Source Documentation				
What Is Acceptable				
Shadow Files				
Electronic Sources				
Case Report Forms as Source Documents				
Document Retention				
Database Management				
DCP OC-RDC (Consortia trials only)				
Other Data Management System(s) to be Used				
Quality Assurance Procedures				
Data Queries and/or Discrepancy Management				
List of Staff who will perform data entry and QA (MAH trials only)				
List of Staff who have been approved for data entry, QA, and monitoring in DCP OC-RDC (Consortia trials only)				
Policy and Procedure Manuals				
DCP Study Site Monitoring Manual (MAH trials only)				
Clinical Trials Resource (CTR) Website				
DCP SOPs (Consortia trials only)				
MIMP (Consortia trials only)				
Master DMP (Consortia trials only)				
Other (list under comments)				
Regulatory Documentation Review				
Site Signature/Delegation of Responsibilities form				
IRB/IEC Documentation				
IRB/IEC - Approval Letter				
IRB/IEC-Approved Informed Consent Form				
IRB/IEC-Approved Advertisements				
IRB/IEC-Approved Participant Information Sheets				
IRB/IEC-Annual Renewal				
Amendments				

ITEMS VERIFIED and/or DISCUSSED	Y	N	NA	COMMENTS
Assurance Number				
Form 1572				
Investigator CVs, signed and dated				
Current medical licenses				
Documentation of Human Participants Protection Training				
Financial Disclosure Form				
Laboratory Certification				
Laboratory Normal Ranges				
DHHS and FDA Regulations/GCP Guidelines				
Documentation of IRB/IEC Submission of Investigator's Brochures				
Documentation of IRB/IEC Submission of Package Inserts				
Documentation of IRB/IEC Submission of Safety Reports				
Submission of Data Safety and Monitoring Plans				
DCP Reporting Requirements				
Amendments				
Adverse Events Reporting Using NCI CTCAE v.3.0				
SAE Reporting				
Case Report Forms				
Progress Reports				
Final Reports				
Protocol Deviations Form and Reporting				
Record Keeping Requirements				
Participant Screening Log				
Participant Identification Logbook				
Site Signature/Delegation of Responsibilities form				
Site Visit Log				
Original Signed Informed Consent Forms				
Source Documents/Confidentiality				
Study-Related Correspondence (including study related e-mails and records of phone conversations)				
Laboratory Procedures				
Specimen Storage and Disposition				

ITEMS VERIFIED and/or DISCUSSED	Y	N	NA	COMMENTS
Shipping Procedures				
Specimen Shipping Log				
Specimen Collection, Processing and Storage				
Pharmacy				
Dissemination of Information to the Pharmacist				
Drug Storage & Accountability				
Pharmacy Guidelines				
Current Protocol Version				
Documentation of Informed Consents				
Investigator's Brochures– Pharmacy Receipt				
Safety Reports– Pharmacy Receipt				
Package Inserts– Pharmacy Receipt				
Communication				
Quality Assurance Plan				
Communication				
With DCP Staff				
With Participating Sites				
With Monitoring Contractor				
With Regulatory Contractor				
Site Monitoring and Auditing				
Purpose				
Frequency				
Reports and Distribution				
Site Monitoring at Participating Sites (by Lead Site)				
Conduct of Pharmacy Audit				
Conduct of Quality Assurance Audit (Consortia trials only)				

ACTION ITEMS IDENTIFIED:

ADDITIONAL COMMENTS/GENERAL IMPRESSIONS OF SITE PERFORMANCE:

Prepared by: Date:

(Signature)

Appendix G

Annual Visit Report Form

DCP PROJECT
PRELIMINARY REPORT OF MONITORING FINDINGS

Name of Clinical Site:	Date(s) of Site Visit:
Principal Investigator:	Westat Team Monitor:
NCI Protocol Number:	DCP Representative(s) Present:

Instructions: For the following categories, indicate the final assessment for each of the 3 components of the monitoring visit.

1. Assessing the IRB and Informed Consent Findings:

_____ **Acceptable:** No deficiencies identified.
Few minor deficiencies identified.
Major deficiencies identified during the site visit that were addressed and/or corrected prior to the site visit for which documentation exists and no further action is required.

_____ **Acceptable, Follow-up:** Multiple minor deficiencies identified.
Major deficiencies identified during the site visit, but not corrected and/or addressed prior to the site visit.

_____ **Unacceptable:** Multiple major deficiencies identified.
A single major flagrant deficiency found.
Excessive numbers of minor deficiencies found.

2. Assessing the Accountability of Investigational Agents and Pharmacy Operations:

_____**Acceptable:** Compliance found for security, drug accountability record forms completed correctly, protocol and drug-specific usage and/or return of study drug in DCP repository.
Non-compliant items identified during the site visit that were addressed and/or corrected prior to the site visit for which documentation exists and no further action is required.

_____ **Acceptable, Follow-up** Category found non-compliant during the site visit which was not corrected and/or addressed prior to the site visit.

_____**Unacceptable:** Inability to track the disposition of NCI/DCP supplied investigational agents.
Multiple non-compliant categories identified.

3. Review of Participant Records:

_____**Acceptable:** No deficiencies identified.
Few minor deficiencies identified.
Major deficiencies identified during the site visit that were addressed and/or corrected prior to the site visit for which documentation exists and no further action is required.

_____**Acceptable, Follow-up:** Multiple minor deficiencies identified.
Major deficiencies identified during the site visit, but not corrected and/or addressed prior to the site visit.

_____Unacceptable: Multiple major deficiencies identified.
A single major flagrant deficiency found.
Multiple minor deficiencies of a recurring nature found in a majority of the participant cases reviewed.

REPORTING DEFICIENCIES

Directions: For each participant chart reviewed, record the total number of deficiencies (major or lesser) for each category. If there were no major or lesser deficiencies identified for a particular category, record a zero (0) in the appropriate cell.

Number of participant cases reviewed: _____

Comments:

DEFICIENCY CATEGORY	MAJOR	LESSER	COMMENTS
Disease Outcome			
Eligibility			
General Data Quality			
IRB			
Informed Consent			
Pharmacy			
Toxicity			
Treatment			
Total			

DCP PROJECT

CLINICAL SITE ANNUAL (INTERIM) VISIT REPORT

SITE INFORMATION

Instructions: Please provide the requested information for each of the items listed below. Provide comments whenever necessary or helpful.

Name of Clinical Site:

Protocol Name:

NCI Protocol Number:

Date(s) of Visit:

Conducted by:

DCP Representative(s) Present:

Clinical Site Personnel Present at the Visit:

NAME	TITLE	PRESENT AT DEBRIEFING (Y/N)
	Principal Investigator	
	Site Coordinator	
	Pharmacist	
	Other	

Additional Comments:

REGULATORY REVIEW

Instructions: Please provide the requested information for each of the items listed below ("Y" = Yes, "N" = No, "N/A" = Not applicable). Please provide comments whenever necessary or helpful.

DOCUMENTS AND STORAGE	Y	N	N/A	COMMENTS
1. Copy of the protocol and all pertinent amendments on file				
2. Initial IRB/IEC approval of protocol				
3. IRB/IEC approval of most recent protocol amendments				
4. Annual IRB/IEC renewal of protocol				
5. IRB/approved consent form and all form revisions on file				
6. Adverse Event Safety reports submitted to IRB/IEC				
7. Serious Adverse Event reports submitted to CCSA				
8. Copy of one of the following IRB/IEC compliance documents: IRB/IEC roster, DHHS Number, or Assurance Number				
9. Research records stored in a secure area				
10. Form FDA 1572 current				
11. Laboratory certification up to date				
12. Copy of normal range values for each laboratory used				
13. Investigator's Brochure(s) on file and securely stored				
14. Site Monitoring Visit log up to date				
15. Site Signature/Delegation of Responsibilities form up to date				
16. DCP approval on file of all protocol versions				
17. Supporting documentation including Medical Licenses and CVs current				
18. Training Logs available listing Human Subject Protection Training for all staff listed on the site signature/delegation of responsibilities form				

Additional comments:

RECORD REVIEW AND SUMMARY

Instructions: Write the patient identification number for each chart reviewed in column one. Record the visit week to begin review for a specific patient in the second column. Record the last visit reviewed for the specific patient in the third column. In the summary table, provide the requested information for each of the items listed ("Y" = Yes, "N" = No). Please provide comments whenever helpful or necessary.

Total # of Charts Reviewed: _____

Participant(s) REVIEWED (ID #)	BEGAN REVIEW (AT WEEK)	TO VISIT (INCLUSIVE)

SUMMARY OF FINDINGS FOR SITE MONITORED CASES	Y	N	N/A	COMMENTS
1. 100% of informed consents appropriately obtained and documented				As Of :____/____/____
2. Participant eligibility verified				
3. Source documentation adequate				
4. Adverse Events (including SAEs) appropriately documented and reported				
5. Endpoints correctly reported				
6. Clinical events (e.g., change in patient status, concurrent illness) and concomitant meds recorded on CRFs				
7. Clinical and laboratory evaluations obtained as per protocol				
8. Laboratory samples correctly collected and shipped/stored/evaluated				
9. Source documents and CRFs indicate compliance with protocol treatment and blinding procedure, if applicable				
10. Protocol deviations noted and reported as needed				
11. DCP OC-RDC data recorded accurately when compared to source documents and CRF entries				

Additional comments:

SITE OPERATIONS ASSESSMENT

Instructions: Please provide the requested information for each of the items listed below ("Y" = Yes, "N" = No, "N/A" = Not applicable). Please provide comments whenever necessary or helpful.

ITEMS EVALUATED	Y	N	N/A	COMMENTS
1. Adequate resources (e.g., facilities, staffing)				
2. Internal quality assurance activities				
3. Participant accrual and retention				
4. Database for study-specific procedures				
5. RDC training records for all staff entering or reviewing study data in DCP OC-RDC				

Additional comments:

STATUS OF PAST FINDINGS: (Have corrections been made to errors that were identified previously?)

DISCUSSION OF CURRENT FINDINGS WITH STAFF: (Include problems identified, if any, and recommendations/action items for corrections.)

TRAINING CONDUCTED DURING VISIT: (Include training performed and names of site personnel present at the time of the training.)

DISCUSSION OF MONITORING ACTIVITIES AT PARTICIPATING SITES: (Include problems identified, if any, and recommendations/action items for corrections.)

ADDITIONAL COMMENTS/IMPRESSIONS OF SITE PERFORMANCE:

Prepared by: Date:

(Signature)

Appendix H

Close-out Visit Report Form

DCP PROJECT

CLINICAL SITE CLOSE OUT VISIT CHECKLIST

I. SITE INFORMATION

Instructions: Please provide the requested information for each of the items listed below. Provide comments whenever necessary or helpful.

Name of Clinical Site:

Protocol Name:

NCI Protocol Number:

Date(s) of Visit:

Conducted by:

DCP Representative Present:

Clinical Site Personnel Involved with the Study:

NAME	TITLE	AVAILABLE DURING DISCUSSIONS (Y/N)
	Principal Investigator	
	Site Coordinator	
	Pharmacist	
	Other	

Additional Comments:

II. CLOSE-OUT REVIEW

Instructions: Please provide the requested information for each of the items listed below ("Y" = Yes, "N" = No). Please provide comments whenever necessary or helpful.

OBJECTIVE	Y	N	N/A	COMMENTS
1. Assure that all case report forms for each subject have been completed				
2. Verify that all data have been keyed on-site or all forms have been submitted to the coordinating center. If they have not, discuss the timeline for accomplishing this and document in the comments				
3. Review the status of all outstanding data edits, queries, or delinquent forms and timeline for their resolution				
4. Verify that a signed, informed consent is on file for each study participant				
5. Confirm that the IRB/IEC has been informed of the study closure				
6. Verify that all regulatory and other pertinent documents for the protocol (IRB approvals, consent documents, etc.) are up to date and on file				
7. Assure that a progress note is included in each participant's medical record indicating that study participant has ended				
8. Verify that the investigator has plans to submit the final report to DCP, and that a deadline for completion has been identified				
9. Assure that the principal investigator understands the requirements for reporting of adverse events for subjects who have completed study				
10. Assure that the principal investigator and study coordinator have received and understand the requirements for retention of study records				
11. Assure that all unused and returned study drug has been returned to the repository				
12. Assure that all participant specimens have been shipped according to client specifications				
13. Assure that all required drug accountability has been reconciled and forms have been completed appropriately				
14. Determine the disposition of participant specimens, including plans for future				

shipments or period of time they will be stored on site				
15. If blinded study drug 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				

Additional comments:

Prepared by: Date:

(Signature)

Appendix I

Pharmacy Audit Report Form

DCP PROJECT

PHARMACY AUDIT REPORT

I. SITE INFORMATION

Instructions: Please provide the requested information for each of the items listed below. Provide comments whenever necessary or helpful.

Name of Clinical Site:

Protocol Name:

NCI Protocol Number:

Name and Address of Pharmacy:

Date of Audit:

Conducted by:

Investigational Pharmacy Personnel:

NAME	TITLE	MET WITH MONITOR (Y/N)
	Pharmacist of Record	
	Other Staff / Title	

Additional Comments:

II. MAINTENANCE OF RECORDS

Instructions: Please provide the requested information for each of the items listed below ("Y" = Yes, "N" = No). Please provide comments whenever necessary or helpful.

ITEMS VERIFIED and/or DISCUSSED	Y	N	*NA	COMMENTS
A. Are the following protocol-specific documents present?				
1. FDA Form 1572				
2. Prescriber signature list				
3. Most recent version of the protocol for which the site has IRB approval				
4. Participant study assignment list				
5. Drug ordering instructions				
B. Are the following records accessible only to the site pharmacist or his/her designee?				
1. Study assignment lists				
2. Investigational agent accountability/inventory records				
3. Order forms/shipping receipts				
4. Participant-specific profiles, if used				

III. SECURITY AND STORAGE OF THE INVESTIGATIONAL DRUGS

ITEMS VERIFIED and/or DISCUSSED	Y	N	*NA	COMMENTS
A. Inspect the investigational drug storage area.				
1. Are the investigational drugs stored according to the manufacturer's specifications?				
2. Are supplies sufficient?				
3. Outdated drugs are not stored together with the active drug supply.				
4. Is refrigerator and/or freezer storage available?				
a. If yes, describe location of refrigerator and/or freezer and method of monitoring temperature				
5. Is study drug stored in a secure, limited access area?				

IV. DRUG ACCOUNTABILITY, PREPARATION AND DISPENSATION

ITEMS VERIFIED and/or DISCUSSED	Y	N	*NA	COMMENTS
A. Accountability				
1. Do the increases in drug inventory on the investigational accountability records agree with the shipment receipts?				
2. Are the accountability records legible and complete with each entry initialed by the pharmacists of record or other authorized personnel?				
3. Are there any entries in the accountability records that indicate dispensing of investigational agents to persons other than participants enrolled in this/these studies?				
4. If study drug is commercially available, are procedures in place to assure that study drug is not stored together with the general supply?				
5. Does the inventory balance documented on the accountability record correspond precisely with the actual physical inventory?				
a. If No, provide actual numbers of the agent counted as well as the amount recorded on the accountability record for each discrepancy noted				

Drug	Accountability Record	Inventory Amount

Explanation/Discussion				
6. Is the amount of drug supply on hand reasonable based on current enrollment and accrual rate?				

IV. DRUG ACCOUNTABILITY, PREPARATION AND DISPENSATION (continued)

ITEMS VERIFIED and/or DISCUSSED	Y	N	*NA	COMMENTS
B. Drug Preparation and Dispensing				
1. Describe the routine procedure for dispensing study drugs.				
a. When, in relation to the participant study visit, is the study drug prepared? Describe:				
b. How does the investigational pharmacist usually receive study drug prescriptions? Describe:				
c. To whom does the investigational pharmacist dispense study drugs? Describe:				

Additional Comments:

_____

_____

_____

_____

Prepared by: Date:

(Signature)

Appendix J

Essential Documents for the Conduct of a Clinical Trial

June 2008

APPENDIX J.

ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

Essential documents are those documents that individually and collectively evaluate the conduct of a trial and the quality of the data produced. These documents demonstrate the compliance of the investigator and sponsor with the standards of Good Clinical Practice (GCP) and all applicable regulatory requirements. Note: The ICH Guidelines have been adopted by the FDA as guidances, not regulations.

The Office of Human Research Protection (OHRP) and Health and Human Services (HHS) regulations (45 CFR 46) and Good Clinical Practice recommendations apply for all trials that receive funding from a Health and Human Service agency. Trials with a Food and Drug Administration (FDA) Investigational Drug Application (IND) must additionally comply with 21CFR regulations.

Document	Purpose	File	Regulation/Reference
Assurance Number	The institution is responsible for obtaining and maintaining a current Health and Human Services (HHS) Assurance Number through the Office of Human Research Protection (OHRP) ▪ The Principal Investigator (PI) is responsible for ensuring that a current Assurance Number is in effect while conducting research on human subjects ▪ All performance sites must maintain the Assurance Number on file and obtain renewal prior to expiration	In a Regulatory Binder at the site A copy of the Assurance Number must be on file with the sponsor	45 CFR 46 45 CFR 46.103(a)
Auditing Reports	1. Document audit visits and findings of the auditor 2. Copies of all audit visit reports are filed at the site and sent to the sponsor	In the Regulatory Binder at the site	ICH Guidance: E6 Good Clinical Practice: Section 5.19.3
Case Report Form	1. Signed, dated, and completed Case Report Forms (CRFs): ▪ Document that the investigator or authorized member of the investigator's staff confirms the observations recorded ▪ Document all changes/additions or corrections made to CRF after initial data were recorded 2. Site retains copy 3. Originals retained by sponsor after study completion and/or site closure	In the patient's research record at the site	21 CFR 312 ICH Guidance: E6 Good Clinical Practice: Sections 8.3.14 8.3.15

Document	Purpose	File	Regulation/Reference
Communications	1. Document all relevant communications other than site visits, for example: ▪ Letters ▪ Meeting Notes ▪ Notes of Telephone Calls ▪ E-Mail Messages	In the appropriate Regulatory Binder or patient's	ICH Guidance: E6 Good Clinical Practice: Section 8.3.11
Communications (continued)	2. Subject specific communications must be filed with source documents in the subject's research record 3. Document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting, etc. 4. Save electronic media, originals, and/or certified copies	Research record at the site	
Consent Form	1. Obtain signed informed consent forms in accordance with the protocol for each prospective subject. The form must be dated prior to participation of each subject in a trial 2. Save all versions submitted and approved by site's institutional review board (IRB) 3. Document revisions of the trial-related documents that take effect during the trial; save any revisions to: ▪ Informed Consent ▪ Re-consent the participant when pertinent and retain the Informed Consent ▪ Any other written information provided to the subjects 4. Retain consents obtained for screening purposes even if the subject was not enrolled in the study 5. Non-English speaking subjects must be consented in a language they can understand Note: Annual Review and/or changes in consent forms due to AEs and/or Safety Memos are at the directive of the site's IRB	IRB approved copies in the Regulatory Binder at the site and signed consents in the participant's research record or in the Regulatory Binder at the site	45 CFR 46.111(a)(4) 21 CFR 50 21 CFR 56.111(a) (4) ICH Guidance: E6 Good Clinical Practice: Sections 8.3.12 8.2.3 8. 3.2
Curriculum Vitae	1. Document the qualifications and eligibility of the investigator(s) subinvestigator(s), and other key personnel to conduct a trial and/or to provide medical supervision of subjects 2. Available for all investigators, subinvestigators, any other person listed on Form FDA 1572, and other key personnel at the site 3. Every two years throughout the course of the study, submit updated/revised investigator(s) and subinvestigator(s) CV to the DCP Regulatory Contractor	In the Regulatory Binder at the site	ICH Guidance: E6 Good Clinical Practice: Sections 8.2.10 8.3.5

Document	Purpose	File	Regulation/Reference
FDA 1572 Form	1. Document that the Investigator of Record (IoR) (i.e., Principal Investigator or PI) agrees to conduct the trial according to the obligations stated in the form 2. Update as study personnel and/or other data on the form changes 3. The original version and any updated form must be retained as per regulatory requirements 4. The Investigator in box 1 of Form FDA 1572 is the individual who must sign and date the signature box 5. Only laboratories specified in the protocol need to be listed in Section 4 to address the following: ▪ Research /academic labs do not need to be listed on Form FDA 1572 ▪ Research /academic labs should be listed in the protocol ▪ Central lab should be listed in the protocol for multi-center study protocol ▪ List individual clinical labs as in the protocol, unless it is a large multi-center study and it would be impractical to list labs for every site 6. Section 6 must list any individual: ▪ Responsible for conducting/ performing study visits ▪ Authorized to prescribe study medication This may include but is not limited to the following: ▪ MDs ▪ Pharmacist of Record ▪ Nurse Practitioner ▪ Physician's Assistant ▪ Research Nurse If there are no individuals that need to be listed, then write "NONE"	In the Regulatory Binder at the site	21 CFR 312
Final Closeout Monitoring Report	Final report by investigator is sent to the IRB where required and, where applicable, to the regulatory authorities, to document completion of the trial. Included is the following information: ▪ Disposition of the subjects ▪ Location of the research records ▪ Disposition of the specimens ▪ Disposition of the study drugs ▪ Other information as required by the institution or local IRB (e.g., number of patients screened, number enrolled, serious adverse experiences)	In the Regulatory Binder at the site	ICH Guidance: E6 Good Clinical Practice: Sections 4.13 8.4.5 8.4.7

Document	Purpose	File	Regulation/Reference
Financial Disclosure	1. Document the financial aspects of the trial and the financial agreement between the investigator/institution and the sponsor for the trial 2. All investigators at active sites of accrual to MAH studies will submit Form 3455 as part of the essential regulatory document package 3. Certification or disclosure statement to: ▪ Certify that there is no financial interest or ▪ Disclose specific financial interests of Investigators and subinvestigators listed on Form FDA 1572, as well as their spouses and dependent children 3. Local institution/IRB and/or Group SOPs may have additional requirements	In the Regulatory Binder at the site	ICH Guidance: E6 Good Clinical Practice: Section 8.2.4 21 CFR 54
Investigational Drug Brochures (IDBs) and Safety Package Inserts	1. Document that relevant and current scientific information about the investigational product has been provided to the investigator 2. Include updates to document that investigator is informed in a timely manner of relevant information as it becomes available 3. Keep a copy on file for EACH study medication used within the protocol 4. Include the following: ▪ The most recent version ▪ Addendum to IDBs ▪ Safety letters 5. Some IDBs must be shredded per protocol/sponsor. Some studies require that a historical trail of IDBs and their individual IRB letters of acknowledgement be retained	In the Regulatory Binder at the site and in the pharmacy	ICH Guidance: E6 Good Clinical Practice: Sections 8.2.1 8.3.1
Investigational Product/Study Drug Accountability	1. The Pharmacist of Record must keep records to account for the disposition of investigational products/study drugs by documenting the following: ▪ Shipment dates ▪ Batch number 2. Document tracking of: ▪ Product batch ▪ Review of shipping conditions ▪ Accountability 3. Document that the investigational products have been used according to the protocol 4. Document the final accounting of investigational products: ▪ Received at the site ▪ Dispensed to subjects ▪ Returned by the subjects ▪ Returned to the sponsor ▪ Destroyed by the site	In the pharmacy records at the site	ICH Guidance: E6 Good Clinical Practice: Sections 8.2.15 8.3.8 8.3.23 8.4.1

Document	Purpose	File	Regulation/Reference
IRB/IEC Correspondence	1. Copies of all materials submitted to the IRB/IEC with dated proof of submission and IRB/IEC approval (when appropriate) for the following: ■ Advertisements: document that recruitment measures are appropriate and not coercive ■ All versions of consent forms ■ All protocols and amendments ■ Annual reports to the IRB/IEC ■ IND safety reports/Adverse Event Report ■ Initial protocol submission ■ Investigational drug brochure or safety package inserts ■ Protocol specific education material ■ Subject compensation ■ Any other documents receiving IRB/IEC approval or their favorable opinion ■ Any other written information to be provided to subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent ■ Any other pertinent communications with the IRB/IEC	In the Regulatory Binder at the site	45 CFR 46 21 CFR 50 21 CFR 56 ICH Guidance: E6 Good Clinical Practice: Sections 3.1.4 4.10 5.17.3 8.2.3 8.2.7 8.3.2 8.3.3 8.3.19
Laboratory	1. Document competence of facility to perform required tests, and support reliability of results of medical/laboratory/technical procedures/tests: ■ Certification or Accreditation. If no certification or accreditation is available, add a "Note-to-File" documenting that the lab does not hold certification or accreditation ■ Update when certifications expire or laboratory changes to document that tests remain adequate throughout the trial period ■ Established quality control and/or external quality assessment 2. Document normal values/ranges (if applicable as they may not be available for research/academic labs) for medical/laboratory/technical procedures/tests included in the protocol 3. Update documentation of normal values/ranges when they are revised during the trial 4. The reference ranges and certifications must be on file for the following listings: ■ Local or central laboratories that analyze specimens for the study ■ Any group central laboratory	In the Regulatory Binder at the site	ICH Guidance: E6 Good Clinical Practice: Sections 8.2.11 8.2.12 8.3.6 8.3.7

Document	Purpose	File	Regulation/Reference
Screening and Enrollment Randomization Logs	1. Document identification of subjects who entered pretrial screening 2. Document chronological enrollment of subjects by number 3. Screening and enrollment/ randomization logs may be separate or combined 4. Include the following information: ▪ Initials of all patients screened for each study ▪ Participant identification number ▪ Date screened ▪ Date randomized ▪ If not randomized, indicate reason	In the screening files or protocol files at the site	ICH Guidance: E6 Good Clinical Practice: Sections 8.3.21 8.4.3
Subject Identification Code List	1. Document that the investigator keeps a confidential list of names of all subjects allocated to trial numbers upon enrolling in a trial 2. Allows investigator/institution to permit identification of all subjects enrolled in the trial in case follow-up is required 3. List needs to be kept in a confidential manner and for agreed upon time	In the protocol file at site	ICH Guidance: E6 Good Clinical Practice: Sections 8.3.21 8.4.3
Serious Adverse Events (SAE)	1. Notification by originating investigator to sponsor of Serious Adverse Events, related reports, and other safety information 2. Notification by sponsor to investigators of safety information 3. Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB of unexpected serious adverse drug reactions and of other safety information	In Regulatory File at site	45 CFR 46 21 CFR 50 21 CFR 56 21 CFR 312 ICH Guidance: E6 Good Clinical Practice: Sections 4.11 5.16.2 5.17 8.3.16 8.3.17 8.3.18

Document	Purpose	File	Regulation/Reference
Delegation of Responsibilities/ Activities Form	1. This form includes a list of individuals who are delegated study-related tasks (ICH GCP 4.1.5). The form must contain the signatures and initials of all study personnel, including those making entries or corrections on the case report forms, (ICH GCP 8.3.24) as well as all ancillary study personnel (e.g., laboratory personnel, data personnel, and pharmacy personnel) 2. The list must be kept current 3. The form may be tailored by each site to accurately reflect the designated tasks at each institution 4. Document signatures and initials of all persons authorized to make entries and/or corrections on CRFs. Include all site staff working on a study, such as: ▪ Clinicians ▪ Physicians ▪ Pharmacists ▪ Data Personnel 5. Include on the log: ▪ Initials ▪ Legal signature, including first and last name ▪ Printed signature ▪ Responsibilities ▪ Start Date ▪ Credentials (if appropriate)	In the Regulatory File at the site	ICH Guidance: E6 Good Clinical Practice: Section 8.3.24 ICH Guidance: 4.1.5
Source Documents	1. Document the existence of the subject and substantiate integrity of trial data collected 2. Original documents and/or certified copies of documents related to the trial, medical treatment, and history of the subject 3. Must be signed and dated	As per requirements of local institutions	21 CFR 11 21 CFR 312 ICH Guidance: E6 Good Clinical Practice: Section 8.3.13
Unblinding	1. Decoding procedures for blinded trials to document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining participant's treatments 2. Document any decoding that may have occurred at the site during the trial	In the protocol files at the site or in the pharmacy files and in the patient record	ICH Guidance: E6 Good Clinical Practice: Sections 8.2.17 8.4.6

APPENDIX K

FDA FINANCIAL DISCLOSURE FORM 3455

APPENDIX K. FDA FINANCIAL DISCLOSURE FORM 3455

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____ , who participated
Name of clinical investigator

as a clinical investigator in the submitted study _____
Name of

_____ is submitted in accordance with 21 CFR part 54. The
clinical study

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
FIRM/ORGANIZATION	
SIGNATURE	DATE

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

FORM FDA 3455 (4/06)

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