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- Completed Form FDA 1572s (current, as well as those outdated);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.