



AUDIT MANUAL

Prepared by the
American College of Radiology Imaging Network
Protocol Development and Regulatory Compliance Department

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P R E F A C E

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. Studies may be conducted independently by ACRIN or collaboratively with another NCI cooperative group.

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,
 - Image-guided therapy, and
 - Imaging phenotype.
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?³

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.

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.

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 (www.fda.gov/oc/gcp/default.htm) and HHS Office for Human Research Protections (www.hhs.gov/ohrp/) regulations.

References

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2. ACRIN Scientific Plan 2008 – 2012. Available at www.acrin.org/RESEARCHERS/CONDUCTINGRESEARCH/SCIENTIFICPLAN20082012/tabid/67/Default.aspx.
3. The NIH Almanac / National Cancer Institute Mission. Available at www.nih.gov/about/almanac/organization/NCI.htm.
4. The NIH Almanac / National Cancer Institute Research Programs. Available at www.nih.gov/about/almanac/organization/NCI.htm.
5. Cancer Imaging Program. Available at <http://imaging.cancer.gov/>.
6. Clinical Trials Monitoring Branch. Available at <http://ctep.cancer.gov/branches/ctmb/default.htm>

CHAPTER 2 - INTRODUCTION TO THE AUDIT PROGRAM

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 an Audit?

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

- [45 CFR part 46 \[FDA/OHRP\]](#)
- [21 CFR parts 50, 56, 312, 812 \[FDA\]](#)
- [ICH E2a and E6 \[GCPs\]](#)
- [CTMB guidelines \[NCI/CTEP\]](#)
- 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 subjects 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: ACRIN trials that involve investigational agent(s) and/or device(s) must adhere to FDA regulations
- NIH, NCI, DCTD, CIP: Oversees ACRIN's auditing program for federally-funded trials. In addition, for IND trials for which CIP is the IND holder, CIP's responsibilities are to ensure the IND study is conducted in compliance with FDA and local regulations.
- NIH, NCI, DCTD, CTEP, CTMB: Establishes QA and audit standards for all clinical trials sponsored by CTEP; ACRIN follows CTMB's guidelines for auditing, even though ACRIN's trials are not sponsored by CTEP
- Office of Public Health and Science (OPHS): Provides resources for ethical considerations and 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:

- 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.
- ACR IRB – Oversees all ACRIN clinical trials. The IRB 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.
- 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 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 web site – 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.

CHAPTER 3 - AUDIT PROGRAM SPECIFICATIONS

What Types of Audits Does ACRIN Conduct?

ACRIN conducts four types of audits: Regular Cycle, Re-Audit, For Cause/Special, and Other/Off-cycle. 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.
- **For Cause/Special** – 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 when 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 of NCI Scientific Misconduct policy, pages 7 – 15)
- **Other/Off-cycle** – 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.

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.

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 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 until the end of the trial. This includes collection of quality data per protocol requirements.

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 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?

CHAPTER 4 – PREPARING FOR THE AUDIT

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 notifications for regular cycle, re-audits, special/for-cause, and/or other/off-cycle 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 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.

It is recommended that the institution perform an internal audit or monitoring review prior to the ACRIN audit to ensure compliance with the protocol and the federal regulatory guidelines. When reviewing participant charts, discrepancies between source documents and submitted data may be resolved, or else annotated with a memo to file if they cannot be resolved. An institution must document and report instances of protocol non-compliance to ACRIN lead data manager immediately. All data corrections and clarifications must be made in accordance with [Good Clinical Practices](#) (GCPs).

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 organized and labeled so that the auditor can quickly locate documents. The order of document filing should be consistent throughout all charts.
- Study documents are assessed for compliance with [GCPs](#), the protocol, SOPs, and applicable local and federal requirements. GCP encompasses many aspects of human subjects research. 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
 - Nursing notes
 - Research / progress notes
 - Electronic tracking records or site-designed shadow databases
 - Other items may apply; per required source documentation specific to each trial

Three important things to know about source documents are:

1. All reports must be the final approved versions and they must be signed and dated; preliminary reports are not acceptable.
2. All notes must be initialed and dated by the person making the entry.
3. 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...)?

If source documents are stored in various locations throughout the institution, the research staff must obtain and have them available at the time of the audit. (Examples of source documents include PET Imaging log sheets, patient questionnaires, and chemotherapy administration records.) The original documents, if available, are preferred; however, copies are acceptable.

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. Oftentimes 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?

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

- 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, and
- Number of auditors present.

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.

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. *More than 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's 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. 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, a 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);
- 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.

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 continuous, open communication with the auditor, you 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.

What Will the Auditor Look At During the Audit?

The audit consists of two 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 (CAPs) is also reviewed, when applicable.

What IRB and Regulatory Documentation Should I Have Ready for the Auditor?

Following is the list of documents, at minimum, that must be ready for review. Additional items may be appropriate depending upon the specifics of the protocol. Refer to [ICH E6 Section 8 of GCP](#): Essential Documents for the Conduct of a Clinical Trial.

- Documentation of full-board IRB of record initial approval of the protocol and informed consent form (ICF).
- Documentation of annual IRB re-approval of the protocol and ICF by the IRB of record.
- Documentation of IRB approval for recruitment material, participant questionnaire, protocol amendments, and ICFs.

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 that 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 IRB approval along with ACRIN approval prior to recruitment, consenting, enrollment, registration, and/or study-specific procedures for any treatment of participant.
- Continuing IRB reviews must be within one year of (or less if the IRB so requires), and prior to expiration of, the prior approval.
 - Lapses of less than 30 days are considered lesser deficiencies.
 - Lapses of 30 days or more are considered major deficiencies.
 - Lapses on protocols closed to accrual for which all participants have completed imaging are considered lesser deficiencies.
 - Missing approvals are considered major deficiencies.
- Expedited IRB 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 registered only during periods of active IRB approval.
- Internal reportable adverse events reported to the IRB, NCI, FDA, and/or ACRIN as appropriate, and in a timely manner.
- IRB approval of protocol amendments must be within 60 days of ACRIN's notification that an amendment is available.
- Evidence of recruitment materials, including participants' educational materials and retention plan (if available) have been submitted, received, and approved by the IRB of record.
- Copies of all protocol versions/amendments from the time of trial initiation at your institution must be available, either printed or electronic. All amendments 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.
- Investigators' Curriculum Vitae (CVs) and Medical Licenses.
- Copy of completed and signed Statement of Investigator (or Form FDA 1572 for IND trials).
- Study Staff Signature and Responsibilities Log(s).
- For IND trials—

- Signed and completed Statement of Investigator/Form FDA 1572 (all versions used throughout trial).
- 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 Agent Accountability Record Form (NCI DARF) or similar documents.
- External safety reports submitted to the IRB for unexpected \geq grade 3 events with an attribution of possible, probable, or definite, per the policy of the IRB of record.
- Additional required documentation for IND trials as per the specific protocol being audited.

ACRIN recognizes that the local IRB of record for each study provides oversight of all human subjects 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 at 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 all other persons as required by the IRB of record. If space/line is provided on the ICF for specific signatures, the IRB requires completion of signatures by those individuals;

- ICF must be signed prior to participant registration, and prior to participant receiving any protocol-specific procedures;
- Participant must be consented on the current IRB-approved ICF version at the time of participant registration;
- Re-consent must be obtained as required by the institution's IRB.
- Eligibility:
 - Documentation must be available to confirm that the investigator or the appropriate 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; 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 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.
 - For IND trials—
 - Dose delivered to the subject must be within +/- 10% of protocol specifications.
 - Documentation of administration of IND must be present and accurate.
 - IND agent must be completely accounted for from delivery to disposal. Radio-active IND agents must show evidence of proper handling, 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.

- 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 SOPs.
- 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 must be managed per protocol:
 - AEs must be assessed by the investigator 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 time frame;
 - AEs as specified in the protocol must be reported.
- 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.

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. 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 already been apprised 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).

CHAPTER 6 – ASSESSING AUDIT FINDINGS AND AUDIT OUTCOMES

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 Subjects Protections as specified in ICH GCP E-6, 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).

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

- Protocol never approved by IRB
- Initial IRB approval documentation missing
- Initial approval by expedited review
- Expedited re-approval for situations other than approved exceptions (see Appendix 3)
- Registration and/or treatment of patient prior to full IRB approval
- Re-approval delayed more than 30 days, but less than one year
- Registration of patient on protocol during a period of delayed re-approval
- Missing re-approval
- Expired re-approval
- Internal reportable adverse events reported late or not reported to the IRB
- Lack of documentation of full-board IRB approval of a protocol amendment that affects more than minimal risk, or IRB approval is greater than 90 days after Group's notification
- Failure to submit, or submitted after 90 days, any external safety reports to the IRB for unexpected \geq 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. 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 persistent 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.

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 inevaluable.
- 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 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. All other study activities should continue unless otherwise specified. 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, accrual privileges are reinstated.
- **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 are 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.

In addition to the injunctions imposed by ACRIN, your local IRB likely has their own policies regarding these situations. 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 C.F.R. 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 where 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 web site and Federal Register](http://ori.dhhs.gov/misconduct/AdminBulletinBoard.shtml). <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, and 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 **either of the two components of an audit** (regulatory and patient case, including pharmacy components for IND trials only). 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 ACRIN to **immediately** notify the CIP PD when its representatives learn of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in its research program. It should be emphasized the 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 a 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:
 - Completion of the Audit Report (by the auditor) and distribution to the institution PI and RA, ACRIN personnel, the CIP, and the Study Chair;
 - Development and submission to ACRIN of a Corrective Action Plan (CAP), should one be required, by the institution PI;
 - Resolution of all audit findings detailed in the report and implementation of a CAP, if applicable, by your institution research staff; and
 - Preparation for a re-audit, should one be required.

What Happens After the Audit?

At the conclusion of the audit, a Preliminary Audit Report is sent to CIP. The auditor next submits the final Audit Report for distribution to the institution PI and RA(s), ACRIN personnel, the CIP, and the Study Chair. The Audit Report is a detailed document that—

- 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 to work with at ACRIN 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.

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 (CAPs) and What Do I Need to Know About Them?*, for more information.

The Audit Report also will 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.

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; the timeline is 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 and is maintained as permanent documentation of the conduct of the trial; therefore, it is imperative that the CAP be comprehensive, clearly written, and address 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, the identified deficiencies, and overall 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?*

Appendix I - Commonly Used Acronyms

Following is a list of acronyms that may be found in this manual or in other ACRIN PDRC documents.

ACRIN	American College of Radiology Imaging Network
AE	Adverse Event
BC	Biostatistics Center
CALGB	Cancer and Leukemia Group B
CAP	Corrective Action Plan
CCOP	Community Clinical Oncology Program
CFR	Code of Federal Regulations
CIP	Cancer Imaging Program
CRF	Case Report Form
CTEP	Cancer Therapy Evaluation Program
CTMB	Clinical Trials Monitoring Branch
CV	Curriculum Vitae
DARF	Investigational Agent Accountability Record
DCTD	Division of Cancer Treatment and Diagnosis
DHHS	Department of Health and Human Services
DM	Data Management
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDQ	General Data Quality
GOG	Gynecology Oncology Group

GQA	General Qualifying Application
HHS	Department of Health and Human Services
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IPC	Institutional Participation Committee
IRB	Institutional Review Board
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
ORI	Office of Research Integrity
PDRC	Protocol Development and Regulatory Compliance
PHI	Protected Health Information
PI	Principal Investigator
PSA	Protocol Specific Application
RA	Research Associate
RTOG	Radiation Therapy Oncology Group

Appendix II - Glossary of Commonly Used Terms

Adverse Event	Per OHRP, an adverse event is “any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.” Refer to ACRIN’s Adverse Event Reporting Manual for further information.
Audit Team	Auditor(s) assigned to perform an audit of a particular trial at an institution
Cancer Imaging Program	Federal oversight body of ACRIN’s NCI-funded trials; ACRIN’s NCI sponsor and grantee; provides advice and technical assistance
Case List	List of participant cases selected for audit
Code of Federal Regulations	General and permanent rules and regulations (administrative laws) divided into 50 policies that represent broad areas of federal regulations
Collaborative Trial	ACRIN trial conducted in conjunction with a trial administered by another group
Curriculum Vitae	Document containing pertinent information regarding the education, background, work history and listing of publications of a professional
Due Diligence	Actions taken to ensure protocol and regulatory expectations are met. In instances when expectations are not met, documentation of attempts to meet those expectations and circumstances blocking achievement is required.
Expedited IRB Review	IRB review carried out by the IRB Chairperson or one or more other IRB members designated by the Chairperson - see <i>45 CFR 46.110</i>
External Safety Report	Applies to IND trials only. Report of an adverse experience associated with an IND from institutions other than your own.
FDA 21 CFR	Encompasses all Food and Drug regulations – see <i>Code of Federal Regulations</i>
Form FDA 1572	Collects information on an investigator and serves as a signed commitment by the investigator to adhere to all FDA regulations and conduct the trial per the protocol. This completed form is required for all trials involving INDs.

Full Board IRB Review	IRB review carried out by all members of an IRB. This method is required except in instances where expedited review is allowed – see <i>45 CFR 46.109</i>
Good Clinical Practice	International ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.
HHS 45 CFR 46	Federal policy for the protection of human subjects from research risks – see <i>Code of Federal Regulations</i>
ICH E6	Good Clinical Practice Consolidated Guidance - see <i>Good Clinical Practice</i>
Imaging Core Lab	A facility to evaluate radiology imaging independent of an institution's radiologist's interpretation
Lead Auditor	Auditor who is responsible for the overall conduct of an audit at a participating institution
National Institutes of Health	The nation's medical research agency; part of the Department of Health and Human Services.
NCI Designated Cancer Center	Institution selected by the NCI to be at the forefront in supporting clinical research and receives federal funding for cancer research trials
Protocol Variation	Any instance when protocol requirements, procedures or expectations are not met
Unannounced Case	Participant case reviewed during audit but not identified on the case list provided to the participating site in advance of the audit.

Appendix III – Additional Online Resources

There is a wealth of information available on regulations and ethical considerations in conducting human research trials. Listed here are some websites we find to be very useful.

ACRIN Links to many useful resources can be found on our website - <http://www.acrin.org/>. To access this listing, click on the 'ADMINISTRATION' tab on the home page, then click on 'REGULATORY RESOURCES'.

You will also find important information about ACRIN here.

CIP <http://imaging.cancer.gov/>

CTEP <http://ctep.cancer.gov/>

**FDA
Information
Sheet
Guidances** <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm>

ICH E6 http://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/good_clinical_practices.pdf

OHRP <http://www.hhs.gov/ohrp/>

ORI <http://ori.dhhs.gov/>