NCI GUIDELINES FOR AUDITING CLINICAL TRIALS FOR THE EXPERIMENTAL THERAPEUTICS CLINICAL TRIALS NETWORK (ETCTN)

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CTMB-AIS DEFINITIONS

Audit Type: Data Audit, Annual Site Visit

Membership Start Date: Date member first joined the ETCTN and date does not change. The roster history indicates changes over time regarding participation in the ETCTN.

Membership Status: Active, Withdrawn, or Terminated

Membership Status Date: Status date is when the ETCTN makes changes to a record such as status change (active, withdrawn, or terminated) or other changes to the membership (change of membership role, change of Lead Academic Organization, name, or audit flag). The ETCTN determines when the change is effective.

Membership Type: Lead Academic Organization (LAO), Integrated Component or Affiliate.

Record: Roster entry of a member per the ETCTN and membership study type.

Record Effective Date: Date record was changed in the CTMB-AIS database.

Record Status: Status is an active record (current roster record). A roster history may include an inactive status (past roster records).

Roster History: A list of all changes made in the CTMB-AIS to the roster for a record per the ETCTN and membership type.

Withdrawn: The member initiates termination of their membership with the ETCTN.
SECTION 1 BACKGROUND AND PURPOSE OF THE EXPERIMENTAL THERAPEUTICS CLINICAL TRIALS NETWORK AND THE NCI’s AUDITING PROGRAM

1.1 Introduction

The ultimate purpose of the Experimental Therapeutics Clinical Trials Network (ETCTN) is to define approaches to cancer treatment based on molecular characterization and biomarker/bioassay development used for patient selection in later phase clinical trials. The ETCTN is complementary to the phase 2 contracts and the National Clinical Trials Network (NCTN) that focus on late phase development with an emphasis on phase 3, disease-specific studies.

The ETCTN accomplishes its objectives by forming multi-site, multi-disciplinary project teams to define development of a drug with the support of the Investigational Drug Steering Committee (IDSC). The Network will collaborate with disease specific steering committees to develop novel treatments requiring patient selection and investigational combination therapies for the wide variety of adult malignancies. Participants, in conjunction with NCI staff, will collaborate cooperatively to achieve ETCTN objectives. NCI will provide centralized support, data management, trial registration and regulatory support activities for approved, early phase trials. ETCTN members, sites, or external ETCTN participants will have the opportunity to enroll patients on all unlimited site trials conducted by the ETCTN, irrespective of the specific site leading the trial. The ETCTN will collaborate with disease specific steering committees to develop novel treatments for the wide variety of adult malignancies requiring patient selection and investigational combination therapies. ETCTN sites are responsible for monitoring and reporting safety information throughout the conduct of their clinical trials.

The goals of the ETCTN include:

Evaluation of innovative cancer treatments consistent with national priorities for developmental therapeutics clinical cancer research using a coordinated, collaborative, and inclusive team-based approach for generating concepts for early phase experimental therapeutic clinical trials.

- Prioritized projects for development and conduct by ETCTN project teams using collective management.
- Activated and conducted clinical trials meeting all regulatory requirements efficiently and timely.
- Utilization of and effective integration of scientific expertise and clinical trials management capabilities.
- Collaboration among sites and investigators with expertise in various medical specialties and research areas/disciplines relevant to treatment of adult and childhood cancers (e.g., molecular characterization, pharmacology, cancer biology, clinical oncology, imaging).
- Enhanced emphasis on education and training of young investigators.

Early phase clinical trials by nature involve agents where the toxicity profile may not be well defined. As a result, the NCI’s approach to auditing and monitoring is a risk-based approach. Sites involved in the conduct of early phase clinical trials are academic medical centers with documented expertise in early therapeutics drug development. Additionally, these sites are audited more frequently than later phase clinical trials. See ETCTN Organization Structure under Figure 1.
Figure 1 – ETCTN Organizational Chart

*For LAOs, the treating site roster is defined by the LAO grant (i.e., updates require an amendment to the grant and to the LAO package in CTEPESYS). For P2Cs, the treating site roster is defined by the P2C contract (i.e., updates require an amendment to the contract and to the P2C package in CTEPESYS).

ETCTN – Experimental Therapeutics Clinical Trials Network
LAO – Lead Academic Organization; MM – Main Member; AO - Affiliated Organization; IC – Integrated Component; P2C – Phase 2 Consortium
1.2 Overview of the Quality Assurance Program

Practitioners of clinical trials have an obligation to take appropriate steps to protect both the integrity of science and the human subjects who participate in research studies. As others have pointed out, the integrity of a data set is a function of the entire process of data collection and analysis. Detailed plans and systems are needed to assure protocol adherence for the uniform collection of data. Vigilance to detect honest errors, systematic or random, as well as data falsification, is especially important to clinical trials since independent replication of most trials is not feasible.

One goal of a quality assurance program is to prevent problems. One of the foremost means of protection against poor adherence to protocol or poor data quality is the selection of responsible investigators and research staff. Another goal of a quality assurance program is to detect problems by implementing routine monitoring procedures. The system should make detection of both random errors and systematic errors feasible during the course of data collection. Procedures for data audit and statistical methods should be implemented to detect certain types of problems, but purposeful fraud may be very difficult to detect. A third goal is to take appropriate action in a timely and effective manner. It should be recognized that some errors will remain undetected and uncorrected regardless of the quality control, editing, and auditing procedures in place. Finally, a well designed and implemented quality assurance program should serve as a valuable educational vehicle. The on-site audit team should use the opportunity to share with the local staff good clinical practice (GCP) techniques and data management and quality control systems that have been successfully implemented at other sites. The local staff can use the results of the on-site audit to identify operational areas where improvements could be made.

As the world’s largest sponsor of clinical trials of investigational antineoplastic agents and cancer clinical trials, the NCI must ensure that research data generated under its sponsorship are of high quality, reliable and verifiable. The NCI’s quality assurance and monitoring policies for clinical trials have been in evolution since the start of the Clinical Trials Cooperative Group Program in 1955. It continues to evolve and has expanded to clinical trials conducted through other funding mechanisms.

In 1963, Congress passed the Harris-Kefauver amendments to the Food, Drug, and Cosmetic Act requiring the Food and Drug Administration (FDA) to oversee Investigational New Drug (IND) testing in human subjects. In 1977, the FDA published proposed regulations on the responsibilities of sponsors and monitors of clinical trials. While they were never finalized, the proposed regulations, which called for an annual site visit to each investigator, had a profound effect on the sponsors of clinical trials of study agents in the United States. Most sponsors changed their practices to conform to these proposals.

To assist CTEP in fulfilling its regulatory responsibilities as an IND sponsor and to assure protocol compliance and source data verification, as part of the Administrative Support Coordination Component of the ETCTN, resources for data management and monitoring will be provided under contract through the Clinical Trials Monitoring Service (CTMS). The benefits of centralized data management included increased efficiency by having a single entity responsible for study build using a core set of common electronic Case Report Forms (eCRFs) to be utilized via Medidata Rave, data management, quality assurance, adverse event analysis, and study reporting generation.

The specific tasks in the contract pertaining to the ETCTN include:

Task I: To provide a resource, and patient/study participant data quality control reviews for the Division of Cancer Treatment and Diagnosis (DCTD) for clinical investigators conducting Phase 0 (exploratory IND), Phase 1 and Phase 2 clinical trials conducted through the ETCTN. All
participating sites must submit data to CTMS using the NCI-procured Clinical Data Management System (Medidata Rave) every two weeks. The CTMS will also provide technical and administrative support for the ETCTN Data Safety Monitoring Board for randomized Phase 2 studies conducted by the ETCTN,

**Task II:** To provide an on-site auditing resource for the DCTD to assure that contractors, grantees and other clinical investigators conducting Phase 0, Phase 1 and selected Phase 2 clinical trials are in compliance with federal regulations, Good Clinical Practices (GCP), and NCI policies and procedures in order to verify submitted patient/study participant data, assure the quality of submitted data, assure protocol compliance, and assure patient/study participant safety through proper reporting.

**Task III:** Not applicable to the ETCTN program, pertains only to the Network Groups under the NCI National Clinical Trials Network (NCTN).

**Task IV:** To assure the DCTD that all cancer centers, single institutions, multi-institutional consortiums and networks conducting clinical trials using DCTD sponsored trials are in compliance with Federal regulations, Good Clinical Practices (GCP), NCI policies and procedures. This oversight shall be accomplished by on site auditing at these institutions at least once every three years.

1.3 **Purpose and Objectives**

As a sponsor for study agents and the funding agency for cancer clinical trials, FDA regulations require the Division of Cancer Treatment and Diagnosis (DCTD) to maintain a monitoring program. The Clinical Trials Monitoring Branch (CTMB) of the Cancer Therapy Evaluation Program (CTEP) in the DCTD, provides direct oversight of monitoring program which includes auditing as one component.

The purpose of an audit is to document the accuracy of data submitted to the Clinical Trials Monitoring Service via the remote data capture system (Medidata Rave) or in some circumstances, summary of the clinical data is submitted to CTEP via the CDUS (see [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/cdus.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/cdus.htm)). The audit program also seeks to verify investigator compliance with protocol and regulatory requirements. Finally, the monitoring program provides an opportunity for the audit team to share with the site staff, information concerning data quality, data management, and other aspects of quality assurance.

The major objective of the audit program to verify study data that could affect the interpretation of primary study endpoints. This is done through independent verification of study data with source documents. On-site audits to ETCTN sites are typically conducted three times per year which consist of two data audits per year involving review of patient cases and one annual visit consisting of a review of all three audit components:

- IRB/Informed consent content
- Pharmacy and Drug Accountability; and
- Patient Case Review

Additionally, if minimal accrual targets are not met, a limited mail-in (ie, off-site) review may be conducted.
SECTION 2  ROLES AND RESPONSIBILITIES FOR THE CONDUCT OF THE QUALITY CONTROL AND QUALITY ASSURANCE PROGRAMS

The Cancer Therapy Evaluation Program (CTEP) has direct oversight responsibilities for the quality assurance and monitoring programs used by the Experimental Therapeutics Clinical Trials Network (ETCTN) as well as the NCI National Clinical Trials Network. CTEP staff work closely with Clinical Trials Monitoring Service (CTMS) and the ETCTN to ensure the integrity of data and the protection of patient/study participants participating in NCI-sponsored clinical trials.

2.1 Clinical Trials Monitoring Branch (CTMB)

The CTMB is responsible for establishing guidance for the conduct of quality assurance activities. CTMS under the direction and oversight of the CTMB is tasked with data management, study monitoring and auditing of ETCTN sites. These activities allow the CTMS to ensure the sites are complying with protocol and regulatory requirements.

In addition, CTMB staff serves as an educational resource to the cancer research community on issues related to monitoring and regulatory requirements for conducting clinical trials. CTMB staff members are responsible for reviewing the scheduling of all audits, for reviewing audit reports and findings, and for assessing the adequacy and acceptability of any corrective actions.

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 CTMB, CTEP, NCI. The CTMB must be notified immediately by telephone (240) 276-6545 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 CTMB. It is the responsibility of the ETCTN Lead Academic Organization (LAO) to immediately notify CTMB when they learn of any significant irregularities or allegations related to scientific misconduct by a staff member or site participating in their research program. It should be emphasized the irregularity/misrepresentation of data does not need to be proven, a reasonable level of suspicion suffices for CTEP notification. It is also essential that involved individual(s) and/or sites follow their own site misconduct procedures in these matters.

2.2 Quality Control

Quality control is a complex topic spanning the entire range of diagnostic and therapeutic modalities. Generalization concerning optimal quality control is impossible. Cost and benefit are obviously important factors in this assessment. The CTMS utilizes a variety quality control procedures:

- Built-in edit checks within the Electronic Data Capture System
- Cross check of data between various electronic reporting systems
- Site performance evaluations
- Special Response reviews to verify outcome data
- Committees for central review of major elements that impact on the outcome of clinical trials, (eg, pathology, radiotherapy, surgery, and administration of study agents); and
- Educational functions which address data collection, data management, and overall data quality
2.3 Quality Assurance

2.3.1 Monitoring Program

Monitoring is the act of overseeing the progress of a clinical trial. All clinical research carries with it the obligation to ensure optimal therapy for patients/study participants and optimal conduct of the research such that the patients’ participation is meaningful. Accurate and timely knowledge of the progress of each study is critical to ensure oversight and appropriate monitoring of the clinical trials, this responsibility that includes many of the following elements:

- Precise tracking of patient/study participant accrual
- Ongoing assessment of patient/study participant eligibility and evaluability
- Adequate measures to ensure timely submission of study data
- Adequate measures to ensure timely medical review and assessment of individual patient/study participant data
- Timely reporting of adverse events and treatment-related morbidity information
- Periodic evaluation of outcome measures and patient safety information

Failure to comply with timely submission and query resolution may result in temporary suspension of site accrual and require submission of a Corrective and Preventive Action (CAPA) plan.

2.3.2 Auditing Program

Auditing is a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the date recorded, analyzed and accurately reported according to the protocol, sponsor’s standard operating procedures, GCP, and the applicable regulatory requirements. It is a snapshot in time, commonly an on-site process, and consists of reviewing a subset of patient/study participants on a trial.

The specific purposes of the auditing program are to document the accuracy of data submitted to CTMS and NCI/CTEP, to verify investigator compliance with protocol and regulatory requirements, adherence to the policies and procedures of each ETCTN and, if necessary provide site staff with resources for a more thorough understanding of the regulatory requirements, good clinical practices (GCP), data collection and data management practices.

2.3.3 Data and Safety Monitoring

For the early phase clinical trials funded by the NCI, in absence of requiring a formal Data and Safety Monitoring Boards (DSMB), a data and safety monitoring plan is still required in accordance with NIH policy (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html).
SECTION 3 AUDITS

3.1 Frequency of Audits

All ETCTN sites (including Lead Academic Organizations [LAOs]), integrated components and affiliates that accrue patient/study participants are subject to audit. Two Data Audits and one Annual Site Visit will be conducted on an annual basis.

3.2 Types of Audits

Data Audit: An audit in which only one component (Patient Cases) is audited. These types of audits are conducted generally twice a year.

Annual Site Visit: An audit in which all components (IRB/ICC, Pharmacy, and Patient Cases) are audited. At each annual site visit, the CTMS monitor/auditor meets with the Principal Investigator (PI) to evaluate the PI's responsibilities and obtain an update on the progress of the clinical trial. These types of audits are generally conducted once a year.

3.3 Comprehensive versus Routine Monitoring/Audits

For clinical trials assigned for CTMS Comprehensive Monitoring (Phase 1 and early Phase 2, or studies where toxicities may be of concern): Data is to be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/CTMS. These on-site audits will be conducted three times annually (one annual site visit and two data audits).

For clinical trials assigned for CTMS Routine Monitoring (Phase 2): Data is to be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/CTMS. These on-site audits will be conducted on a 18 to 36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission.

3.4 Special Audits/‘For Cause’ Audits

Special audits or ‘for cause’ audits (off-cycle) may be warranted when there are significant irregularities found through quality control procedures or when allegations of possible scientific misconduct are made. It is the responsibility of the ETCTN Lead Academic Organization to immediately notify CTMB upon learning of any significant irregularities or allegations related to scientific misconduct by a staff member or site participating in their research program. CTMB may coordinate or request that the CTMS coordinate the special audits/‘for cause’ audits. Selection of auditors to conduct special/‘for cause’ on-site audits will be made by the NCI. Other federal agencies or offices may be invited to participate in a special audit at the discretion of the NCI.

A Response Audit (special audit) may be conducted when there are initial promising findings. Such audits may include independent radiologic review for confirmation of disease response. CTEP or a sponsor may request a ‘response audit’ and CTEP determines if this type of audit is warranted.

3.5 Auditing Withdrawn or Terminated Sites

If an ETCTN Lead Academic Organization (LAO), integrated component or affiliate site is withdrawn or terminated, continued collection of follow-up data of enrolled patient/study participants according to the study schedule is required. Therefore, these sites remain eligible for an audit. The selection of withdrawn/terminated sites for audit is at the discretion of the CTMB.
SECTION 4  PREPARATIONS FOR CONDUCTING THE AUDIT

This section discusses the timing of notifying a site of an audit, selecting the audit team, and selecting the protocols and patient cases for review.

4.1 Arranging the Audit

A planned audit date is entered into the CTMB-AIS database by CTMS when the previous audit is considered complete (ie, final audit report and CAPA plan are reviewed and acknowledged by CTMB staff). The site to be audited is usually contacted two months in advance of the audit date to ensure sufficient notification for the site to prepare for the audit.

The site is provided with a list of protocols and patient cases selected for audit one month in advance of the audit date to allow the site staff sufficient time to prepare, assemble and label the required materials.

In the event of a ‘for cause’ audit, advance notice for conducting an audit and the selection of protocols and/or patient cases to be audited may be limited due to the nature of the audit.

4.2 Selection of Protocols and Patient Cases

The CTMS selects the protocols and patient cases for review. While most cases will be selected from patients/study participants accrued since the previous audit, any patient case is at risk for an audit, at any time.

4.3 Selection of Audit Team

The audit team is composed of staff from the CTMS and that may include Clinical Research Associates (CRAs), nurses, pharmacists and physicians. In some cases, the audit team may be augmented with staff from the NCI or extramural physicians who serve as volunteer auditors.

4.4 Site Responsibilities in Preparation for the Audit

The Lead Academic Organization (LAO) is responsible for ensuring that all relevant materials are available for review at the time of the audit. In most cases, audits will be conducted on-site at participating ETCTN sites. However, in some circumstances (low accrual, geographical proximity) integrated components and/or affiliate sites may be requested to be available at the LAO for auditing. In this case, the LAO must ensure that the integrated component(s) and/or affiliates provide either the original patient/study participant source documents or copies of the complete record. This includes x-rays, scans, research notes, IRB documents, NCI DARFs, informed consent documents, and other relevant information. It is recommended that an affiliate staff person, familiar with the submitted cases, be present.

To facilitate the review process, it is advisable that site staff label all documents such as hospital/clinic records, research notes, on-study labs, scans and imaging studies, consent forms, etc.
SECTION 5  CONDUCTING THE AUDIT

During the audit, the auditors review specific data related to research and regulatory requirements as described in this section. Source documents must be used to independently verify submitted study data and for protocol compliance. Source documents may include but are not limited to the following:

- IRB documents and Informed Consent Forms
- NCI Drug Accountability Record Forms (DARFs) and/or log for imaging/ radiopharmaceutical agents
- Inpatient and outpatient medical records
  - Progress notes
  - Dictated report of all imaging studies (X-rays, scans, MRIs, PET, etc.)
  - Laboratory data
  - Admission forms
- Study flow sheets and other research records that are signed and dated on a real time basis by the health care practitioner evaluating the patient/study participant
- For advanced imaging studies, source documentation worksheets would include the acquisition, processing, quality assurance documentation, reader’s interpretation, record of imaging administration, patient/study participant monitoring (vital signs, monitoring of contrast reactions, etc.), and log of staff signatures and imaging responsibilities
- Protocol or study roadmaps
- Registration/enrollment tracking sheets
- Patient diaries/calendars

In preparation for the audit certain documents such as IRB documentation, informed consent forms and DARFs may be reviewed prior to the conduct of the on-site audit.

5.1 Assessing Audit Findings

An audit consists of reviewing and evaluating: (1) documentation and conformance to IRB and informed consent requirements, (2) pharmacy operations and use of NCI DARFs, or NCI approved drug logs, and (3) individual patient cases. During the audit, each of these three components will independently be assigned an assessment of either Acceptable rating; Acceptable Needs Follow-up rating, or Unacceptable rating; based on findings at the time of the audit. An inclusive and precise definition of what constitutes an unacceptable finding is difficult to construct. Rather than developing an inclusive quantitative definition, the CTMS will use a common set of terms or examples of ‘Major’ and ‘Lesser’ deficiencies, a common system for assessing each component of an audit, and a standard audit report format using the Clinical Trials Monitoring Branch - Audit Information System (CTMB-AIS).

5.2 Review of IRB Documentation and Informed Consent Content

5.2.1 IRB Documentation

For each protocol selected for an audit, the following should be the minimum items to be reviewed:
- Documentation of full initial IRB approval
• Documentation of full IRB annual reapproval
• Documentation of IRB approval (or disapproval) of protocol amendments that affects more than minimal risk
• Documentation of IRB approval or reapproval prior to patient registration

The following descriptive terms should be used in assessing compliance:

• Delayed reapproval: Protocol reapproval by the IRB delayed up to one year
• Expired reapproval: Protocol reapproval by the IRB delayed for > one year
• Missing reapproval: Missing documentation of protocol reapproval (eg, no letter from IRB stating reapproval granted, IRB minutes not available)
• Expedited review: A review by the IRB chairperson or one or more experienced members of the IRB of research which involves no more than minimal risk or involves minor changes in previously approved research (see OHRP guidance http://www.hhs.gov/ohrp/policy/exprev.pdf)
• Other: Any regulatory concern not described above

Amendments (addendums or updates) must be approved (or disapproved) by the IRB of record within 90 days of posting on the CTSU website. Amendments that are editorial or administrative in nature are exempt from the 90 day requirement. Typographical corrections, rephrasing a sentence/section to add clarity, reformatting the document and/or changes made related to contact information are examples of an editorial or administrative change.

Unanticipated problems as defined by the Office of Human Research Protections (OHRP) [see OHRP guidance http://www.hhs.gov/ohrp/policy/advevntguid.pdf] including external safety reports must be reported to the IRB within 90 days of posting on the CTSU website.

For institutions that use the NCI Central Institutional Review Board (CIRB) [see CIRB website: https://www.ncicirb.org] as the IRB of record, the following items must be provided for auditing:

• Approval letter from CIRB to the Principal Investigator (PI) for study specific worksheet (local context)
• Documentation that IRB approval was obtained prior to patient registration
• Reporting of any unanticipated problems per OHRP/FDA policy
• Other correspondence with CIRB

If the CIRB is not the IRB of record, the PI will need to provide documentation of IRB approval from the IRB of record.

The following are examples of major and lesser deficiencies that are applicable if a local IRB is utilized when assessing IRB compliance. This list does not represent an all inclusive list of major and lesser deficiencies that may be found during an audit.

Major IRB deficiencies may include but are not limited to:

• Protocol never approved by IRB
• Initial IRB approval documentation missing
• Initial approval by expedited review
• Expedited reapproval for situations other than approved exceptions
• Registration and/or treatment of patient prior to full IRB approval
• Reapproval delayed greater than 30 days, but less than one year
• Registration of patient on protocol during a period of delayed reapproval or during a temporary suspension (ie, Request for Rapid Amendment)
• Missing reapproval
• Expired reapproval
• Internal reportable adverse events reported late or not reported to the IRB
• Lack of documentation of IRB approval of a protocol amendment that affects more than minimal risk or IRB approval is greater than 90 days after Network Group's notification; this includes a 'Request for Rapid Amendment (RRA)' resulting from an Action Letter indicating temporary suspension of accrual with expedited review permitted
• Failure to submit or submitted after 90 days, any reportable external safety report to the IRB that is considered an unanticipated problem as defined by OHRP

Lesser IRB deficiencies may include but are not limited to:
• Protocol reapproval delayed 30 days or less
• Delayed reapproval for protocol closed to accrual for which all patients/study participants have completed therapy

5.2.2 Informed Consent Content

The content of the local informed consent documents for at least three protocols (if there are three or more protocols) must be reviewed for content regardless of patient/study participant enrollment to ensure the informed consent forms contain the elements required by federal regulations. If there are three or less protocols reviewed, all informed consent documents must be reviewed. In addition, each of the informed consent documents selected for audit must be reviewed to ensure they contain the risks and alternatives listed in the model informed consent document approved by the NCI. For CIRB-approved consent forms, the only change allowed is the incorporation of the CIRB-approved boilerplate (local context).

The following are examples of major deficiencies related to informed consent content. This list does not represent an all-inclusive list of the major deficiencies that may be found.

• Omission of one or more risks/side effects as listed in the model informed consent document.
• Omission of one or more revisions to the informed consent document per an amendment or failure to revise an informed consent document in response to an NCI Action Letter regarding risks that require a change to the informed consent document.
• Omission of one or more required informed consent document elements per the federal regulations.
• Changes made to the informed consent document not approved by the IRB of record.
• Multiple cumulative effects of minor problems for a given informed consent.
5.2.3 Assessing the IRB and Informed Consent Content Findings

The following categories should be used in assigning a final assessment to this component of the audit:

Acceptable
- No deficiencies identified
- Few lesser deficiencies identified
- Any major deficiency identified during the audit that was addressed and/or corrected prior to the audit for which a written and dated CAPA plan exists and no further action is required by the site or the Principal Investigator because no similar deficiency has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a deficiency is associated with a safety concern and determined that further action is necessary. In either case, CTMB must receive a copy of the CAPA plan at the time the final audit report is submitted or by the date follow-up is due.

Acceptable Needs Follow-up
- Any major deficiency identified during the audit but not corrected and/or addressed prior to the audit
- Multiple lesser deficiencies identified

Unacceptable
- Multiple major deficiencies identified
- A single major flagrant deficiency found
- Excessive number of lesser deficiencies identified

If this component is rated as Acceptable Needs Follow-up or Unacceptable, the site will be required to submit a written response and/or CAPA plan to the CTMS. A copy of the written response/CAPA plan must be forwarded to CTMS within 45 calendar days from the date the final audit report is submitted to the site via the CTMB-AIS database. Upon receipt, CTMS will download the response into the database for CTMB review.

A re-audit is mandatory if the site continues to participate in the ETCTN, for any component rated as Unacceptable. A re-audit should be done no later than a year after an Unacceptable audit

5.3 Review of Accountability of Investigational Agents and Pharmacy Operations

Agent accountability and storage procedures described in this section are required under federal regulations and NCI policy for NCI-supplied study agents (by PMB/CTEP or designated company/Group for DCP and imaging agents). See NCI/CTEP policies under: http://ctep.cancer.gov/protocolDevelopment/agents_drugs.htm

An Oral NCI Investigational Agent (Drug) Accountability Record Form (Oral DARF) has been created and all transactions with oral agents must be recorded on this DARF. Agent transactions for formulations other than oral must be recorded on the NCI Investigational Agent (Drug) Accountability Record Form (DARF).

The auditing of DARFs is by protocol and study agent. When capturing the number of DARFs pages entered on the final audit report, it is the number of study agents (including different 'strengths') reviewed, not the number of DARF pages.
A waiver statement allowing use of electronic DARFs (eDARFs) has not been issued by the NCI and the NCI does not endorse any eDARF pharmacy package. Institutions that choose to use an electronic accountability system must ensure the database is capable of producing a paper printout that is identical to the NCI DARF. Electronic accountability system database limitations are not valid reasons for improper accountability documentation according to NCI policy.

5.3.1 Control Dispensing Area/Pharmacy

The Control Dispensing Area for each investigator is identified by the shipping address provided on the Supplemental Investigator Data Form (IDF) or on the institution’s Primary Shipping Designee Worksheet. The IDF is submitted with the annual CTEP Investigator Registration packet.

The location is responsible for:

- Direct receipt of NCI-supplied agent from the NCI
- Appropriate storage and security of agent
- Dispensing agent to patients/study participants as prescribed by CTEP registered investigators and dictated by the protocol
- Overall inventory control (including provision of agent to satellite dispensing areas, as applicable, oversight of satellite dispensing areas, and dissemination of agent stock recovery information)
- Final disposition of NCI-supplied agents (returns, transfers and authorized local destructions)

5.3.2 Satellite Dispensing Area/Pharmacy

The Satellite Dispensing Area receives NCI-supplied agent from a Control Dispensing Area. The Satellite Dispensing Area must store and secure agent appropriately. Agents are to be administered for research-related treatment to eligible patients/study participants as prescribed by CTEP registered investigators and dictated by the protocol. The Satellite Dispensing Area is under the direct responsibility of the Control Dispensing Area. The Satellite Dispensing Area is responsible for:

- Receiving agent from the Control Dispensing Area
- Dispensing agent to a patient/study participant
- Returning agent to the Control Dispensing Area for further disposition (eg, continued clinical use, transfers, authorized local destruction, return to NCI)

5.3.3 Cancer Control/Imaging Studies

Imaging study agents may or may not be managed by the pharmacy depending on the protocol. However, imaging study agents are usually delivered directly to the imaging department or center that is performing the imaging study. Cancer control/prevention and imaging study agents are usually manufactured on-site or purchased from and distributed by commercial vendors. Even though these study agents are not usually distributed by the NCI, cancer control/imaging studies should also abide by the same NCI/CTEP policies. It is strongly suggested that NCI DARFs be utilized to track these study agents. However, if NCI DARFs are not utilized, the imaging study agent/radiopharmaceutical accountability logs must at least capture the same information as on the NCI DARFs.
5.3.4 Guidelines for Conducting the Pharmacy Review

There are challenges with categorizing major and lesser deficiencies for the pharmacy component of the audit. As a result, the auditors/Network Group determines the rating based on identified non-compliance items. The auditor will review: drug accountability, proper use of NCI DARFs, required procedures being followed, and appropriate storage and security measures are adhered to for NCI-sponsored trials using NCI-supplied study agents, including cancer control/ prevention and imaging agents. Cancer control/ prevention and imaging agents may be supplied by other vendors. The following is a detailed listing of compliance and non-compliance descriptions:
## NCI DARFs COMPLETELY AND CORRECTLY FILLED OUT

### Compliance

- Maintain accurate and timely records of agent disposition of all NCI-supplied study agents using NCI Investigational Agent (Drug) Accountability Record Forms (DARFs)
- Oral NCI-supplied study agents are documented on the Oral DARF
- NCI DARFs are utilized to track cancer control/imaging agents, or other accountability log captures the same information as NCI DARF
- Paper and/or electronic DARFs (eDARFs) contains all required information; paper printout of eDARF is identical to NCI DARF
- Corrections on DARFs are lined out, initialed and dated with no erasures and whiteouts; corrections on eDARFs are documented
- An institution or centralized pharmacy service (Control) may receive NCI-supplied study agent directly from NCI and is permitted to deliver (transport, not re-ship or repackaged) NCI-supplied study agent to investigator offices, clinics, or other institution’s Satellite Dispensing Areas
- Agent has been transferred to an investigator who is actively registered with CTEP; agent was dispensed to a registered patient/study participant and documented on the appropriate DARF

### Non-Compliance

- NCI DARF not maintained or not maintained completely and accurately
- Oral NCI DARF not maintained or not completely and accurately filled out
- NCI DARF not maintained on timely basis
- Inability to track the receipt, use and disposition of NCI-supplied study agents
- Incorrect agent, dose, or dates dispensed, incorrectly prepared drug, and/or incorrectly documented
- Paper and/or electronic DARFs (eDARFs) do not contain all information or are not completed as required; paper printout of eDARF is not identical to the NCI DARF
- Erasures or “whiteouts” on paper DARF
- Corrections are not lined out, initialed and dated on paper DARF
- Corrections are not appropriately documented on eDARF in electronic inventory system
- NCI-supplied study agents are repackaged and/or reshipped to other investigators, patients, or locations by mail or express carrier
- Study agent has been transferred to an investigator who is not actively registered with CTEP
- Dispensing of NCI-supplied study agent to a registered patient/study participant and not recorded or not recorded on the appropriate DARF
DARFs PROTOCOL AND AGENT SPECIFIC

**Compliance**

- NCI-supplied study agent used only for patient/study participant entered onto an approved NCI-sponsored protocol
- NCI-supplied study agent used to treat NCI patient/study participant when supplied by the NCI
- NCI-supplied study agent used for more than one protocol has a separate DARF for each protocol
- Protocols using multiple investigational agents have a separate DARF for each agent
- Separate DARFs are maintained by protocol, study agent, different strength or ‘dosage form’ (eg, oral, injectable), and by ordering or designated ordering investigator
- A separate patient-specific DARF is maintained for each patient/study participant on a patient-specific supply study, as dictated by the protocol
- Appropriate documentation of agent dispensing to multiple patients/study participants of multi-dose medication on separate lines of the DARF

**Non-Compliance**

- Patient/study participant identified on DARF is not a registered patient/study participant
- NCI-supplied study agent used for pre-clinical or laboratory studies without written approval by NCI
- Substitution of any NCI-supplied study agent, with non-NCI supplied study agent, including commercial agents
- Lack of a DARF(s) to verify NCI-supplied study agents are administered to patients/study participants or transported and delivered to investigators at Satellite Dispensing Areas and administered to patients/study participants
- Each NCI-supplied study agent not accounted for separately by protocol
- DARF maintained by lot #
- One DARF used for more than one protocol
- One DARF used for a protocol using multiple study agents
- One DARF used for multiple strengths, dosage forms of an agent, or multiple ordering investigators
- Single DARF used for multiple patients/study participants on study when patient-specific DARF should be maintained
- Multiple dose vials recorded for one patient/study participant instead of multiple patients/study participants, or multiple doses recorded on a single line of the DARF
SATELLITE RECORDS OF DISPENSING AREA

**Compliance**
- Satellite Dispensing Area DARF is used at each location where NCI-supplied study agents received from the Control dispensing area are stored more than a day
- Satellite Dispensing Area records are available the day of the audit
- Satellite Dispensing Area and Control records match and are accurately maintained
- Unused agent is documented on Satellite Dispensing Area DARF as returned to Control for disposition (ie, transfer, return and/or to be locally destroyed)

**Non-Compliance**
- No satellite DARFs in use when required
- Satellite DARFs not available at the time of the audit
- Satellite and Control records do not match or are not accurately maintained
- Unused study agent is not documented or returned to Control dispensing area; Satellite Dispensing Area is inappropriately transferring and/or locally destroying NCI-supplied study agent

NCI DARFs KEPT AS PRIMARY TRANSACTION RECORD

**Compliance**
- NCI-supplied study agent order receipts (Shipment Record of Clinical Drug Request) retained and available for review
- Documentation on Control DARF of agent transaction such as agent returns, agent transfers or agent destruction
- Written documentation of NCI authorization for transfer of agent between investigators, protocols or institutions or for local destruction of unused NCI-supplied study agent (undispensed or expired) is maintained
- Balance on DARF matches physical inventory

**Non-Compliance**
- NCI-supplied study agent order receipts (Shipment Record of Clinical Drug Request) not retained or not available for review
- Lack of documentation on Control DARF of NCI-supplied study agent transactions and destruction
- NCI-supplied study agents have been borrowed
- Transfer Investigational Agent Form not used when transferring NCI-supplied study agent
- No written documentation of NCI authorization of transfer or local destruction of NCI-supplied study agent maintained
- Quantities not accounted for in physical inventory; quantity does not match DARF
RETURN OF STUDY AGENT

Compliance

• Return of NCI-supplied study agent to NCI or locally destroyed with NCI authorization when notified study agent is no longer suitable for clinical use; Return Form or local destruction authorization is maintained

• For studies that are completed or discontinued, return of NCI-supplied agent to the NCI, or locally destroyed upon NCI authorization or transferred to another NCI protocol (with NCI approval), and Return Form or local destruction authorization or transfer approval is maintained

• NCI-supplied study agent is returned, transferred or locally destroyed within 90 days of study completion, when requested by the NCI, or when patients/study participants are in follow-up and NCI-supplied agent is not being administered

• Patient/study participant returns of NCI-supplied study agents are recorded on the patient-specific DARF for patient-specific supply studies

• Patient/study participant returns of oral NCI-supplied study agents are documented appropriately on the oral DARF

• Patient/study participant returns of non-oral, non-patient-specific supplies are not recorded on the DARF

Non-Compliance

• NCI-supplied study agent is not returned, not transferred to an appropriate NCI protocol or not destroyed within 90 days; NCI-supplied study agent is destroyed without NCI authorization or not destroyed per local institution’s destruction policy

• Failure to maintain Return Form or documentation of local destruction; no written NCI authorization for transfer or for local destruction

• NCI-supplied study agents not returned, transferred or destroyed when patients/study participants are in follow-up and no NCI-supplied study agent is being administered

• Patient/study participant returns of NCI-supplied study agents are not recorded on the patient-specific DARF for patient-specific supply studies

• Patient/study participant returns of oral NCI-supplied study agents are not documented appropriately on the Oral DARF

• Patient/study participant returns of non-oral, non-patient-specific supplies are not recorded on the DARF
STUDY AGENT STORAGE

Compliance
• Each NCI-supplied study agent is stored separately by protocol, different strength or ‘dosage form’ (eg, oral, injectable) and by ordering or designated ordering investigator (by Group)
• NCI-supplied study agent used for more than one protocol is kept in separate physical storage for each protocol
• NCI-supplied study agent is stored under proper conditions (ie, refrigeration, freezer or room temperature) with appropriate documentation and maintenance of temperature monitoring

Non-Compliance
• NCI-supplied study agents not stored separately by protocol, different strength or ‘dosage form’ (eg, oral, injectable) and by ordering or designated ordering investigator (by Group)
• NCI-supplied study agents used for more than one protocol combined in storage
• NCI-supplied study agent not stored under proper conditions; temperature monitoring documentation not maintained

ADEQUATE SECURITY

Compliance
• NCI-supplied study agent is stored in a secure area that can be locked
• Storage areas shall be accessible only to authorized individuals; unauthorized individuals are supervised by an authorized individual

Non-Compliance
• NCI-supplied study agent is stored in an insecure area
• Unauthorized individuals have access to a secure area without supervision

AUTHORIZED PRESCRIPTION(S)

Compliance
• Investigator prescribing or cosigning a prescription for NCI-supplied study agent has an active investigator registration with CTEP
• An order must be signed by an active registered investigator or co-signed if order is from other staff prior to study agent dispensing and administration
• Procedures are in place in the pharmacy and followed to ensure that the person prescribing or cosigning prescriptions for NCI-supplied study agent has an active investigator registration with CTEP

Non-Compliance
• NCI-supplied study agent is prescribed by a person not registered with CTEP as an investigator, or order was not co-signed by an active registered investigator
• An order was not signed or co-signed by the registered investigator prior to study agent dispensing and administration
• Pharmacy does not have procedures in place to ensure person prescribing or cosigning prescriptions for NCI-supplied study agent has an active investigator registration with CTEP
5.3.5 Assessing the Accountability of Study Agents and Pharmacy Operations

Auditor discretion can be used for minor problem(s) identified during the review of the pharmacy. The number of active patient/study participants on NCI-sponsored clinical trials, and the number of open protocols reviewed should be considered in the evaluation.

The following categories should be used in assigning a final assessment to this component of the on-site audit:

Acceptable

- Compliant in all categories
- Any non-compliant item identified during the audit that was addressed and/or corrected prior to audit for which a written and dated CAPA plan exists and no further action is required by the site or the Principal Investigator because no similar non-compliance issue has occurred since the CAPA plan was implemented. However, this approach may not be applicable if the non-compliance is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, CTMB must receive a copy of the CAPA plan at the time the final audit report is submitted or by the date follow-up is due.

Acceptable Needs Follow-up

- Category found non-compliant during the audit which was not corrected and/or addressed prior to the conduct of the audit

Unacceptable

- Inability to track the disposition of NCI-supplied study agents
- Multiple non-compliant categories

No Assessment Required

- No IND or NCI-supplied study agent is in stock or in use during the audit period and the pharmacy is not inspected

If this component is rated as Acceptable Needs Follow-up or Unacceptable, the site will be required to submit a written response and/or CAPA plan to the CTMS. A copy of the written response/CAPA plan must be forwarded to CTMS within 45 calendar days from the date the final audit report is submitted to the site via the CTMB-AIS database. Upon receipt, CTMS will download the response into the database for CTMB review.

A re-audit is mandatory, if an site continues to participate in the ETCTN for any component rated as Unacceptable. A reaudit should be done no later than a year after an Unacceptable audit or when there is sufficient activity to assess the effectiveness of the CAPA plan. If the pharmacy requires a reaudit due to non-compliance related to storage and/or security, the re-audit must be conducted on-site.

5.4 Review of Patient Case Records

Each patient case will be reviewed for major and lesser deficiencies in each of the following categories:

- Properly signed and dated informed consent document
- Eligibility
• Correct treatment and treatment sequence
• Evaluation of disease outcome/tumor response
• Adverse events related to treatment
• General quality of the data collected

If records are not in English then a qualified translator chosen by the audit team or institution must be present. Documentation for patient case findings identified as missing at the time of the audit and requested by the audit team must be supplied within 10 business days of the audit.

5.4.1 Examples of Major Deficiencies

A major deficiency is defined as a variance from protocol-specified procedures that makes the resulting data questionable. The following are examples of major deficiencies. This does not represent an all-inclusive list of major deficiencies that may be found during the audit. The term ‘intervention’ is intended to include non-treatment studies such as cancer control, prevention, advanced imaging, etc.

Informed Consent

Failure to document properly obtained informed consent such as:

• Consent form document missing
• Consent form document not signed and dated by the patient/study participant
• Translated consent or short form not signed and dated by a non-English speaking patient/study participant
• Consent form not signed by patient prior to study registration/enrollment
• Consent form does not contain all required signatures
• Consent form used was not the current IRB-approved version at the time of patient registration
• Consent form not protocol specific
• Consent form does not include updates or information required by IRB
• Re-consent not obtained as required
• Consent of ancillary/advanced imaging studies not executed properly

Eligibility

• Review of documentation available at the time of the audit confirms patient/study participant did not meet all eligibility criteria and/or eligibility requirements were not obtained within the timeframe as specified by the protocol
• Documentation missing; unable to confirm eligibility
  Exception: Patients deemed ineligible based on laboratory/pathology reports following registration and changes based on central review of material.

Treatment

• Incorrect agent/treatment/intervention used
• Additional agent/treatment/intervention used which is not permitted by protocol
• Dose deviations, modifications, or incorrect calculations (error greater than +/- 10%)
• Dose modifications/treatment interventions not per protocol
• Treatment/intervention incorrect or not administered correctly, incorrectly calculated, or not adequately documented
• Timing and sequencing of treatment/intervention not per protocol
• Unjustified delays in treatment/intervention

**Disease Outcome/Response**

Failure to evaluate response according to the protocol, for example:

• Inaccurate documentation of initial sites of involvement
• Tumor measurements/evaluation of status or disease not performed or not documented according to protocol
• Protocol-directed response criteria not followed
• Claimed response (PR, CR, etc.) cannot be verified or auditor could not verify the reported response
• Failure to detect cancer (as in a prevention study) or failure to identify cancer progression

**Adverse Events**

Failure to assess and report adverse events according to protocol, for example:

• Grades, types, or dates/duration of serious adverse events inaccurately recorded
• Adverse events cannot be substantiated
• Follow-up studies necessary to assess adverse events not performed
• Failure to report or delayed reporting of an adverse event that would require filing an expedited Adverse Event (AE) report or reporting to the Group
• Recurrent under- or over-reporting of adverse events

**General Data Management Quality**

• Recurrent missing documentation in the patient/study participant records
• Protocol-specified laboratory tests not reported or not documented
• Protocol-specified diagnostic studies including baseline assessments not done, not reported or not documented
• Protocol-specified research/advanced imaging studies not done or submitted appropriately
• Frequent data inaccuracies
• Errors in submitted data
• Delinquent data submission (≥ 4 weeks past due is considered a major deficiency; < 4 weeks but greater 2 weeks is considered a lesser deficiency)
5.4.2 Lesser Deficiency

A lesser deficiency is a deficiency that is judged to not have a significant impact on the outcome or interpretation of the study and is not described above as a major deficiency. An unacceptable frequency/quantity of lesser deficiencies should be treated as a major deficiency in determining the final assessment of a component.

5.4.3 Assessing the Findings from the Patient Case Review

The following categories should be used in assigning a final assessment to this component of the audit.

Acceptable

- No deficiencies identified
- Few lesser deficiencies identified
- Any major deficiency identified during the audit that was addressed and/or corrected prior to the audit for which a written and dated CAPA plan exists and no further action is required by the site or the Principal Investigator because no similar deficiency has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a deficiency is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, CTMB must receive a copy of the CAPA plan at the time the final audit report is submitted or by the date follow-up is due.

Acceptable, Needs Follow-up

- Multiple lesser deficiencies identified
- Any major deficiency identified during the audit not corrected and/or addressed prior to the audit

Unacceptable

- Multiple major deficiencies identified
- A single major flagrant deficiency identified
- Multiple lesser deficiencies of a recurring nature found in a majority of the patient cases reviewed

If this component is rated as Acceptable Needs Follow-up or Unacceptable, the site will be required to submit a written response and/or CAPA plan to the CTMS. A copy of the written response/CAPA plan must be forwarded to CTMS within 45 calendar days from the date the final audit report is submitted to the site via the CTMB-AIS database. Upon receipt, CTMS will download the response into the database for CTMB review.

A re-audit is mandatory if the site continues to participate in the ETCTN for any component rated as Unacceptable. A re-audit should be done no later than a year after an Unacceptable audit.

5.5 Role of the Investigator During the Audit

The Principal/Responsible Investigator or designee and his/her research staff must be available throughout the audit to answer any questions and help the auditors locate necessary information in the source documents.
5.6 Exit Interview

It is expected that the Principal/Responsible Investigator and designated staff will be present at the exit interview. During the exit interview the audit team will review with the institution, the preliminary findings, items reviewed ‘off-site’, and discuss any recommendations from the audit team. This interview provides opportunity for education, immediate dialogue, feedback, and clarification.
SECTION 6 REPORT OF AUDIT FINDINGS AND POSSIBLE ACTIONS

6.1 Final Audit Report

6.1.1 Submission

CTMS sends a letter summarizing the audit findings via email (and hard copy to follow) to the LAO Principal Investigator (PI) and Study Coordinator (SC) at the site for both Data Audits and Annual Audits. Final audit reports are also generated via the CTMB-AIS database and they must be submitted to the audited ETCTN site within 10 working days of the last day of the audit.

A final audit report for each type of audit is submitted electronically to the LAO Principal Investigator, Study Coordinator, and if applicable, to the Lead Protocol Organization (LPO). For Annual Audits a site-specific report summarizes the audit findings for each of the three components (IRB/ICC, Pharmacy and Patient Cases). For Data Audits, a site-specific report summarizes the audit findings for the only component (Patient Cases) audited. Recommendations from the audit team are noted in the General Comments or Exit Interview sections.

6.1.2 Content

The following information should be included in the final audit report:

6.1.2.1 General Information

- Provide information specific to the site such as number of cases audited, average annual accrual, and site staff present at the audit
- Identify members of the audit team; indicating title and affiliation

6.1.2.2 IRB and Informed Consent Content (ICC)

- Provide the title of each protocol audited and list the number of patients/study participants audited, the IND drugs, treatment modalities used and the disease(s) studied in each protocol
- For each protocol, indicate whether OK, major, or lesser deficiencies were found and describe each major and lesser deficiency
- Indicate Yes or No that informed consents were reviewed
  - If reviewed, identify any deficiencies
  - Indicate if the informed consent content was reviewed ‘off site’

6.1.2.3 Accountability of Investigational Agents and Pharmacy Operations

- Indicate Yes or No if INDs or NCI supplied agents were used at this institution during the period covered by this audit
- Indicate the number of DARFs reviewed (ie, number of study agents reviewed)
- For off-site audits, indicate ‘Not Reviewed’ for return of drug (unless verified by returned receipt from PMB/sponsor), storage, and security
• Indicate Compliant, Non-compliant, or Not Reviewed for maintaining accurate records, including primary transaction and satellite records, and specific regulations related to protocol and drugs, storage and security; for each item identified as non-compliant, select the appropriate non-compliant item or items

• The pharmacy narrative must provide an overall assessment for this component and can include guidance provided to the institution

Examples of information that may be included under the pharmacy narrative are: descriptions of non-compliance issues not outlined in the audit guidelines; review of temperature logs and excursions; rationale of why IND or NCI-supplied study agents were not selected for review, etc.

6.1.2.4 Patient Cases

• For each category, indicate if major or lesser deficiencies were found and describe, otherwise indicate OK or Not Reviewed

• The CTMB Audit Information System (CTMB-AIS) pre-populates and summarizes the deficiencies for each patient/study participant and category in a table; this table identifies the total number of major and lesser deficiencies for the total patient cases reviewed

6.1.2.5 Audit Procedures

This section indicates audit procedures such as how the audit was conducted, if any items were reviewed 'off-site', and other pertinent information.

6.1.2.6 General Comments

This section may be used to indicate if any additional data or correspondence submitted by the site to the CTMS following the audit.

6.1.2.7 Exit Interview

Indicate who was present. Summarize discussion of the audit findings, clarifications by the staff, and any recommendations by the audit team. If any portion of the audit was conducted off-site, the findings of that review should be discussed at the exit interview.
6.2 Possible Actions Due to Delinquent Data and/or Audit Findings

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, no more than 10 business days an event (e.g., Treatment, Adverse Event, Follow-up). The data will undergo a centralized clinical QA review at the CTMS and queries will be issued by CTMS staff directly within Rave. The queries will appear on a Task Summary Tab within Medidata Rave for the CRA/site staff at the ETCTN site to resolve. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS staff. Metrics for timeliness will be followed and assessed on a quarterly basis.

All major deficiencies identified during an audit need to be addressed in writing by the audited site. It must consist of actions to be taken that address each concern and/or action to be taken in order to prevent future occurrences.

6.2.1 Probation of Participating Sites

For the purpose of Site Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due. Sites with data greater than 20% past due at the end of the quarter will be placed on probation.

If a participating site is deemed Unacceptable for the same audit component on two consecutive audits, the site will be placed on probation. During the probationary period, accrual will be closely monitored with increased utilization of quality control procedures at the time of patient registration and timely review of data submission.

6.2.2 Suspension of Participating Sites

If delinquent data issues persist and are not resolved at the time of the following quarterly assessment, registration privileges to the ETCTN site will be suspended until all delinquent data are submitted and approved by the CTMS and the ETCTN NCI Program Director.

If an audited site fails to provide a CAPA plan for one or more audit components rated as Acceptable needs Follow-up or Unacceptable within the required 45 calendar days, the following actions will be imposed:

A written notice will be provided by CTMB/CTMS to the Lead Academic Organization Principal Investigator at the site stating that the response/CAPA plan is overdue and a five business day grace period will be granted.

- If follow-up or a CAPA plan is not received within the five day grace period, the patient registration privileges to ETCTN studies at the site will be immediately suspended.
- If the audited site is an integrated component or affiliate of a Lead Academic Organization (LAO), all new patient registrations will be suspended from both the LAO and the integrated component(s) and/or affiliate(s).
- If follow-up or a CAPA plan is not submitted during the five business day grace period, a written explanation from the Principal Investigator detailing the reason for the delay must be included. Suspension of patient registration will not be lifted until the site submits the response/CAPA plan to the CTMS which must be approved by CTMB. Failure to submit a timely response/CAPA plan may result in permanent termination from participation in ETCTN as well as through other NCI-sponsored clinical trials mechanisms.
6.2.3 Withdrawal Participating Sites

If improved performance is not documented at the time of the second re-audit, the site may be permanently withdrawn. Any such action will be done in consultation with CTMB and the ETCTN NCI Program Director. A ‘for cause’ audit may take place at any ETCTN site, at any time, if patient safety or scientific misconduct is suspected.

6.2.4 Clinical Trials Monitoring Branch – Audit Information System (CTMB-AIS)

The CTMB has designed an information system which permits the on-line submission of all data related to quality assurance on-site monitoring. The system allows restricted access to the stored data and will keep a record of any data changes.