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PREFACE

What Is the Purpose of The Audit Manual?

The purpose of the audit manual is to provide the ACRIN participating institution with a usable guide to the ACRIN Audit Program. The manual explains everything you need to know about ACRIN audits. It is designed so that you may quickly find the information you are looking for. In order to accomplish this, you will notice that this manual includes:

- Clear, concise headings in the form of questions - Questions and Answers (Q & A) format,
- A list of Commonly Used Acronyms (Appendix I), and
- A Glossary of Commonly Used Terms (Appendix II).

It would be impossible to describe, or even foresee, all situations and circumstances that may arise during an audit. The information in the manual addresses the most commonly encountered situations and the usual practices of the ACRIN Audit Program. Other extenuating circumstances will be managed on an individual basis as they are encountered.

Are Non-NCI-Funded Trials Audited Differently Than NCI-Funded Trials?

ACRIN audit standards and procedures (described later in the manual) are the same whether the trial is funded by the National Cancer Institute (NCI) or not. Oversight of the trial, and the body charged with oversight, will depend upon the source of funding.

In an effort to keep the manual as straightforward as possible, this manual is written as if all trials are NCI-funded and overseen by the NCI/Cancer Imaging Program (CIP). If your trial is not NCI-funded, references to CIP may not apply to you and an alternate oversight body may apply. You may consult the ACRIN protocol manager or contact the ACRIN Protocol Development and Regulatory Compliance (PDRC) representative for further details.

What Should I Know About Using This Manual?

Some acronyms are not defined within the body of this manual. Please refer to Appendix I Commonly Used Acronyms as needed.

The make up of ACRIN site research staff and the knowledge and experience of staff members in the field of clinical research may vary widely. The manual is intended to be useful to persons at all levels of experience in conducting clinical research trials. Therefore, some of the information in the manual may seem basic or redundant. We strongly feel that everyone will benefit from the information available in this manual.
CHAPTER 1 - INTRODUCTION TO ACRIN AND THE NCI

What is ACRIN?\(^1\)

The American College of Radiology Imaging Network (ACRIN) is an integrated group of imaging researchers, other physician specialists, and basic and clinical scientists, patient advocates, and a wide array of research support personnel.

ACRIN was established as an NCI clinical trials cooperative group in 1999 for the purpose of creating a research network to conduct a broad spectrum of medical imaging trials. Unlike other NCI cooperative groups, ACRIN was established as a “non-member” network. This open membership design allows for the flexibility of imaging facilities (including academic centers, community hospitals, and freestanding imaging centers) to choose the trials in which they wish to participate.

What Types of Imaging Studies Does ACRIN Conduct?

ACRIN conducts multi-institutional medical imaging trials. The types of imaging trials conducted are diverse and include screening, diagnostic, and interventional. Studies may involve investigational new drug agents (IND trials), with focus on evaluation of therapy response, or may involve investigational devices.

What Are ACRIN’s Research Objectives?\(^2\)

Through clinical trials involving screening, diagnostic imaging and image-guided therapeutic technologies, ACRIN seeks to obtain and develop information that:

- Improves the length and quality of cancer patients' lives, and
- Results in the earlier diagnosis of cancer.

Primary Research Objectives

ACRIN has developed three primary research objectives:

1. Screening of populations at high risk for cancer, including:
   - Tailored, organ-specific screening,
   - Combining in vitro and imaging techniques, and
   - Surveillance for recurrence.

2. Diagnosing and staging disease to guide targeted therapy, including:
   - Anatomical and functional characterization,
3. Investigations of biomarkers of treatment response, including:
   - General response markers (anatomic and functional), and
   - Targeted response markers (perfusion), and adaptive trials.

Secondary Research Objectives

ACRIN’s secondary research objectives are critical for the continued advancement of medical imaging research and serve both ACRIN and the broader cancer research community. These secondary objectives include:

1. Develop an imaging core laboratory and related services,
2. Establish a culture for imaging research,
3. Support the development of imaging informatics standards, and
4. Collaborate with the cancer research community.

What Is the NCI? 

The National Cancer Institute (NCI) is the world's largest organization solely dedicated to cancer research. NCI supports researchers at universities and hospitals across the United States and at NCI-Designated Cancer Centers, a network of facilities that not only study cancer in laboratories but also conduct research on the best ways to rapidly bring the fruits of scientific discovery to cancer patients.

The NCI leads the National Cancer Program through its operation of 11 research components that provide support for extramural and intramural cancer-related research and through its outreach and collaborations within the cancer community worldwide.

Cancer research is conducted with NCI funding in nearly every state in the United States and more than 20 foreign countries, in addition to research conducted at its own facilities. NCI supports cancer research training, education, and career development, and provides leadership for setting national priorities in cancer research.
What Is the DCTD? 4

The Division of Cancer Treatment and Diagnosis (DCTD) is one of the 11 research components of the NCI. DCTD takes prospective detection and treatment leads, facilitates their paths to clinical application, and expedites the initial and subsequent large-scale testing of new agents and interventions in patients. The DCTD has 8 major programs.

What Is CIP? 5

The Cancer Imaging Program (CIP) plays a major role in support and oversight of ACRIN imaging trials.

The CIP is one of DCTD’s 8 major programs. The CIP uses new technologies to expand the role of imaging in noninvasive diagnosis, identification of disease subsets in patients, disease staging, and treatment monitoring. 4

The mission of the CIP is to promote and support: Cancer-related basic, translational and clinical research in imaging sciences and technology, and integration and application of these imaging discoveries and developments to the understanding of cancer biology and to the clinical management of cancer and cancer risk.

CIP, acting in the study sponsor and/or IND sponsor role(s), may act when necessary, through ACRIN or directly, to ensure quality and compliance at the trial and/or site level.

What Is CTEP? 4

The Cancer Therapy Evaluation Program (CTEP) is another of DCTD’s 8 major programs. The CTEP functions as NCI’s primary clinical evaluator of new anticancer agents, radiation treatments, and surgical methods. The program administers the 11 cooperative research groups (of which ACRIN is one) that unite researchers around the nation and the world in the pursuit of distinctive and effective new treatments for cancer.

DCTD provide key clinical trial infrastructure (e.g. trial review, management, and reporting systems, written processes, etc.) that play a role in ACRIN trials (e.g. reporting of certain Adverse Events through the AdEERS system).

What is CTMB? 6

The Clinical Trials Monitoring Branch (CTMB) is responsible for on-site auditing of all clinical trials sponsored by the CTEP/DCTD, NCI and the auditing of selected cancer prevention trials sponsored by the Division of Cancer Prevention (DCP). This includes all trials conducted by the Cooperative Groups/CCOPs and studies conducted at Cancer Centers or other individual institutions which utilize DCTD, NCI-sponsored investigational agents.

CTMB is responsible for oversight of the Clinical Trials Monitoring Service (CTMS). CTMB sets guidelines and standards for the conduct of clinical trials in order to assure data quality and compliance with regulatory requirements for clinical research – FDA regulations (http://www.fda.gov/oc/gcp/default.htm) and HHS Office for Human Research Protections (http://www.hhs.gov/ohrp/) regulations.
References

What Does ACRIN’s Quality Assurance Program Consist Of?

There are many aspects to ACRIN’s Quality Assurance (QA) Program. The ACRIN Audit Program is just one aspect of this comprehensive Quality Assurance Program. However, the responsibilities for quality assurance are shared by many areas of ACRIN, including the QA Committee, Institutional Participants Committee (IPC), PDRC, Data Management, Imaging, Administration, and the Biostatistics Center. Below is a brief description of each area’s contribution to the quality assurance process:

- QA Committee – Review of specific aspects of clinical trial development and operations, including tracking data, site monitoring and auditing, image quality assurance, and adverse events.

- IPC – Review of site and investigator qualifications prior to participation in any ACRIN clinical trials.

- PDRC Auditing – On-site (most often) in-depth review of regulatory documentation and participant cases for compliance with federal and international regulations and guidance, and with protocol procedures.

- PDRC Monitoring – Review of regulatory documents throughout the course of the trial, and participant cases during initiation and at subsequent phases of the trial.

- Data Management – Control and review of data entered into the database.

- Imaging – Qualification, collection, and evaluation of study images.

- Administration – Project management, including review and approval for study activation at each institution (including General Qualifying Applications (GQAs), Protocol Specific Applications (PSAs), passwords, reader identifications (IDs), etc.).

- Biostatistics Center – Review and analysis of data for evidence of trends and outliers in submitted data.

What Is the Monitoring?

ACRIN’s monitoring program assures compliance with requirements for the protection of the rights of human subjects and to ensure the safety and well-being of all subjects involved in clinical trial, data integrity and quality of the resulting data submitted and compliance with all applicable regulatory requirements. The PDRC Monitoring Program provides continuous oversight of institution progress on ACRIN research studies. Monitoring activities are generally conducted at ACRIN HQ. Study-specific monitoring plans are developed for each ACRIN trial, especially for the IND trials.
The monitoring process includes:

- Regulatory Institutional Review Boards (IRB) documentation, ongoing during the course of the trial;
- Informed Consent content;
- Study participant case record review to ensure all images, labs are per protocol

Monitors collect essential regulatory documents during study set-up and site approval and throughout the conduct of the trial. In addition, Monitors conduct detailed review of participant cases on a pre-determined schedule, usually based on site accrual. For more information about the Monitoring Program, please refer to the ACRIN website.

**What Is an Audit?**

The International Conference of Harmonisation (ICH) E6 guidance document defines audit as “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).”

**What Is the Purpose of Auditing?**

Researchers in clinical trials have an obligation to take appropriate steps to protect both the scientific integrity of data and the rights and well-being of human subjects who participate in research studies. Consequently, the purpose of the Audit Program is to verify and document the accuracy of data submitted to ACRIN and to ensure compliance with the protocol, regulatory requirements, and safeguards for the study participants. Additionally, an audit provides an opportunity for the audit team to share information with the institution staff concerning data quality, data management, and other aspects of quality assurance.

The primary objectives of an audit are to ensure the safety and welfare of ACRIN study participants and to verify study data that could affect the primary study endpoints. This is accomplished through verification of study data with source documents. All institutions participating in ACRIN trials are eligible for audit.

**Where Do ACRIN’s Audit Standards and Policies Come From?**

Key regulations and guidance documents that establish the standards observed in ACRIN audits include, but are not limited to:

- [45 CFR part 46](https://www.hhs.gov/ohrrspp/research/regs/part46.html) [Department of Health and Human Services (DHHS)]
- [21 CFR parts 50, 56, 312, 812](https://www.fda.gov/RegulatoryInformation/Legislation/RegulatoryGuidance/ucm070191.htm) [FDA]
- [ICH E2a and E6](https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6(R1)_final.pdf) [GCPs]
- [CTMB guidelines](https://www.cancer.gov/about-cancer/research/organization/crmb) [NCI/CTEP]
ACRIN documents include:

- Audit Manual
- Adverse Event Reporting Manual
- Principal Investigator Manual
- Study-specific Protocols

What Agencies and Entities Provide Guidance on Human Subjects Research?

For human subject research, there are multiple levels of oversight. These levels include federal agencies, local entities, and ACRIN. The oversight bodies include the following.

Federal oversight bodies:

- Offices within HHS: All ACRIN trials adhere to HHS regulations
  - FDA: All ACRIN trials must adhere to FDA regulations
  - NIH, NCI, DCTD, CIP: As a sponsor of ACRIN, CIP provides oversight of ACRIN’s auditing program for federally-funded trials. In addition, for IND trials for which NCI or CIP is the IND sponsor, CIP’s responsibilities are to ensure the IND study is conducted in compliance with FDA and local regulations. In this sponsorship role, CIP must also ensure that ACRIN and the investigators and sites conducting research under its purview are complying with Human Subject Protection regulations (i.e., 21 CFR 50, 21 CFR 56, and 45 CFR 46) and guidance, which include the underlying principles described in the Declaration of Helsinki, the Belmont Report, and the ICH E6 Good Clinical Practice: Consolidated Guidance.
  - NIH, NCI, DCTD, CTEP, CTMB: Establishes QA and audit standards for all clinical trials sponsored by CTEP; ACRIN follows CTMB and CIP guidelines for auditing, as they apply to imaging clinical trials.
  - Office of Public Health and Science (OPHS): Provides resources for ethical considerations. Subordinate offices include:
    - Office of Research Integrity (ORI): Monitors investigations of research misconduct.
    - Office of Human Research Protection (OHRP): Provides guidance and clarification, maintains regulatory oversight, and provides advice on ethical and regulatory issues.

Local oversight bodies:

ACRIN, and the participating site investigators and staff that conduct research under its purview, are all obligated to be familiar with, and to comply with, applicable regulations for investigational products (e.g., 21 CFR 312, 21 CFR 812, etc.), Human Subjects Protection related
guidance and regulations [e.g., 21 CFR 56 and 45 CFR 46], as well as the principles that underlie them [e.g., The Declaration of Helsinki, the Belmont Report, ICH GCP E6], and the particular procedures and requirements of individual Institutional Review Boards (IRBs). Sites must report any non-compliance, whether identified by the site, or during ACRIN monitoring and/or auditing activity, to the site’s local IRB per federal regulatory and IRB requirements. For any non-compliance findings identified by the site, it will require reporting to ACRIN. ACRIN may be required to report the finding to NCI/CIP. IND sponsors may be required to report to FDA.

- Institutional Review Boards (IRBs) – may also be referred to as Ethics Committees, Independent Research Committees or Research Ethics Boards. In the United States, the IRB of record is charged with the review, approval, and oversight of all human subjects research conducted by the institution. They apply ethical guidance and regulations to help protect the rights and safety of human research subjects through the informed consent process and other mechanisms.

- Institutional quality assurance departments – may be referred to by many different names (e.g., Clinical Research Office).

ACRIN oversight:

- Various departments as identified in the first section of this chapter.

- ACRIN Data and Safety Monitoring Board (DSMB) – Monitors clinical trial activities to ensure the safety and welfare of study participants and to evaluate the status of the trial; operates independently of study leadership.

- ACRIRB – Oversees all ACRIN clinical trials. The ACRIRB approves regulatory documentation including the protocol and amendments, informed consent documents, case report forms, and all literature and marketing directed towards participants and prospective participants. The ACRIRB is separate and distinct from the local IRB. It does not provide oversight to individual sites interested in participating in an ACRIN trial. The local IRB provides ongoing site specific oversight, review and approvals as noted above.

- ACRIN Quality Assurance Committee / ACRIN Steering Committee / ACRIN Institutional Participation Committee – Oversee quality assurance aspects of each protocol and each participating institution, and make recommendations for any institutions identified as deficient.

Do International Participating Institutions Adhere to the Same Regulations as Domestic Sites?

Studies conducted outside of United States jurisdiction may be overseen by foreign regulatory agencies. Per ACRIN policies, the stricter rules will apply; i.e., the foreign country’s regulations or US federal regulations. ACRIN will request documentation or information from the institution’s ethics committee to ensure compliance with US regulations. These documents must be translated into the English language. During an audit, the international institutions will be requested to provide an English speaking research associate RA for translation of regulatory and source documents, as necessary.
Who Are The ACRIN Auditors and How Do I Contact Them?

All ACRIN personnel and their contact information may be found on the ACRIN website – www.acrin.org. This includes the auditors. This information is located at the ‘Contact Us’ link, found under the ‘Administration’ tab on the home page. Auditors are part of the Protocol Development and Regulatory Compliance Department. For questions or concerns regarding audits or quality assurance matters, please feel free to contact us.
What Types of Audits Does ACRIN Conduct?

There are four types of audits ACRIN conducts: Regular Cycle, Re-Audit, For Cause, and Other. The description of each type of audit is provided below.

- **Regular Cycle** – A routine audit conducted per specifications of the protocol, the protocol-specific audit plan, and the audit manual. It is usually conducted on-site at the institution by an ACRIN auditor but there are occasions when a mail audit may be conducted.

- **Re-Audit** – A follow-up audit prompted by a prior audit which had an unfavorable audit outcome. These audits are prompted by an ‘Unacceptable’ audit outcome, but may also be prompted by an ‘Acceptable Needs Follow-up’ audit outcome. The audit report indicates if a re-audit is to be conducted.

- **Special Audits or For-cause Audits** – An audit may be prompted either by significant irregularities identified through the quality assurance procedures, or due to allegations of scientific misconduct. If significant irregularities or allegations of possible research misconduct by a staff member or institution participating in their research program are revealed to ACRIN from any source, ACRIN will immediately notify the Program Director of record, Cancer Imaging Program, National Cancer Institute (CIP/NCI PD). CIP may coordinate or request that ACRIN coordinate a special/for-cause audit. Selection of the audit team will be made jointly by NCI and ACRIN and a joint course of action will be planned. Other Federal agencies may be invited to participate at the discretion of the NCI. (See sections G – H on Scientific Misconduct pages 7 - 15)

- **Off-cycle/Other** – Additional audits may be conducted off-cycle for reasons other than those described above. For example, this type of audit may be prompted by slow or fast accrual or changes in key site research personnel. CIP/NCI will be notified of the need for and timing of such audits and will be given the opportunity to participate as a member of the audit team.

Additionally, site-specific circumstances may prompt an audit at any time. Circumstances when additional audits may be necessary are listed below. These instances include, but are not limited to, the following indications:

- **Monitoring** identifies a need for immediate on-site audit focused on site/staff education and insurance of protocol compliance.

- **Trend of protocol deviations or violations**, especially for the primary end point data and/or the investigational agent.
• 20% or more of cases monitored determined to be ineligible

• Failure to follow the protocol

• Failure to keep adequate and accurate records

• Problems with IRB documents, including ICF

• Failure to assess and report adverse events or adverse events reported late per protocol:
  o Recurrent under-reporting of adverse events
  o Failure to report, in a timely manner, an adverse event that would require an expedited reporting
  o Follow-up procedures necessary to assess adverse events not performed

• Failure to account for the management of investigational agent from receipt through destruction or return.

Regardless of the circumstances by which reportable events or circumstances may be disclosed, regulatory reporting requirements set forth by the FDA, IRB, ACRIN, NCI, HHS, or any other authority must be met in addition to any ACRIN QA program specific timetables set forth herein. Events discovered at the time of audit must be reported as required. Documentation that confirms proper reporting must be furnished by the site to ACRIN, by ACRIN to CIP, and by CIP to other Federal regulatory agencies in a timely manner. In the absence of proper documentation, ACRIN and/or NCI have the option of suspending (placing on hold) all or part of a site’s trial activities until clarification and compliance have been achieved.

What Are Mail Audits?

Audits are usually conducted on-site at the institution by an ACRIN auditor. There are some occasions when it is determined that an audit may be conducted as effectively and accurately by requesting the institution’s research documents to be submitted to ACRIN headquarters. This is referred to as a ‘mail audit’. If a mail audit is to be conducted, detailed instructions are provided. The institution’s research staff will be instructed to submit relevant, de-identified source documents to ACRIN headquarters for review and verification.

For simplicity and clarity, the audit manual is written as if all audits are conducted at the institution. However, if a mail audit is conducted, all significant standards and procedures defined in this audit manual will still apply.

Who Performs the Audit?

The number of auditors and composition of the audit team varies depending upon the complexity of the trial and amount of material to be reviewed during the audit. An ACRIN auditor is always
present and acts as the Lead Auditor. Most often, the entire team will consist of one ACRIN auditor.

Besides the ACRIN auditor(s), members of the audit team may include, but not be limited to, other ACRIN personnel, CIP personnel, physicians, and/or observers. NCI/CIP may designate authorized individuals to assist with or observe the audit. Site personnel will always be advised prior to the audit, as to the size and composition of the audit team, and the purpose thereof. Observations made by any participant of the ACRIN audit team, including non-ACRIN personnel as described above, may be included in the ACRIN audit report, and may be reported to third parties as appropriate.

What Are the Qualifications for Auditors?

ACRIN auditors are trained and knowledgeable about ACRIN policies and procedures. The auditors are knowledgeable with certifications and trainings about scientific technique, regulations and requirements pertinent to human subject research, use of investigational products, and the protocol(s).

Who Will Be Audited?

All institutions that are participating in an ACRIN trial and have enrolled participants are eligible for audit.

How Often Do Audits Occur?

The number of audits at any one institution may vary depending upon audit outcomes and site-specific situations. Regular cycle audits are planned on a protocol-specific basis. The audit guidelines for other NCI Cooperative Groups differ from ACRIN’s audit guidelines due to ACRIN’s open membership policy. ACRIN audits are not planned on an institution-specific basis but on a protocol-specific basis.

The number of Regular Cycle Audits for each protocol is dependent upon several factors, including, but not limited to, size of accrual, duration of active data collection, trial phases and design, and significant amendments.

When Do Audits Occur?

The timing of regular cycle audits is pre-determined and will be outlined in the protocol. If an audit other than a regular cycle audit (refer to section What Types of Audits Does ACRIN Conduct?) is deemed necessary, the institution will be provided with the reason and timeline for the audit.
If My Institution Is Withdrawn or Terminated, Am I Still Audited?

Any institutions that have enrolled study participants will be audited regardless of status of participation in the trial. Per the ACRIN Statement of Investigator/Form FDA 1572, and GCPs, any information obtained for the purpose of human research will be audited. ACRIN and the institution are obligated to carry out study responsibilities in accordance with federal, state, and local laws and regulations. This includes quality data collection and record retention.

If All Participants at My Institution Have Prematurely Discontinued Participation (e.g., Withdrawal or Death), Am I Still Audited?

In instances when all participants have prematurely discontinued participation at an institution, due to death or participant withdrawal, eligibility for an audit will be determined on a site-specific basis. Factors that are considered include, but are not limited to:

- Have the monitors already reviewed all the participant(s) data?
- Were deficiencies cited in the monitor’s report?
- Are there outstanding items or unresolved issues?
- How many study visits did the participants complete prior to premature discontinuation?
- How many participants were enrolled?
- What was the reason for discontinuation?
How Am I Notified of an Audit / What Is the Process for Scheduling Audits?

ACRIN auditor will notify the Principal Investigator (PI) and lead Research Associate (RA) when the institution has been identified to be audited. This includes notification for regular cycle, special/for-cause, and/or off-cycle audits, including re-audits. An email notification will be sent to the institution usually 4 weeks or more prior to the anticipated audit date, requesting tentative audit dates within the specified date range. Notification related to the two types of audits (special and for-cause) may vary from this rule. Once mutually agreeable dates are determined, a confirmation notification of the audit dates will be sent.

As the audit dates approach, an email reminder of the upcoming audit will be sent approximately 2 weeks prior to the audit.

What Are the Physical Requirements for the Audit?

The following items are required for the audit:

- A work area that is quiet and secure where confidential documents, including Protected Health Information (PHI), may be reviewed and discussed in private;
- Work space to accommodate the number of auditors attending, with adequate space for each auditor to review documents and use a laptop computer;
- A reasonably convenient electrical outlet for each auditor;
- Access to telephone service, in the room or nearby.

Internet access (wireless or wired) is not required, however, it is appreciated.

How Do I Prepare for the Audit?

Preparation for audit is an on-going process that begins at study activation of an ACRIN trial at the institution. Keeping accurate, up-to-date, and complete documentation, and ensuring documentation is appropriately organized in the study folders and binders will prepare the institution to be audit-ready throughout the conduct of the trial. It is also an invaluable tool to manage the trial throughout the lifecycle of the study at the institution.

For audit preparation, the following information will be provided 2 weeks prior to the audit:

- Number and name of auditors that will be conducting the audit,
- Study-specific Instruction Sheet,
- Partial Case List, and
• Estimated duration of the audit.

Compliance with all applicable requirements is expected to be ongoing. Each site should have a plan in place for monitoring quality assurance that includes periodic quality control reviews. It is recommended that the institution perform an additional internal quality control review prior to the ACRIN audit to further re-assess compliance with the protocol and the federal regulations and guidelines. Internal QA process findings may be corrected per ICH guidance and format, and items may be flagged for clarification or discussion with the ACRIN auditor as necessary.

When reviewing participant charts, please ensure the files are complete and all pertinent data have been reported. If any discrepancies are identified between source documents and submitted data during the review, ensure they are resolved and corrected in the participant charts and the ACRIN database in accordance with strict GCP guidelines. A memo to file documenting the problem and how addressed should be generated and included in the study documentation at the trial site, and provided to the Sponsor either in a monitor’s report or separately for the Sponsor’s files.

An institution must document and report instances of protocol non-compliance to the ACRIN lead data manager immediately. All data corrections and clarifications must be made in accordance with Good Clinical Practices. As stated in previous sections, for any non-compliance findings identified by the site, reporting to ACRIN is required. ACRIN may be required to immediately report the finding to NCI/CIP. IND sponsors may be required to report to FDA.

For more specific information on how to prepare for the audit, Chapter 5 provides the specifics of what the auditor will be reviewing.

In preparation for audit review, the following steps should be taken:

• Regulatory documents should be organized and labeled so that the auditor can quickly locate documents. This can be accomplished in many different ways. Tabbing or flagging documents is recommended.

• Participant case records should be complete, organized, and labeled so that the auditor can quickly locate documents. The order of document filing should be consistent throughout all charts.

• For Investigational New Drug (IND) trials: Study documentation following the guidelines in ICH E6 Section 8 “Essential Documents for Conduct of a Clinical Trial” should be available for the audit. (This includes, but is not limited to, all documentation regarding protocol components and approvals, Form FDA-1572s, the management, handling, and administration of radiopharmaceutical agents, investigational agent accountability records, and study specific process and procedures documentation.)

• Study documents are assessed for compliance with GCPs, the protocol, SOPs, and applicable local, state, and federal requirements. For assessment of study documentation, the following will be reviewed:
Completion of CRFs per instructions

Proper documentation practices, including appropriate corrections, additions, and deletions are made, dated, and explained, if necessary, and initialed by authorized trial staff

Availability of source documents to support submitted data

Accuracy of CRF completion and data entry

Timeliness of CRF completion

Timeliness of data submission to ACRIN database

Organization of research charts

Labeling / identification of source documents

Resolution of issues from ACRIN Monitoring Reports

Resolution of issues from prior Audit Reports

Source documentation is reviewed to ensure compliance with protocol requirements and to substantiate data submitted to ACRIN. Examples of source documents include, but are not limited to:

Diagnostic imaging reports

Laboratory reports, including pathology and histology reports

Chemotherapy administration and planning records

Radiation therapy administration and planning records

Physician orders, clinical visit reports, admissions and discharge records

Physician / nursing notes

Research / progress notes

Electronic tracking records or site-designed shadow records/databases

Other items may apply; per required source documentation specific to each trial.

Three important things to know about source documents are:

All reports must be the final approved versions and they must be signed and dated; preliminary reports are not acceptable.
All notes must be initialed and dated by the person making the entry.

For on-site audits, source documents should not be de-identified.

**What Requirements Are There for Source Documents Stored as Electronic Records?**

If source documents are available in electronic format, the electronic records must be accessible to the auditor for source verification during the audit. The institution may provide either electronic access to the electronic medical records, or printed hard copies.

**What Requirements Are There for Source Documents Belonging to Other Departments (such as PET Imaging, Oncology, etc…)?**

All relevant source documents should be available to the auditor. The original documents, if available, are preferred, however, copies are acceptable. If the original documents belong to other departments or that otherwise cannot be available at the time of the audit, site may provide a copied version of the documents, or access should be arranged in advance via electronic medical records or scheduling a time for review at the department(s). This issue should be resolved with the auditor in advance to avoid access or time constraint problems at audit.

(Examples of source documents include PET Imaging log sheets, patient questionnaires, and chemotherapy administration records.)

**What Special Considerations Are There for Collaborative Trials With Other Cooperative Groups (Such as CALGB, GOG, RTOG, etc…) in Regard to Source Documentation?**

With collaborative trials ACRIN typically collects data on the imaging portion of the trial while the collaborative group collects data on the treatment portion of the trial. Often times the collaborative group is in possession of source documents that the ACRIN auditor requires to verify study data and protocol compliance, such as timing of imaging procedures. For example, if the trial requires imaging to be performed within a specified timeframe after administration of a treatment, the auditor will need to review the source document for the treatment in order to verify timing of the imaging. When it is necessary to obtain source documents from a collaborative group, the auditor will provide a listing of source documentation in advance of the audit.

**Do I Need to Have Images Available for Review?**

Assessment of imaging quality and acquisition parameters is typically not performed as part of the audit. ACRIN has alternate methods in place to assess imaging quality and compliance with the protocol, such as reader studies and quality reviews performed by ACRIN Imaging personnel or other specialists. However, there may be circumstances when the images will be requested for the audit. The institution will be notified in advance if it is necessary.
How Long Does the Audit Last?

Prior to the audit, you are given an estimated time for the length of audit duration which allows you to plan your schedule as necessary.

The time required to complete an audit depends upon several factors, including:

- Type of trial – IND trials versus diagnostic imaging trials,
- Amount of Regulatory Documents being reviewed,
- Number of Participant Cases being reviewed,
- Amount and complexity of the data being reviewed,
- Condition and completeness of the materials provided to the auditor,
- Management of the trial at your site,
- Number of adverse events, safety concerns, data quality issues, and
- Number of auditors present.

During the audit, adverse events documentation and reporting will be reviewed, as well as participant cases to ensure proper safety assessments have been conducted and reported as per the protocol. See below for additional information. Depending on the number of events and compliance concerns, this may increase the time the audit takes.

For IND trials, auditors require additional time for also visiting the pharmacy or investigational product preparation and storage areas to conduct interviews with persons involved in key aspects of agent handling and administration, and to review trial documentation such as the product accountability records, product handling logistics, etc.).

How Many Cases Are Audited and When Do I Find Out Which Ones?

Following are the guidelines used to determine the total number of cases to be audited for a trial over the duration of a trial. These guidelines are based on the total projected trial accrual. The number of cases to be audited at each institution depends on the timeline of audits and site accrual. The number of cases audited at a particular institution may be increased depending on the results of a previous audit. The numbers listed below are best estimates; the actual number of cases may be slightly different.

1. *Up to 250 participants enrolled in study*
   - A minimum of 30% of cases per institution
• For site accrual between 5 and 15 participants, a minimum of 5 cases will be audited

• For site accrual less than 5 participants, all cases will be audited

2. **251-1000 participants enrolled in study**

• A minimum of 20% of cases per institution

• For site accrual between 10 and 50 participants, a minimum of 10 cases will be audited

• For site accrual less than 10 participants, all cases will be audited

3. **1001-3000 participants enrolled in study**

• A minimum of 10% of cases per institution

• For site accrual between 10 and 100 participants, a minimum of 10 cases will be audited

• For site accrual less than 10 participants, all cases will be audited

4. **Over 3000 participants enrolled in study**

• A minimum of 10% of cases per institution, with a maximum of 150 cases

• For site accrual between 10 and 100 participants, a minimum of 10 cases will be audited

• For site accrual less than 10 participants, all cases will be audited

A partial case list will be provided at least 2 weeks prior to the scheduled audit. The full case list will be provided upon arrival of the auditor at the institution. The percentage of unannounced cases varies per study, but is consistent across all institutions participating in a particular trial. Cases are selected for audit per protocol-specific criteria.
CHAPTER 5 – DURING THE AUDIT

What Responsibilities Does the Principal Investigator Have During the Audit?

Although most interaction during the audit may be with the institution RAs, the PI is ultimately responsible for all study activities at the institution. The PI must be available on an as-needed basis throughout the audit to provide information or clarification, if needed. In addition, the PI must be available to participate in the Exit Interview.

What Am I Expected to Do While the Audit Is in Progress?

On the first day of audit, an appropriate member of the research staff (or designee), must be available to:

- Meet the auditor upon arrival at the institution;
- Orient the auditor to surroundings;
- Provide the auditor with institution personnel contact information for use during the audit;
- Provide the auditor with study-specific regulatory binder(s), including the drug accountability log if an IND trial;
- Provide the auditor with requested research charts –
  - A partial case list is provided prior to the audit;
  - Unannounced cases are typically requested at the time of audit;
  - If the anticipated length of the audit is longer than one day, it may not be necessary to have all charts available on the first day;
  - Access to and training to use the electronic medical records system, if hard copies of the source documents are not available;
- Provide the auditor with a description of the research chart layout and guide the auditor through an initial chart;
- Discuss with the auditor the processes in place at your institution to ensure compliance with protocol-specific procedures, regulatory requirements, and CRF instructions.

As the audit progresses, the appropriate institution’s research staff must be available throughout the audit to review findings, respond to questions, and/or provide information, additional source documentation, and/or clarification. It is not expected for staff to sit with the auditor during the audit; the time required for review with the auditor will be dependent upon the condition and contents of the research charts.
A tour of the institution may be requested depending upon the procedures and requirements of the protocol being audited. For IND trials, a tour of the pharmacy, product storage area, regulatory binders, and/or radiochemistry department will also be requested, including the areas where IND agents are prepared, measured, and administered.

Upon completion of the audit, the research staff must be available to participate in the Exit Interview.

**Will I Know How My Audit Is Going As the Audit Progresses?**

There will be on-going communication between the auditor and the research staff. With the continuous, open communication with the auditor, all can assess the progress of the audit and ask any questions regarding the audit and/or the trial. Audit findings are either discussed with the research staff on an on-going basis or after the end of each day to give the institution the opportunity to provide clarification, additional source documentation, and evidence of due diligence. Discussion at the Exit Interview and findings reported on the Audit Report are reiterations of what has already been communicated throughout the audit process.

If significant issues related to human subject protection and/or significant protocol non-compliance are identified during the audit, the auditor will notify ACRIN leadership and CIP. The auditor will also request that the IRB of Record be notified immediately. The study site PI is primarily responsible for all activities and reporting related to the site. ACRIN administration may begin to work with the PI to identify reporting timeframes and to facilitate proper reporting during the audit, as necessary and appropriate. If appropriate reporting is not, or cannot, for any reason, be completed in a timely fashion, further notification will be made to ACRIN QA staff and ACRIN administration. ACRIN staff will in turn promptly notify CIP. ACRIN and CIP staff may take action, as appropriate and necessary, to secure compliance. ACRIN and CIP will ensure proper reporting to IND sponsor, FDA (this occurs primarily through the IND Sponsor), or other regulatory authorities, and to the study Principal Investigator.

**What Will the Auditor Look At During the Audit?**

The audit consists of two primary components - Regulatory Document Review and Participant Case Review. In addition, the auditor will follow-up on the monitoring reports and previous audit reports, if any, to ensure all issues have been addressed. Implementation of Corrective Action Plans (CAP) is also reviewed, when applicable.

**What Regulatory (IRB and/or FDA Required) Documentation Should I Have Ready for the Auditor?**

At a minimum, the following documents should be ready for review. Additional items may be requested, as appropriate, depending upon the specifics of the protocol and the type of audit. Refer to [ICH E6 Section 8 of GCP: “Essential Documents for the Conduct of a Clinical Trial”](#) for a comprehensive table of what documents/records are to be maintained by the investigator at
the trial site before, during, and after conduct of the clinical trial. IRB-related documents to be maintained include:

- Documentation of full board IRB of record initial approval of the protocol and informed consent form (ICF).
- Documentation of continuing IRB review and approval, without lapses, of the protocol, the ICF, and any amendments thereto, by the IRB of record.
- Documentation of IRB approval for recruitment material, participant questionnaires, protocol amendments and ICFs.
- Source documentation, as requested.

Reportable, or potentially reportable events will be brought to the attention of the PI for review and assessment before the conclusion of the audit, and reportable events are expected to be reported per protocol, IRB and other regulatory requirements; e.g., ICH, Code of Federal Regulations (CFR).

The following are examples of what is assessed for IRB regulatory compliance per 21 CFR 50 and 56. Failure to comply with the following list will result in major deficiencies being assigned, except where noted that lesser deficiencies apply. NOTE: This list does not represent an all-inclusive list of requirements. Additional regulatory documentation may be required depending on the type of the trial.

- Full-board initial IRB approval prior to site activation – must have ‘local IRB of record’ approval, along with ACRIN approval prior to participant recruitment, obtaining consent, enrollment, registration and/or conduct of any study specific procedures.
- IRB continuing review and approval must be current and continuous.
  - Prior lapses of IRB approval of less than 30 days are considered lesser deficiencies.
  - Prior lapses of IRB approval of 30 days or more are considered major deficiencies.
  - Lapses of IRB approval on protocols closed to accrual for which all participants have completed imaging are considered lesser deficiencies if the lapse is less than 30 days, and major deficiencies if 30 days or more.
  - Missing IRB approval documents at the time of audit are considered major deficiencies.
- Expedited review and approval is acceptable for situations which are approved exceptions to full board IRB review requirements, as determined by the IRB of record.
- Participants must be registered only during periods of active IRB approval, using the approved ICF at the time consent is obtained.

- Documentation to show proper reporting, per protocol and regulations, of unanticipated problems, protocol violations, and/or adverse events. Such reporting may include reports to the IRB, IND Sponsor, ACRIN, NCI, and/or FDA as appropriate, and in a timely manner. Any potentially reportable events identified at the time of audit will be immediately brought to the attention of the site PI or designee during the audit, for review and assessment, to ensure appropriate reporting. Note: Events that pertain to an investigational agent will be brought to the immediate attention of the IND Sponsor [e.g., CIP] for independent assessment and action, as may be indicated.

- IRB approval of protocol amendments must be within 60 days of ACRIN’s notification that an amendment is available.

- Documentation that recruitment materials, including participants educational materials and retention plan (if available), have been approved by the IRB of record prior to use.

- Copies of all protocol versions/amendments and ‘change memos,’ from the time of trial initiation at your institution, must be available, either printed or electronic. All such documents must have been IRB approved prior to implementation.

- Copies of all ICF versions used from the time of trial initiation at your institution must be available, and must have been IRB approved prior to use.

- All versions of Statement of Investigator/Form FDA 1572.

- Investigators’ Curriculum Vitae (CVs) and Medical Licenses.

- Study Staff Signature and Responsibilities Log(s).

- **When using investigational agents/devices -**
  
  - Signed and complete Statement of Investigator/Form FDA 1572 (all versions used throughout trial including a current one). NOTE: If at any time the site PI is noted to be negligent in the commitments made in the Form FDA 1572, ACRIN or CIP/NCI may elect to take action to ensure compliance, or else may suspend all or part of the site’s trial related activities. Such action may require reporting to the IRB of record and FDA.

  - CVs for all investigators listed within Form FDA 1572. It is highly recommended that CVs should be signed and dated.

  - Medical licenses, financial disclosure forms, and conflict of interest forms for all investigators listed within the Form FDA 1572.

  - Investigational Drug Brochure (IDB) - all versions used throughout trial.
Investigational Agent Accountability Record, NCI DARF, or similar documents as required per protocol and federal regulatory requirements.

External safety reports for adverse events that are unexpected and > Grade 3 (attribution of possible, probable, or definite [i.e., reports of adverse events from other sites or trials with the same IND agent - generally distributed by the IND Sponsor] must be submitted to the local IRB within 90 days of notification per CTMB guidelines and FDA requirements or as required per the IRB.

Additional required documentation for IND trials, as per the specific protocol being audited.

See ICH E6 & 21 CFR 312 for additional guidance.

ACRIN recognizes that the local IRB of record for each study provides oversight of all human subject research conducted at each institution (per HHS 45 CFR 46, 21 CFR 50 and 56, and ICH E6 [GCP]), and has its own policies and procedures. ACRIN will work in concert with each institution and its local IRB. Any disparity between ACRIN policies and procedures and those of the local IRB must be identified, and resolved. The solution must be clearly documented, and the documentation must be available for the audit.

What Documentation Should I Have Ready in the Participant Research Charts?

Review of participant cases is performed as part of the audit. Following are examples of the types of items reviewed for each case. Source documents such as medical records must be available for review to verify the research data per regulatory requirements. This includes documents such as chemotherapy records, office visit notes, and/or participant questionnaires.

- Informed Consent Form (ICF):
  - Original participant-signed and dated ICF must be maintained in the institution; if not readily available to the auditor, a copy may be reviewed, however a description of filing procedures for original ICFs is required;
  - ICF must be signed and dated by the participant, and any and all other appropriate persons, as required by the IRB of record.

Note: for cases where, based upon the trial population or other likely circumstance, chronic or acute cognitive impairment of a potential participant in the clinical trial may reasonably be anticipated, the protocol will contain language that addresses adequate protections for this vulnerable population. Protocol required documentation of active evaluation, by the PI or a qualified clinician, that the subject is of appropriate cognitive status to participate in the consent process, will be required. The evaluation should be documented in a manner that is timely and relevant to the subject’s ability to complete the
consent process, and must address the potential need for a Legally Authorized Representative consent. The protocol and the ICF should agree with each other, and with the IRB determination on the matter, and site documents must have been reviewed and approved by the IRB of record before implementation. Additional information regarding HHS/OHRP policies on vulnerable populations and informed consent is available at http://www.hhs.gov/ohrp/policy/populations/index.html and http://www.hhs.gov/ohrp/policy/consent/index.html.

- ICF must be signed prior to participant registration, and prior to participant receiving any protocol-specific procedures;

- Participant must provide consent using the current IRB-approved ICF version at the time of participant registration (see Note above for cases of cognitive impairment and use of LAR in the consent process.);

- Revisions to the consent document must be presented to subjects, agreed to, and documented as required by the institution’s IRB.

- Eligibility:

  - Documentation must be available to confirm that the investigator or an appropriately qualified investigator-designee has determined that the participant has met the inclusion criteria, and there is no evidence that exclusion criteria apply;

  - Participants who are deemed ineligible based on information that could not have been known prior to registration or on information based on central review of material must be properly reported as such, however, deficiencies will not be assigned in these instances.

- Adherence to protocol-specific procedures:

  - Protocol-specified imaging, agent or treatment must be used;

  - Imaging, agent or treatment which is not permitted per protocol may not be used;

  - Timing and sequencing of imaging and treatment must be per protocol specifications;

  - Laboratory tests must be performed and reported per protocol specifications.

- **When using investigational agents/devices** -

  - Dose delivered to the subject must be per protocol agent specifications;

  - Documentation of administration of investigational agent as per protocol must be present and accurate. Documentation of any and all
protocol specified precautions or procedures required for agent administration is required.

- IND agent must be completely accounted for from delivery to disposal. Radioactive IND agents must show documented evidence of proper handling, administration, storage, and terminal decay.

- Study Images:
  - As ACRIN auditors are typically not imaging specialists, review of imaging data is limited to assessment of reasonableness between source documents and reported data.
  - The ACRIN Imaging Department is responsible for quality assurance of study images. ACRIN auditors will obtain and review signed documentation from the ACRIN Imaging Core Laboratory that QA was performed. Documentation will be maintained in the appropriate ACRIN master files.
  - More in-depth review of images and image-related data is performed via central reading and/or other quality control measures as specified in the protocol, the protocol-specific image management plan and/or ACRIN standard operating procedures.
  - ACRIN auditors will work with the ACRIN Imaging Department to identify any outstanding site-related imaging issues prior to audit. The outstanding imaging issues will be addressed with the site at the time of the audit.

- Adverse Events (AEs) related to imaging and/or imaging agent(s) must be managed per protocol:
  - All AEs that occur within the AE reporting timeframes as specified in the protocol must be assessed by the investigator regardless of attribution or the appropriate investigator-designee;
  - AEs must be accurately recorded and reported in a timely manner;
  - Circumstances pertaining to AEs must be clearly documented;
  - Follow-up studies necessary to assess AEs must be performed until resolution of the AE or until 30 days after study completion;
  - Expedited AE Reports must be submitted within the specified timeframe;
  - AEs must be reported as specified in the protocol and/or IDB, as in the case of ‘events of special interest.’
  - When using investigational agents/devices - (in addition to the above mentioned items) -
Safety monitoring, written assessment, and reporting are performed per protocol-specific requirements and in compliance with applicable FDA regulations, NCI/CIP Guidance, and local IRB AE reporting policies;

- Data Quality:
  - Source documentation must be available to verify the reported clinical and/or imaging data;
  - Case Report Forms (CRFs) must be completed per CRF instructions;
  - Data must be submitted to the ACRIN database in a timely manner and per CRF instructions; this is critical for trial surveillance by the ACRIN Data And Safety Monitoring Committee;
  - For randomized trials, randomization (registration) must occur prior to study-specific procedures being performed;
  - Follow up to prior Monitor’s Reports and Audit Reports to ensure resolution of all issues observed and implementation of the submitted Corrective Action Plan.

NOTE: If serious or continuing non-compliance with ANY of the above, or other significant observations, are made at the time of audit, or during the conduct of the trial, ACRIN may suspend some or all ACRIN trial activities at the site until clarification and/or compliance is achieved. Reporting of observations to third parties may be required.

What Is Required for Investigational New Drug (IND) Trials?

Specific documentation required for IND trials is specified in the individual protocol, other study specific documentation, 21 CFR 312 (FDA IND Regulations), ICH E6 Consolidated GCP, and NCI/CIP guidance documents and templates. The auditor will review and evaluate these documents and specific data as related to the research and regulatory requirements for IND trials. For detailed requirements specific to each IND trial, please refer to the study protocol, ACRIN website, and/or IDB. Drug accountability and storage/decay-disposal procedures are required under Federal Regulations and CTEP, DCTD, NCI policy.

- Ordering, storage, preparation, and/or administration methods must be documented and compliant with the protocol and Investigator’s Brochure;
- Receipt, preparation, administration, and/or decay-disposal of the investigational agent must be documented on an ACRIN provided drug accountability form or a similar document;
- Assessments of Adverse Events (AEs) that occur on the trial must be compliant with procedures and timelines as specified in the protocol, and per FDA regulations:
  - Accurate and complete reports and source documents for review and verification;
Reportable AEs must be reported per protocol, local IRB policies and procedures, and other federal regulatory requirements;

- Personnel must be trained and qualified to prepare and administer the investigational agent prior to initiation of the trial;

- Form FDA 1572 with CVs and licenses of investigators must be completed and submitted to ACRIN for submission to the IND Sponsor;

- Compliance with procedures stated in the protocol and the Investigator’s Brochure must be documented.

NOTE: ACRIN may advise, or may require the site to advise the IND holder [e.g., CIP/NCI] of any observations made at the time of audit where notification of the IND Sponsor and/or further action is thought to be appropriate.

**How Am I Informed of the Audit Outcome?**

At or near the conclusion of the audit visit (depending on availability of site personnel), the auditor conducts an Exit Interview. Attendees required to participate are the institution PI and research staff, the ACRIN auditor, and, if appropriate, ACRIN leadership and research staff. Other institution research staff members that are involved with the study and wish to attend are welcome. If the Audit Outcome is ‘Unacceptable’ or serious audit findings were observed, additional personnel may participate via telephone; these individuals may include, but are not limited to, ACRIN QA Committee Chair, Sr. Director of ACRIN Administration, ACRIN Study Chair, ACRIN Project Manager, ACRIN Data Manager, and PDRC Director.

During the Exit Interview, a summary of audit findings is presented by the auditor. At this point, the institution has been informed of all findings since the findings are discussed on an on-going basis throughout the audit. Discussion regarding corrective action, should it be warranted, is encouraged at this time. This interview is normally the final opportunity for audit-specific face-to-face education, dialogue, feedback, and clarification. The auditor provides a preliminary outcome for each of the 2 audit components. However, this may be changed upon closer review of audit findings after the audit or upon receipt of additional information and/or documentation from institution. If the audit outcome is changed, a notification will be sent immediately (prior to receiving the final Audit Report).

For any potentially reportable adverse events identified during the audit but not reported to ACRIN, the auditor will request the study site PI to review and assess the event, if the adverse events meet the protocol reporting criteria. The auditor may offer recommendations with regard to reporting, and may consult with ACRIN QA resources or ACRIN leadership. However, it remains the responsibility of the institution PI to submit such reports within the protocol-specified timeframes upon first knowledge of the event. PI must provide appropriate documentation and/or explanatory material in a timely manner.

NOTE: It is important to note that these adverse events must be reported immediately and within the protocol specific reporting timelines regardless of the timing of the ACRIN audit, Audit reports, and/or any corrective action. Sites must comply with protocol and the local IRB, IND Sponsor, FDA, or NCI requirement.
What is a Major Deficiency?

A major deficiency is defined as a variance that renders the resulting data questionable, or that compromises the capacity to scientifically reach a conclusion regarding study objectives due to missing or in-evaluable data. In addition to data related major deficiencies, major deficiencies may be assessed for findings that represent significant lapses in Human Subject Protections as specified in ICH GCP E6, the protocol, 21 CFR parts 50 and 56, or NCI CTMB Guidance as well as applicable FDA regulations (e.g., 21 CFR 312, Investigational New Drug Application).

It is essential to note that major deficiencies in the scientific validity of the data produced by a site have the potential to impact the benefit/risk profile of the trial from a human subject protection perspective.

Examples of data related major deficiencies, but not limited to, are as follows:

- Missing IRB approvals
- Initial protocol approval by expedited IRB review
- Registration and/or study treatment of patient prior to IRB approval
- Previous (now resolved) lapse in IRB approval of more than 30 days, but less than one year
- Registration of patient on protocol during a lapse in IRB approval
- Missing continuing review and approval documentation (approval is subsequently found to have been in effect)
- Lack of documentation of IRB approval of a protocol amendment
- Expired IRB-approval [NOTE: if IRB approval is not in effect at the time of audit, the trial is subject to being suspended/placed on immediate hold (with the exception of subject safety related activities) per 21 CFR part 56.]
- Adverse events reported late or not reported to the IRB or Sponsor (NCI/CIP through appropriate reporting mechanisms)
- Unanticipated problems or other events not reported as required per the protocol, IRB, Sponsor, FDA, OHRP, ICH GCP, or other applicable institutions
- Trial activities that violate IRB or FDA specified terms of approval
- IRB not provided with complete, accurate, and timely information necessary for review and approval, as required in 21 CFR 56, or per the IRB of record
- Failure to submit, in a timely manner, any safety information [e.g., reports provided to the site by the sponsor with regard to the safety profile of the IND agent] or other safety related notifications to the IRB for unexpected ≥ grade 3 events with an attribution of possible, probable or definite, unless the local IRB policy does not mandate reporting of external safety reports
It is important to note that, due to the nature of clinical research there is no single comprehensive list of major deficiencies. The trained professional discretion of the experienced auditor, and of ACRIN QA staff, will ultimately determine assessment of major and lesser deficiencies.

**What is a Lesser Deficiency?**

A lesser deficiency is defined as a variance that is judged to not have a significant impact on the outcome of the study or interpretation of the study data and is not a major deficiency. Lesser deficiencies are expected to occur occasionally; however, the number of occurrences and evidence of trends will determine the impact these deficiencies will potentially have on data integrity and therefore the outcome of the audit.

**What Are Possible Audit Outcomes and How Are They Determined?**

There are 3 possible Audit Outcomes: Acceptable, Acceptable Needs Follow-up, and Unacceptable. An audit outcome is assigned for each of the 2 components of the audit (Regulatory Document Review and Participant Case Review) and a final audit outcome is assigned for the overall audit.

The assessments of Acceptable, Acceptable Needs Follow-up, or Unacceptable are based on the number of deficiencies assigned during the audit, the gravity of the deficiencies, and the impact the deficiencies potentially may have on the capacity to accurately analyze the resulting data or to reach a scientifically reliable conclusion as to the study objectives, especially impact on the safety and welfare of human subjects. In general, the following apply:

- **Acceptable** – No major deficiencies assigned. There may be some lesser deficiencies and/or other observations noted in the Audit Report that require follow up on your part.

- **Acceptable Needs Follow-Up** – Major deficiencies or a significant number of recurring lesser deficiencies are identified. Follow up by the institution is required.

- **Unacceptable** – Findings of the audit indicate there is evidence of serious and/or non-compliance on the part of the investigator / institution that put participants and/or the results of the trial in jeopardy and that must be addressed immediately. Probation, suspension or termination may be appropriate for any continuing non-compliance and seriousness of the findings, and may be imposed by ACRIN, and CIP/NCI may be consulted. Additional reporting [e.g., to CIP and/or the IRB of record] may be required, particularly in the case of an IND trial. FDA notification may be required, if determined necessary.

**What Are the Implications and Consequences of an ‘Unacceptable’ Audit?**

If your institution receives an audit outcome of ‘Unacceptable’, consequences may be imposed by several different entities, including ACRIN, your local IRB, and/or the CIP or other federal agencies, such as the Food and Drug Administration (FDA). Several factors dictate the severity of repercussions, these factors include:
- The degree to which the identified deficiencies compromise participant safety.

- The degree to which the identified deficiencies render your data unusable or un-evaluable.

- The degree to which identified deficiencies may be resolved (for instance, imaging performed out of window may not be rectifiable whereas an improperly completed CRF may be).

- The perceived ability and willingness of your current staff to devise and implement an effective corrective action plan and to resolve the identified deficiencies.

ACRIN’s policies allow for 3 levels of restriction for institutional researchers who do not meet an acceptable level of compliance with study requirements per their audit findings. These 3 levels are Probation, Suspension, and Termination; a description of each follows:

- **Probation** – Accrual of participants to the trial may continue, however, activities at the institution, especially those identified during the audit as being deficient, are closely monitored by ACRIN. The institution PI must implement corrective actions addressing the deficiencies observed during the audit, and a re-audit is mandatory. Once an audit outcome of ‘Acceptable’ or ‘Acceptable Needs Follow-up’ is achieved, probationary status is lifted.

- **Suspension** – Accrual of participants to the trial may not continue. Only specified study activities should continue. The institution PI must implement corrective actions addressing the deficiencies observed during the audit, and a re-audit is mandatory. Once an audit outcome of ‘Acceptable’ or ‘Acceptable Needs Follow-up’ is achieved, some or all trial activities are reinstated.

  NOTE: ACRIN, CIP, or regulatory authorities may impose additional terms or otherwise modify a suspension, as defined above. For example, in an IND trial, shipments of the IND agent may be suspended and some or all non-safety related trial activities may be placed on hold.

- **Termination** – This is the highest level of disciplinary action and is only applied under the very gravest of situations. Termination is permanent. Accrual must cease immediately. Depending on the circumstances, the institution staff must continue study activities for those participants already accrued. The institution PI is responsible for ensuring all necessary data is submitted to ACRIN until all participants enrolled complete study activities. In the event of termination, instructions are supplied to assist the institution staff with completion of the trial. ACRIN devises a plan for permanent closure of a participating institution based on study- and site-specific considerations.

ACRIN leadership, in conjunction with the auditor, decides on the level of restriction or heightened observation assigned, based on the findings of the audit. Re-audits are mandatory for all institutions receiving an audit outcome of ‘Unacceptable’. The timing of the re-audit is
dependent upon the time needed to implement a corrective action plan and to resolve all identified issues, and on trial status, but usually occurs within one year.

NCI/CIP will be immediately notified if any level of restrictions is assigned to the site. For IND trials, NCI/CIP and/or IND sponsor will notify the FDA of any site’s study termination. In addition to the injunctions imposed by ACRIN, your local IRB likely has their own policies regarding these situations. ACRIN will work with your institutional PI to ensure compliance with the reporting requirements. Please consult your IRB for details.

In severe instances where particularly egregious violations are observed, the CIP and/or other federal agencies may impose further sanctions and restrictions. The actions taken are dependent upon the specifics of the situation, the worst case being a permanent ban on conducting research; legal intervention may also apply.

What is Research/Scientific Misconduct and How is it Addressed?

Research or scientific misconduct is defined in the Public Health Service Policies on Research Misconduct and Final Rule, 42 CFR Parts 50 and 93, as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

The Department of Health and Human Services (DHHS) has the ultimate oversight authority for research supported by the Public Health Service (PHS). This includes the right to assess allegations and perform inquiries or investigations at any time. Investigations and inquiries of research misconduct are usually conducted by the Institution/organization at which the alleged misconduct occurred with oversight and review by ORI as needed. The ORI publishes findings and places the names of those found to have committed misconduct or fraud on/in the PHS Administrative Actions Bulletin Board, NIH Guide, ORI website and Federal Register. http://ori.dhhs.gov/misconduct/AdminBulletinBoard.shtml

Any data irregularities identified through quality control procedures or through the audit program that raise any suspicion of intentional misrepresentation of data must be immediately reported to the CIP, NCI, specifically, to the CIP Program Director (PD) of record. The CIP PD must be notified immediately by telephone [(301) 594-5225] of any findings suspicious and/or suggestive of intentional misrepresentation of data and/or disregard for regulatory safeguards for any of the three (regulatory, pharmacy and patient case) components of an audit. Similarly, any data irregularities identified through other quality control procedures suspicious and/or suggestive of intentional misrepresentation of data must be immediately reported to the CIP PD. It is the responsibility of the ACRIN to immediately notify the CIP PD when they learn of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their research program. It should be emphasized that irregularity/misrepresentation does not need to be proven; a reasonable level of suspicion suffices for CIP PD notification. It is also essential that involved individual(s) and/or institutions follow their own institutional misconduct procedures in these matters.

Immediately upon learning of an allegation of research misconduct the CIP PD will notify the Director, Division of Extramural Activities, NCI (the NCI Research Integrity Officer (RIO)). Again, it is important to note that these allegations need not be proven; a reasonable level of suspicion suffices to trigger an investigation, which would be conducted in accordance with the policies of the ORI/DHHS. The NCI RIO will then manage communications related to the
allegation in accordance with the policies and procedures contained in the NCI Manual Chapter 1303 ‘Extramural Research Misconduct Policy’ on an as-need-to-know basis.

In some cases, the allegation may be forwarded to other federal offices for review and appropriate action. For example: management of NIH funds would be directed to the NIH Office of Management and Assessment (OMA); protection of human subjects from research risks would be directed to the Office of Human Research Protections (OHRP, DHHS; humane care and use of laboratory animals is handled by the NIH Office of Laboratory Animal Welfare (OLAW); criminal offences are handled by the Office of the Inspector General (OIG).
CHAPTER 7 – AFTER THE AUDIT

What is the Exit Interview?

The Exit Interview is the final phase of the audit visit. It is conducted at (or near) the end of the audit (see Chapter 5, Q & A section How Am I Informed of the Audit Outcome?). The objectives of the Exit Interview include -

- Presentation and explanation by the auditor of the audit process, including what specifically was reviewed and what was observed.

- Presentation by the auditor of audit findings. Although the institution research staff is continually kept apprised of all findings throughout the course of the audit, the findings are summarized one last time at this point.

- Provision of a final opportunity for the institution research staff to address outstanding audit issues and findings, including clarification of discrepancies, response to questions, and presentation of evidence of due diligence.

- Discussion of resolution to the audit findings is encouraged at this time.

- Announcement of the Audit Outcome. Although this is a preliminary assessment and may change upon further examination of information collected during the audit, typically this is indeed the final assessment.

- Discussion of the next steps to be taken by ACRIN and your institution research staff. These next steps include:
  
  o Completion of the Audit Report (by the auditor) and distribution to the institution PI and RA, ACRIN personnel, the CIP, and the Study Chair;

  o Development and submission to ACRIN of a Corrective Action Plan (CAP), should one be required, by the institution PI;

  o Resolution of all audit findings detailed in the report and implementation of a CAP, if applicable, by your institution research staff; and

  o Preparation for a re-audit, should one be required.

Per the outcome of the audit, ACRIN leadership may participate in the Exit Interview. Your institution will be notified of the final audit outcome assignment at the end of the audit. However, during the course of the audit, you will be updated with findings which may impact the audit outcome. For any audits assigned an outcome of “unacceptable” regardless of type of trial, ACRIN Leadership will participate in the Exit Interview. ACRIN Leadership includes, but not limited to, the Network Chair, Co-Deputy Chair(s), and/or Protocol Study Chairs(s), along with the Director of Protocol Development and Regulatory Compliance and lead protocol staff members (i.e. project manager, data manager, monitor). For IND trials, ACRIN Study Chair(s), specifically an imaging physician, will participate in the Exit Interview via teleconference for an audit assigned an outcome of “acceptable with follow-up”.

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What Happens After the Audit?

At the conclusion of the audit, a Preliminary Audit Report is sent to CIP for review. If appropriate, feedback to ACRIN may be passed on to the site. Next the auditor submits the final Audit Report for distribution to the site PI and RA, ACRIN personnel, the CIP and the Study Chair. The Audit Report is a detailed document which –

- Describes all observations made and deficiencies cited for every case and all regulatory/IRB documents reviewed, clearly describes actions that are to be taken by the institution, and who at ACRIN to work with to rectify discrepancies;
- Clearly specifies whether a Corrective Action Plan (CAP) is required from the institution; and
- Clearly specifies whether a re-audit is necessary.

Once in receipt of the Audit Report, the institution is responsible for ensuring that all observations and deficiencies described within the report are resolved or addressed, if not already done so.

If the audit report indicates that a CAP is required, the institution is required to submit an acceptable CAP to ACRIN within a specified time frame. Please refer to the Q & A below, What Are Corrective Action Plans and What Do I Need to Know About Them?, for more information.

The audit report will also specify whether a re-audit is necessary, along with the requested CAP. Please refer to the Q & A below, What Do I Need to Know About Re-Audits?, for more information.

What Are My Responsibilities After the Audit?

Upon receipt of the audit report, or immediately after the audit, all audit findings must be resolved. The audit report contains very detailed information on audit findings and often provides direction and recommendations on resolution methods. The entire ACRIN team is available to help resolve the audit findings, and ACRIN encourages the institution staff to contact ACRIN for any assistance or further guidance.

Regulatory reporting recommended or required by ACRIN must be evaluated and initiated as required immediately. Consultation with ACRIN and documentation of reports may be required.

If a CAP and/or a re-audit are necessary, as indicated in the Audit Report, please refer to the following two Q & As of this Chapter.

Individual IRBs have their own requirements regarding audits and reporting of findings; please contact your local IRB, the IRB of record, for details.
What Are Corrective Action Plans (CAPs) and What Do I Need to Know About Them?

A CAP is a document collaboratively developed and approved by the institution PI that addresses the deficiencies and observations noted in the audit report, specifically. It should address what caused the deficiency to occur, what will be implemented to resolve it, when it will be resolved, and what corrective measures have been implemented to ensure that deficiencies do not continue to occur.

The audit report clearly indicates if a CAP is required. If one is required, a CAP template is provided to assist with the development of the process. A timeline for submission of the CAP to ACRIN PDRC to the attention of the lead auditor is specified in the Audit Report, typically within 28 – 30 days after the receipt of the final audit report.

When developing the CAP, consider the following questions:

- Does the CAP address the observation/deficiency?
- Does your institution have the appropriate resources to implement the CAP?
- Does the CAP address the root cause of the deficiency and aim to resolve it?
- Does the CAP ensure that all discrepancies observed will be addressed and that un-audited cases where the same discrepancy likely exists will also be addressed?
- Does the CAP implement controls to ensure trends identified will not continue?
- Does the CAP include an educational component if one is indicated?

The CAP should be submitted to ACRIN PDRC within the requested time period. If you have difficulty meeting the timeline, please contact the ACRIN auditor for request of an extension to the timeline. Failure to submit an acceptable CAP prompts the initiation of 1 of the 3 levels of restrictions for participation – please refer to Chapter 6, Assessing Audit Findings and Audit Outcomes, for more information.

The submitted CAP is forwarded to the CIP, where it is reviewed and acceptability to NCI/CIP is determined. ACRIN may receive feedback from CIP regarding any portion of the Audit Report or CAP, which may in turn be passed on the site for action. The CAP is ultimately maintained as permanent documentation of the conduct of the trial; therefore, it is imperative that the CAP be comprehensive, clearly written, and that it addresses the issues cited.

Upon receipt of the submitted CAP, ACRIN PDRC evaluates the CAP as either acceptable or unacceptable. Acceptable CAPs are forwarded to the CIP and a letter of acceptance is sent to the institution. If the CAP is not acceptable, ACRIN will advise the institution to provide missing information or to address any inadequate responses for clarification. ACRIN will expect a revised version without delay, but will provide the institution with an appropriate timeline for revisions.
What Do I Need to Know About Re-Audits?

Re-audits are mandatory for all audits with outcomes of ‘Unacceptable’, and in some cases when there is an audit finding that does not warrant an outcome of ‘Unacceptable’ but is serious enough that participant safety or data integrity is potentially in question. The Audit Report clearly indicates if a re-audit is mandated. If a re-audit is required, the entire audit process is again initiated.

The process for scheduling the re-audit is the same as that for scheduling a regular cycle audit – please refer to Chapter 4. The timing of a re-audit is such that it allows sufficient time to adequately address the deficiencies which prompted it. Although circumstances specific to your institution and the identified deficiencies, and trial status, dictate the amount of time needed, a re-audit typically occurs within one year. Although most re-audits are conducted at the institution, re-audits may be conducted off-site (mail audit) depending on the types of deficiencies. If a mail audit is conducted, instructions on how to prepare for an off-site audit will be provided.

The purpose of the re-audit is to follow-up on findings from the prior audit. Therefore, evaluation of the effectiveness of the acceptable CAP implementation is the major objective of the re-audit. In most instances, the auditor will review documents and information specific to those previously identified issues.

An audit outcome will be assigned and an audit report completed. If improved performance is not demonstrated at the time of the re-audit, another CAP will be required and possibly, another re-audit. Failure to demonstrate improved performance on the second re-audit could result in termination of the trial at your site. Please refer to Chapter 6 - What Are the Implications and Consequences of an ‘Unacceptable’ Audit?