GUIDELINES FOR AUDITING OF CLINICAL TRIALS FOR COOPERATIVE GROUPS, CCOP RESEARCH BASES, AND THE CANCER TRIALS SUPPORT UNIT (CTSU)

Prepared by:
Clinical Trials Monitoring Branch
Cancer Therapy Evaluation Branch
Division of Cancer Treatment and Diagnosis
National Cancer Institute

Revised October 2012 (Effective 1/1/13)
Revised October 2006 (Effective 1/1/07)
Revised June 2002
Revised August 2001
Revised October 1998
Revised March 1994
Note: Versions prior to March 1994 not listed

TABLE OF CONTENTS

LIST OF APPENDICES

CTMB-AIS DEFINITIONS

Auditable Flag: The auditable flag indicates how the CCOP and CCOP components will be audited. The flag applies only to CCOP and CCOP components and can be changed by the Cooperative Groups.

Audit Type: Routine, Reaudit or Off-cycle

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

Membership Status: Active, Withdrawn, or Terminated

Membership Status Date: Status date is when the Group makes changes to a record such as status change (active, withdrawn, or terminated) or other changes to the membership (change of membership role, change of Main Member/CCOP, name, or audit flag). The Group determines when the change is effective.

Membership Study Type: Designation of a specific roster type based on a study category such as Treatment, Prevention, UCOP, STAR, SELECT, CICRS, etc.

Membership Type: Main Member, Affiliate, CCOP, CCOP Component, or Special Member

Record: Roster entry of a member per Group 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 Group and membership type.

Terminated: The Group terminates membership of the member.

Withdrawn: The member initiates termination of their membership with the Group.

SECTION 1 BACKGROUND AND PURPOSE OF THE NATIONAL CANCER INSTITUTE'S AUDITING PROGRAM FOR COOPERATIVE GROUPS, CCOP RESEARCH BASES, AND THE CANCER TRIALS SUPPORT UNIT (CTSU)

1.1 Introduction

Practitioners of clinical trials have an obligation to take appropriate steps to protect both the integrity of science and 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.

Dr. Curtis Meinert has defined quality assurance as any method or procedure for collecting, processing, or analyzing study data that is aimed at maintaining or enhancing their reliability and validity. Quality assurance includes prevention, detection, and action from the beginning of data collection through publication of the results. Special efforts should be made to assure unbiased treatment assignment, adequate assessment of eligibility, compliance with protocol treatment and regulatory requirements, and complete collection of data on the primary outcome measures.

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 institutions. The local staff can use the results of the on-site audit to identify operational areas where improvements could be made.

1.2 Background

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. One important aspect of the quality assurance program is that investigators in the Clinical Trials Cooperative Group Program undergo peer review as part of the funding process. As the NCI's clinical research program has increased in size and complexity, the systems for quality assurance and monitoring have become more formal and systematic.

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 investigational agents in the United States. Most sponsors changed their practices to conform to these proposals.

In 1982, the NCI made on-site monitoring a requirement for the Clinical Trials Cooperative Group Program, cancer centers, and other investigators conducting clinical trials under its sponsorship. Because quality assurance programs were in place in most Cooperative Groups, the NCI delegated much of its responsibility for on-site monitoring of investigational agent studies and clinical trials to the Cooperative Groups. The guidelines were later expanded to include on-site monitoring of Community Clinical Oncology Program (CCOP) components by cancer centers which serve as their research bases.

The Cancer Trials Support Unit (CTSU) was implemented in 1999. The CTSU was mandated by the NCI in 1997 after the Report of the National Cancer Institute Clinical Trials Program Review Group report was issued. There was low participation in clinical trials and the incidence of cancer had increased, therefore the primary goal of the CTSU is to increase participation in NCI sponsored clinical trials. Several of the key functions of the CTSU are designed to streamline clinical trials through the development and operation of a comprehensive system for clinical trials management, including a regulatory support unit, an audit function, development of a clinical trials informatics support system, and the development and conduct of education and training in the CTSU system.

1.3 Purpose and Objectives

As a sponsor for investigational 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 each Cooperative Group’s monitoring program which includes auditing as one component. The purpose of an audit is to document the accuracy of data submitted to the Cooperative Groups and to verify investigator compliance with protocol and regulatory requirements. In addition, the monitoring program provides an opportunity for the audit team to share with the institution staff, information concerning data quality, data management, and other aspects of quality assurance.

The major objective of the audit program used by the Cooperative Groups is 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. The NCI CTMB Guidelines for On-Site Auditing of Clinical Trials for Cooperative Groups, CCOP Research Bases, and Cancer Trials Support Unit (CTSU) require all institutions to be audited at least once every 36 months.

In order for NCI to review the Group's compliance with this requirement, each Group should conduct a comprehensive review of its current membership including main members, affiliates, CCOPs and CCOP components, and provide in the competing or non-competing continuation application an accounting in tabular format for all institutions (Main Member, Affiliate, CCOP and CCOP component) to include: (1) date of affiliation with or termination from the Group; (2) accrual for the immediate preceding 36 months broken down by year; (3) the projected accrual for the upcoming year; (4) the date of the institutions' last audit; and (5) the date (projected month/year) of the next proposed audit. This requirement is also part of the 'NCI Clinical Trials Cooperative Group Program Guidelines' which includes a suggested format of the roster and on-site auditing activities table (see Appendix 1). A copy of the NCI Clinical Trials Cooperative Group Program Guidelines can be found under:
http://ctep.cancer.gov/investigatorResources/docs/coopgrpguidelines.pdf

SECTION 2 ROLES AND RESPONSIBILITIES FOR THE CONDUCT OF QUALITY ASSURANCE PROGRAMS

The Cancer Therapy Evaluation Program (CTEP) has direct oversight responsibilities for the quality assurance and monitoring programs used by the Cooperative Groups, CCOP Research Bases, and CTSU. CTEP staff work closely with the Cooperative Groups and CTSU to design, implement, and evaluate their quality assurance programs. This helps to ensure uniformity across the programs. The quality assurance and monitoring guidelines are the minimum set of guidelines that must be met by Cooperative Groups, CCOP Research Bases and CTSU. It is recognized that there are inherent differences in the methodologies and procedures utilized for clinical trials by the Groups, CCOP Research Bases and CTSU. While the Groups, CCOP Research Bases and CTSU must meet the minimum standards of the CTMB audit guidelines, more stringent policies and procedures may be established and enforced by the Groups, CCOP Research Bases and CTSU.

2.1 Clinical Trials Monitoring Branch (CTMB)

The CTMB is responsible for establishing guidance for the conduct of quality assurance audits. CTMB provides oversight and monitors compliance of the Cooperative Groups, CCOP Research Bases, and CTSU with the NCI's monitoring guidelines. Compliance with applicable Federal regulations is also monitored by CTMB.

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 is 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. Additionally, a co-site visitor/auditor (CTMB staff or designee) may be present at an audit to observe the audit process.

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 (301) 496-0510 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 Cooperative Group, CCOP Research Base or CTSU to **immediately** notify CTMB when they learn of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their research program. It should be emphasized 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 institutions follow their own institutional misconduct procedures in these matters.

2.2 Cooperative Groups

The multi-center and multi-modality nature of Cooperative Group clinical trials presents a variety of challenging procedural problems relating to assurance of quality and consistency in study conduct. The need for formal mechanisms of medical review and quality assurance is obvious. The Cooperative Groups have developed a number of approaches to address these issues.

2.2.1 Quality Control

Quality control is a complex topic spanning the entire range of diagnostic and therapeutic modalities employed by each Cooperative Group. Generalization concerning optimal quality control is impossible. Cost and benefit are obviously important factors in this assessment. The Cooperative Groups have well established quality control procedures defined by their constitutions and by-laws. Some of the items included in these quality control procedures are:

- Institutional performance evaluations
- Committees for central review of major elements that impact on the outcome of clinical trials, e.g., pathology, radiotherapy, surgery, and administration of investigational agents
- Educational functions which address data collection, data management, and overall data quality

2.2.2 Study Monitoring

Monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and applicable regulatory requirements. It is a continuous process, can be conducted on-site or off-site, and involves oversight of all patients on a trial.

All clinical research carries with it the obligation to ensure optimal therapy for participating patients and optimal conduct of the research such that the patients' participation is meaningful. Accurate and timely knowledge of the progress of each study is a critical Cooperative Group responsibility that includes many of the following elements:

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

2.2.3 Data and Safety Monitoring

For Phase 3 clinical trials, Cooperative Groups are required to establish Data and Safety Monitoring Committees (DSMCs) that are independent of study leadership, are free of conflicts of interest, and have formal policies and procedures approved by the NCI/NIH. The main objectives of the DSMCs are to:

- Ensure that patients in the clinical trial are protected
- Ensure that evaluation of interim results and decisions about continuing, modifying, or terminating a clinical trial and reporting results are made competently
- Assure that the credibility of clinical trial reports and the ethics of clinical trial conduct are above reproach

2.2.4 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 patients on a trial.

The specific purposes of the auditing program are to document the accuracy of data submitted to the Cooperative Groups, to verify investigator compliance with protocol and regulatory requirements, adherence to Group policies and procedures, and to provide information to institution staff on good clinical practices (GCP) related to regulatory requirements, data collection and data management.

2.3 Community Clinical Oncology Program (CCOP)

The CCOPs utilize the same quality assurance programs as those used by the Cooperative Groups. The overall purpose is to ensure that clinical trials conducted by the CCOPs and CCOP components adhere to the federal regulations, GCP and the CTMB audit guidelines. A CCOP may have a Cooperative Group or a Cancer Center serve as its research base. A CCOP may have affiliates and components (hospitals, clinics, HMOs, etc…) per the Division of Cancer Prevention (DCP); however, in this document and in the CTMB-AIS database they are referred to as CCOP components.

2.3.1 Cooperative Groups

Cooperative Groups follow the same monitoring procedures for CCOPs and CCOP components as they follow for their other members.

2.3.2 Cancer Centers

Cancer Centers that serve as CCOP Research Bases must develop their own quality assurance and monitoring programs that meet the minimum requirements established by the NCI.

2.4 CTSU

The CTSU will facilitate coordination by incorporating CTSU enrolled patient cases into the credited Cooperative Group and CCOP Research Base audit. CTSU in conjunction with the Group will determine if CTSU auditors are needed to augment the team to review CTSU protocols and CTSU patient cases. CTSU will coordinate the supply of audit materials. The CTSU will operate in accordance with the CTMB audit guidelines and the CTSU Standard Operating Procedures (SOPs) developed and updated annually by the CTSU (see Appendix 2).

SECTION 3 AUDITS

All institutions (main members, affiliates, CCOPs and CCOP components) that accrue patients to Cooperative Group, CCOP Research Base, or CTSU clinical trials during a three-year period are eligible for an audit at least once every 36 months but may be selected for audit at any time.

Each Group is responsible for timely and accurately maintaining their roster in the CTMB-AIS. The definition below, per the Unified Site Coding Procedure (Appendix 3) will be used to determine which institutions must be listed on the Group roster in the CTMB-AIS.

An institution must be listed on the Group roster in the CTMB-AIS if it meets one or more of the following criteria:

1. Direct receipt of agent from CTEP;
2. Enrollment of patients/research participants;
3. Institution's whose employees, representatives, and/or agents are authorized to obtain informed consent from patients consistent with their institutional review board policies;
4. Direct receipt of federal funds; and/or
5. Directly responsible for submission of data to the study sponsor or their designee.

3.1 Cooperative Group Membership Type

Investigators participating in Cooperative Group research may come from a wide variety of academic and/or community practice settings. Categorization of membership type is based on policies determined by each Cooperative Group. All participants must be recognized as one of the following membership types:

- Main Member Institutions: These are largely academic or major medical centers that make significant contributions to Group activities. Main member institutions provide significant accrual to Group protocols, contribute institutional scientific resources to clinical research activities, oversee and hold responsibility for mentoring and monitoring affiliate institutions.

- Affiliates: Affiliate institutions represent sites of scientific or clinical expertise which main member institutions have determined contribute significantly to Group activities. Such institutions are often community-based or are institutions with lower accrual rates. Affiliates administratively function and interact with the Cooperative Group through the main member institution. Affiliate institutions may also be private physician's offices or community clinics.

- CCOPs/CCOP Components: Funded through the Division of Cancer Prevention (DCP), CCOPs function as an outreach initiative to expand access of clinical trials to community physicians. CCOPs are comprised of any of the following: hospitals, clinics, Health Maintenance Organizations (HMO), groups of practicing physicians, or a consortium which agrees to work with a principal investigator through a single administrative unit. All hospitals, clinics, HMOs, etc. are considered CCOP components within the CTMB-AIS database. Since their accrual counts towards the CCOP, these participating institutions must be included in the roster and are held to the same standards as all other clinical trial participants.

- Special Members: A non-member participant that has specific limitations set by the Group. Examples include provisional status, restrictions related to Group activities and/or protocol participation, when lead Group is required to audit non-Group members for a particular protocol. Prior to making this designation, discussion with CTMB is necessary.

For the same Group and the same Membership Type an institution cannot be:

- Both a Main Member and a CCOP.
- Both an Affiliate and a CCOP component.
- Both a Main Member and CCOP component, or CCOP and an affiliate.

3.2 CTSU

Participants may be funded through subcontracts or other mechanisms. There is a funding and system process within the CTSU system which supports a wide variety of protocols for the NCI, other institutes, and other research activity within and outside the NIH. The participants and their institution may also be members of the Cooperative Groups. The non-Cooperative Group members may be managed by CTSU for patient registration, data management and auditing.

3.3 Main Member Institution

Main member institutions will be audited within eighteen months after entry of the first patient. If an institution accrues rapidly, the initial on-site audit should be done sooner than 18 months. Following the initial audit, main member institutions must be audited at least once every 36 months. For large accruing main member institutions, it may be appropriate for the Cooperative Group to audit these institutions on a more frequent interval given the large number of cases for review.

If a main member institution moves to a new location which requires a new NCI code and/or a decision is made by the NCI's Site Code Committee to change the NCI code to a new NCI code, the eighteen month rule does not apply as long as the institution has been previously audited by the same Group or legacy Group.

3.4 Affiliate Institution

For affiliates, an on-site audit may be conducted by the main member institution utilizing the same on-site audit procedures used by the Cooperative Group. If possible, a member of the Group who has auditing experience and is versed in the Group's audit policies and procedures should attend. Alternatively, these affiliates may be audited when the Cooperative Group conducts the on-site audit of the main member institution. Affiliate institutions must supply:

- Complete medical records (or copies)
- X-rays, scans, MRIs, PET, etc.
- NCI Drug Accountability Record Forms (DARFs)
- IRB documents and copies of the locally utilized informed consent form, etc.

These documents must be available at the main member institution the day of the audit or earlier if determined by the Cooperative Group. It is recommended that a representative from the affiliate be present at the main member institution during the audit. A separate Preliminary Report of Audit Findings and Final Audit Report are required for the main member institution and each affiliate institution audited.

3.5 Community Clinical Oncology Program (CCOP) and CCOP Components

A Cooperative Group may utilize one of three approaches to conduct an audit of its CCOPs and/or CCOP components:

- A separate audit may be conducted for each CCOP component. Separate preliminary and final reports must be submitted for each CCOP component.

- One audit may be conducted for the CCOP as a whole. Protocols and cases must be selected for review from each component where accrual has occurred. If the CCOP is audited as one entity, only one preliminary and final audit report is required. In instances when there are separate IRBs or pharmacies (receives drug directly from PMB or other sponsors) each must be audited and identified (by IRB name, institution, pharmacy location, or applicable NCI Code) in the final report, if there is a deficiency cited. The final report must also identify the patient cases by institution when generating the final audit report by entering the applicable NCI Code for the CCOP or the CCOP component next to patient ID#.

- A combination of the two above methods may be utilized.

An “audit” (yes) or “no-audit” (no) flag is included in the CTMB-AIS roster to determine the method chosen by the Cooperative Group or CCOP Research Base.

3.6 Satellite Clinics

Non-rostered institutions (satellite clinics) are defined as health care facilities used solely for the convenience of patients and do not need to be added to the Cooperative Group, grantee, or contractor rosters for reporting or auditing. These locations may be used to administer research related treatment as allowed by protocol, research related exams and test, or for follow up and consulting purposes. These locations may not directly receive CTEP agents, hold the agents for greater than one cycle of treatment (defined as treatment for one patient for one visit), or enroll patients. For example a physician office that is primarily used for patient follow-up visits. The Frequently Asked Questions (FAQs) document includes diagrams with scenarios under which a health care location can be defined as a satellite clinic.

3.7 Terminated/Withdrawn Institutions

If an institution’s membership or participation in a Cooperative Group, CCOP Research Base or CTSU is withdrawn or terminated, continued long-term follow-up of enrolled patients and the collection of good quality data according to the study schedule are required. Therefore, these institutions remain eligible for an audit. The selection of withdrawn/terminated institutions for audit is at the discretion of the Cooperative Group, CCOP Research Base or CTSU. The selection must be based on the number of total

patient cases and protocols with emphasis on important or pivotal trials, have a large number of patients in follow-up, or are not meeting acceptable quality standards for follow-up data.

3.8 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 Cooperative Group, CCOP Research Base or CTSU to **immediately** notify CTMB upon learning of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their research program. CTMB may coordinate or request that the Group, CCOP or CTSU coordinate the special audits/'for cause' audits. Selection of auditors to conduct special/'for cause' on-site audits will be made jointly by the NCI, the Cooperative Group, CCOP Research Base, or the CTSU, and a joint course of action will be planned. Other federal agencies or offices may be invited to participate in a special audit at the discretion of the NCI.

SECTION 4 PREPARATIONS FOR CONDUCTING THE AUDIT

A Cooperative Group, CCOP Research Base or CTSU must carefully plan for an audit months in advance. This section discusses the timing of notifying an institution of an audit, selecting the audit team, and selecting the protocols and cases for review.

4.1 Arranging the Audit

The audit date must be entered into the CTMB-AIS database at least 6 weeks in advance of the scheduled routine audit or reaudit. This will ensure sufficient notification to the institution and will allow CTMB staff to decide which on-site audits they or their designee will attend. This will also allow sufficient time for CTSU to coordinate efforts with the Cooperative Group conducting the audit if CTSU cases are to be included. The Group must contact CTMB for approval prior to scheduling any audit within 6 weeks. At the time of contacting CTMB, the Group must forward written documentation to CTMB from the institution to be audited (routine or reaudit) stating they are aware of the minimum 6 week requirement and agree with the proposed date.

The institution must be supplied with a list of protocols and patient cases selected for review at least two but no more than four weeks prior to the audit. This will allow the institution staff sufficient time to prepare, assemble and label the required materials.

4.2 Selection of Protocols and Patient Cases

The statistical, operations, data management office for the Cooperative Group, CCOP Research Base, or CTSU selects the protocols for review. A minimum of three protocols representing studies conducted at the institution must be selected when applicable. Emphasis should be given to the following types of studies: IND, multi-modality, intergroup, designated prevention trials and potential licensing trials, as well as those with high accrual.

Prevention trials may be audited under a different mechanism. These trials may be excluded from the selection process.

A <u>minimum</u> number of cases equivalent to 10% of patients accrued since the last audit will be reviewed. Ten percent of patient cases accrued must be selected from each participating institution (Main Member, Affiliate, CCOP, each individual CCOP component and Special Member). For selection purposes, the 10% of chosen cases must be rounded up. For example if 12 patient cases are eligible for selection, at least two cases will be audited. For selection of patient cases the following apply where appropriate: 1) 10% of Group/CCOP cases, 2) 10% of Group/CCOP “endorsed” cases, 3) 10% of “non-endorsed” cases credited to the Group or CCOP, and 4) 10% accrual from DCP/Cancer Control cases through the CTSU mechanism.

While most cases will be selected from patients accrued since the previous audit, any patient case may be at risk for selection for audit. In addition, at least one or more <u>unannounced</u> cases will be reviewed, if the total accrual warrants selection of unannounced cases. These cases may have a limited audit consisting at a minimum of

informed consent and eligibility. However, if the unannounced cases only receive a limited review, then these cases do not count towards the minimum of 10%. The unannounced cases and type of review must be documented in the final report.

4.3 Selection of On-site Audit Team

Selection of the on-site audit team should receive special consideration. Persons should be chosen who are knowledgeable of the protocols to be reviewed and of Cooperative Group, CCOP Research Base or CTSU audit procedures.

4.3.1 Cooperative Group, CCOP Research Base and CTSU

The audit team should include Cooperative Group, CCOP Research Base, or CTSU staff such as clinical research associates, data managers or statistical center personnel. The team must include a physician or other qualified individual capable of providing medical assessments, evaluating protocol compliance, and conducting an effective exit interview with the Principal/Responsible Investigator and institution personnel. The auditors must be knowledgeable about clinical trials methodology, NCI policies, and Federal regulations.

4.3.2 National Cancer Institute

As determined by the NCI, representatives from the CTEP or their designee and representatives from other Federal regulatory agencies may attend on-site audits as observers. The CTMB or their representative will notify the Cooperative Group, CCOP Research Base or CTSU operations office of the audits the observers will attend. If CTMB staff or NCI designee are present during an audit they must have full access to all documents and materials present for the audit. The exit interview is an intregral part of the audit, NCI staff or designee must be included in all exit interview discussions.

4.4 Institutional Responsibilities Preparing for the On-site Audit

The institution is responsible for ensuring that all relevant materials are available for review at the time of the audit. If affiliate institution records are audited at the time of the main member institution's audit, the affiliate must provide either the original patient 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 institution staff label all documents such as hospital/clinic records, research notes, on-study labs, scans and imaging studies, consent forms, etc. The Cooperative Group, CCOP Research Base, or CTSU should provide guidance on how preparation of documents for the audit should be done.

If the institution utilizes electronic medical records (EMRs) and/or scans, the records may be printed for viewing by the auditors, or computers with EMR access must be provided. Also, a staff member must be present to assist with negotiating through the system.

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:

- Inpatient and outpatient medical records
  - Progress notes
  - Diagnostic reports (x-rays, scans, ECGs, 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
- Protocol or study roadmaps
- Enrollment tracking sheets
- Subject diaries/calendars
- NCI Drug Accountability Record Forms (DARFs)
- Informed consents and IRB documents

At the discretion of the Group, CCOP Research Base or CTSU, certain documents such as DARFs, informed consent forms and IRB documentation may be reviewed prior to the conduct of the on-site audit. Findings from 'off-site' reviews must be included in the Preliminary Report, discussed at the Exit Interview, and explained in the Final Audit Report which items were reviewed 'off site'.

5.1 Assessing Audit Findings

An audit consists of reviewing and evaluating (1) documentation and conformance to IRB and informed consent requirements, (2) the pharmacy 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; Acceptable Needs Follow-up, or Unacceptable;** 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, all Cooperative Groups, CCOP Research Bases, and CTSU 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).

For each component rated as **Acceptable Needs Follow-up** or **Unacceptable**, the institution will be required to submit a written response and/or a Corrective and Preventive Action (CAPA) plan to the Cooperative Group, CCOP Research Base or CTSU. A copy of the written response/CAPA plan, along with an assessment of adequacy by the Cooperative Group, CCOP Research Base or CTSU of the response/CAPA plan, must be forwarded to CTMB within 45 days of the date the final audit report is submitted in the CTMB Audit Information System. Cooperative Group, CCOP Research Base, or CTSU policies and procedures may recommend and/or require additional actions or sanctions. A re-audit is mandatory, if an institution continues to participate in the Group, CCOP Research Base or CTSU, for any of the three components rated as **Unacceptable**. A reaudit should be done no later than a year after an Unacceptable audit or when sufficient patients have been accrued.

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 members of the IRB of research which involves no more than minimal risk or involves minor changes in previously approved research (see Appendix 4 and Appendix 5, Table A).
- 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 the Group's notification. Each Group, CCOP Research Base or CTSU has its own methods for notifying their institutions. Notification of temporary suspension of new patient registration will be disseminated by the Group as quickly as possible with further instructions, as necessary. 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 OHRP policy (see Appendix 6) including external safety reports must be reported to the IRB within 90 days of the Group's notification. A random sample of at least 10% of external safety reports reportable per OHRP policy must be reviewed for each protocol selected for an audit.

If the NCI Central Institutional Review Board (CIRB) is utilized by the local IRB through facilitated review, all documentation of CIRB approvals must be obtained by the local institution. Since the local IRB has assumed responsibility through facilitated review, these documents (hard copy or downloaded into a local electronic database) must be present at the time of the audit.

The following are examples of major and lesser deficiencies to be considered when assessing IRB compliance (see Appendix 5, Table A). 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 (see Appendix 4)
- 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 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 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 enrollment to ensure the informed consent forms contain the elements required by federal regulations (see Appendix 5, Table A). If there is a CTSU protocol selected, at least one of the required three informed consent documents must be from the CTSU protocol. If there are three or less protocols reviewed, all informed consent documents must be reviewed regardless if it is a Group or CTSU protocol. 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.

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 per an amendment or failure to revise an informed consent in response to an NCI Action Letter regarding risks that require a change to the informed consent.
- Omission of one or more required informed consent elements per the federal regulations. The informed consent document must also include the following statement (applicable for clinical trials initiated on or after 3/7/12): “A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.”
- 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 Corrective and Preventive Action (CAPA) plan exists and no further action is required by the Cooperative Group, CCOP Research Base, CTSU, the institution, or the principal investigator because no similar deficiency has occurred since the CAP 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 CAP at the time the final 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 institution will be required to submit a written response and/or CAPA plan to the Cooperative Group, CCOP Research Base or CTSU. A copy of the written response/CAPA plan, along with an assessment of adequacy by the Cooperative Group, CCOP Research Base, or CTSU of the response/CAPA plan, must be forwarded by the Cooperative Group to CTMB within 45 calendar days from the date the final audit report is submitted in the CTMB-AIS. Cooperative Group, CCOP Research Base, or CTSU policies and procedures may recommend and/or require additional actions or sanctions. A re-audit is mandatory, if an institution continues to participate in the Group, CCOP Research Base or CTSU, 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

Drug accountability and storage procedures described in this section are required under federal regulations and NCI/DCTD/CTEP policy. Due to the difficulty categorizing major and lesser deficiencies related to investigational drug accountability and storage, auditors will determine the rating of this component based on the findings of compliance to the required procedures for drug accountability and storage (see procedures and forms under Appendix 7).

5.3.1 Guidelines for Conducting the Review

The following are guidelines for assessing compliance and noncompliance with drug accountability, use of NCI DARFs, and storage regulations for CTEP-sponsored trials using agents supplied by CTEP (see Appendix 5, Table B):

NCI DARFS COMPLETELY AND CORRECTLY FILLED OUT

Compliance

- Maintain accurate records of the disposition of all CTEP supplied agents using NCI DARFs
- Agents supplied by the Pharmaceutical Management Branch (PMB) for NCI-sponsored protocols are shipped from PMB directly to the investigator's primary institution or office.
- In situations where two or more institutions are operating as a "centralized research base", a centralized pharmacy service can provide pharmacy services (such as agent storage, preparation and accountability) for investigators in the local community, if the investigators designate that pharmacy service as their shipping designee on their FDA form 1572 submitted to PMB; the centralized pharmacy is then permitted to deliver **(transport, not re-ship)** CTEP supplied investigational agents to the investigators' offices, clinics, or other institutions
- Agents may be dispensed, delivered, and accounted for at the treatment site in response to an individual patient's treatment order or a prescription for a single dose; in this situation, there is no need for satellite accountability records
- If the physician's office, clinic, research staff, or other institution receives or obtains a multiple day or overnight storage supply of CTEP supplied investigational agents, the DARF is maintained at the appropriate location

Non-Compliance

- Inability to track the receipt, use and disposition of DCTD/DCP supplied investigational agents
- NCI DARF not maintained
- Inability to track the agent because of omissions
- Paper and/or electronic DARFs do not contain all information or are not completed as required on NCI DARF; paper printout is not identical to the NCI DARF
- Incorrect agent, dose, or dates dispensed, incorrectly prepared drug, and/or incorrectly documented
- Registered patients who have received IND agents are not recorded on DARF
- Systematic incorrect entries on the DARF
- NCI DARF not kept on timely basis
- There are erasures or "whiteouts"
- Corrections are not lined out, initialed and dated
- Agent has been transferred to an investigator who is not registered with PMB, DCTD, NCI
- CTEP supplied investigational agents are repackaged and/or reshipped to other investigators, patients, or locations by mail or express carrier

DARFs PROTOCOL AND DRUG SPECIFIC

Compliance

- Agents received from PMB, DCTD are used only for patients entered onto an approved DCTD-sponsored protocol
- Each agent accounted for separately by protocol
- An agent used for more than one protocol must have a separate DARF for each protocol
- Multi-agent protocols have a separate DARF for each agent
- Separate accountability forms maintained for each different strength or dosage form of a particular agent
- A separate DARF is used for each patient, if stated in the protocol (double-blinded studies)
- Appropriate documentation of drug dispensing to multiple patients of multi-dose medication on separate lines of the DARF

Non-Compliance

- Patients identified on DARF are not registered patients
- Substitution with any non-DCTD supplied agents, including commercial agents
- Agents supplied for clinical trials used for pre-clinical or laboratory studies without written approval of PMB
- Lack of source documentation to verify agent supplies distributed to investigators or administered to patients
- Each agent not accounted for separately by protocol
- One DARF used for more than one protocol
- One DARF for a multi-agent protocol
- One DARF used for multiple strengths or dosage forms of an agent
- DARF incorrectly used (single DARF used for multiple patients for double blinded study; multiple dose vials recorded for one patient instead of multiple patients, or multiple doses recorded on a single line of the DARF)

SATELLITE RECORDS

Compliance

- DARF used at each location where doses for multiple patients are received and dispensed and/or stored overnight (such as satellite pharmacy, physician's office, or other dispensing areas) and available for site auditor
- Satellite and control records match

Non-Compliance

- No satellite DARFs in use when required or not available for review
- Satellite and control records are not accurately maintained
- Satellite and control records do not agree

NCI DARFs KEPT AS PRIMARY TRANSACTION RECORD

Compliance

- Agent order receipts (Shipment Record of Clinical Drug Request, NIH 986-1) retained and available for review
- Documentation on DARF of other agent transaction such as agent returns or broken vials
- Transfer of DCTD investigational agents between institutions is approved or authorized by PMB
- Balance on DARF matches supply

Non-Compliance

- Agent order receipts (Shipment Record of Clinical Drug Request, NIH 986-1) not retained or not available for review
- Lack of documentation of other agent transactions
- Agents have been borrowed
- Transfer Investigational Drug Form (NIH-2564) not used when transferring agent
- Quantities not accounted for; shelf counts and inventories do not match
- No written documentation from PMB of approval for transfer of agent

RETURN OF DRUG TO NCI

Compliance

- Return to DCTD/DCP agents (a) that are outdated, or (b) that are unusable; within 90 days from when agent expired or became unusable
- For studies that are completed or discontinued, return DCTD/DCP agents to the NCI, transferred to another NCI protocol (with PMB approval), or agent destroyed per site's local destruction policy; all appropriately conducted
- Return to DCTD/DCP agents within 90 days of study closure; and Return Form is maintained
- Patient returns of IND supplied agents are not recorded on DARFs unless agents are supplied as double blinded

Non-Compliance

- DCTD/DCP agent not returned to NCI; not transferred to an appropriate NCI protocol; or agent not destroyed per site's local destruction policy
- Failure to maintain Return Form
- DCTD/DCP agents not returned for patients in follow-up when no DCTD/DCP agent is being administered
- Patient return of IND supplied agents are recorded on the DARF for non-double blinded studies

AGENT STORAGE

Compliance

- Each investigational agent stored separately by protocol
- An agent used for more than one protocol kept in separate physical storage for each protocol
- Agent stored under proper conditions (such as refrigerator or freezer) with validation documentation

Non-Compliance

- IND not stored separately by protocol
- Agents used for more than one protocol combined in storage
- Agent not stored under proper conditions

ADEQUATE SECURITY

Compliance

- A secure area is an area that can be locked with a minimum of people having access (the key or combination).
- Storage areas shall be accessible only to an absolute minimum number of specifically authorized employees; when it is necessary for unauthorized persons to be present in or pass through, an authorized person must provide adequate observation of the area

Non-Compliance

- Agent stored in insecure dispensing area
- Unauthorized people having access to a secure area without supervision

AUTHORIZED PRESCRIPTION(S)

Compliance

- Investigator ordering and/or dispensing agents is registered with PMB, DCTD, NCI or co-signs for others prescribing agents
- Procedures are in place in the pharmacy and followed to ensure that person prescribing the DCTD-agent is an investigator registered with PMB and/or the prescription is co-signed by the registered investigator

Non-Compliance

- Agent prescribed by a person not registered by PMB as an investigator, or order was not co-signed by registered investigator
- Pharmacy does not have procedures in place to ensure person prescribing the agent is registered with PMB or prescription was not cosigned by registered investigator

5.3.2 Assessing the Accountability of Investigational Agents and Pharmacy Operations

Auditor discretion can be used for minor problem(s) identified during the review of the pharmacy. The number of active patients 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 Corrective and Preventive Action (CAPA) plan exists and no further action is required by the Cooperative Group, CCOP Research Base, CTSU, the institution, or the principal investigator because no similar non-compliance issue has occurred since the CAP 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 CAP at the time the final 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 DCTD-supplied investigational agents
- Multiple non-compliant categories

No Assessment Required

- No IND or NCI-supplied study drug 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 institution will be required to submit a written response and/or CAPA plan to the Cooperative Group, CCOP Research Base or CTSU. A copy of the written response/CAPA plan, along with an assessment of adequacy by the Cooperative Group, CCOP Research Base, or CTSU of the response/ CAPA plan, must be forwarded to CTMB by the Cooperative Group within 45 calendar days from the date the final audit report is submitted in the CTMB- AIS. Cooperative Group, CCOP Research Base, or CTSU policies and procedures may recommend and/or require additional actions or sanctions. A re-audit is mandatory, if an institution

continues to participate in the Group, CCOP Research Base or CTSU, 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 Corrective and Preventive Action (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.

For institution audits that are performed 'off-site', it is strongly recommended that an 'on-site' visit be conducted every other 3 year cycle. An on-site pharmacy inspection can be done by the main member institution, CCOP or the Cooperative Group. This would assure that pharmacy inspections and inventory controls are adequately reviewed on-site.

5.4 Review of Patient Case Records

As part of the audit, a minimum number of patient cases equivalent to 10% of patients accrued since the last audit will be reviewed as per Section 4.2. Each patient case will be reviewed for major and lesser deficiencies in each of the following categories:

- Properly signed and dated informed consent
- 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 identified as missing at the time of the audit and requested by the audit team must be supplied within a maximum of two weeks following the audit to clarify patient case findings.

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. Following are examples of major deficiencies. This does not represent an all inclusive list of major deficiencies that may be found during the audit (see Appendix 5, Table C).

Informed Consent

Failure to document properly obtained informed consent such as:

- Consent form missing
- Consent form not signed and dated by the patient
- Consent form signed after patient started on treatment
- Consent form does not contain all required signatures

- Consent form used 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
- Reconsent not obtained as required
- Consent of ancillary studies not executed properly

Eligibility

- Review of documentation available at the time of the audit confirms patient 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 used
- Additional agent/treatment used which is not permitted by protocol
- Dose deviations, modifications, or calculations incorrect (error greater than +/- 10%)
- Dose modifications not per protocol
- Treatment incorrectly administered, calculated or not adequately documented
- Unjustified delays in treatment

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/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 charts
- 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 studies not done or submitted appropriately
- Frequent data inaccuracies
- Errors in submitted data
- Delinquent data submission (> 6 month delinquency is considered a major deficiency; a 3-6 month delinquency is considered a lesser deficiency)

The Groups, CCOP Research Bases and CTSU have established guidelines and acceptability of the timeliness, completeness and accuracy of submitted data. A disregard of or untimely data reporting per Group, CCOP Research Base or CTSU guidelines may be rated as a major 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 Corrective and Preventive Action (CAPA) plan exists and no further action is required by the Cooperative Group, CCOP Research Base, CTSU, the institution, or the principal investigator because no similar deficiency has occurred since the CAP 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 CAP at the time the final 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 institution will be required to submit a written response and/or CAPA plan to the Cooperative Group, CCOP Research Base or CTSU. A copy of the written response/CAPA plan, along with an assessment of adequacy by the Cooperative Group, CCOP Research Base, or CTSU of the response/CAPA plan, must be forwarded to CTMB by the Cooperative Group within 45 calendar days from the date the final audit report is submitted in the CTMB- AIS. Cooperative Group, CCOP Research Base, or CTSU policies and procedures may recommend and/or require additional actions or sanctions. A re-audit is mandatory, if an institution continues to participate in the Group, CCOP Research Base or CTSU, for any component rated as **Unacceptable**. A reaudit should be done no later than a year after an Unacceptable audit or when sufficient new patients have been accrued. If sufficient new patients have not accrued within a year of the previous audit, further discussion with CTMB is necessary prior to requesting an extension of the reaudit timeline in the CTMB-AIS.

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

At the conclusion of the visit, the audit team will conduct an exit interview with the Principal/Responsible Investigator(s) and research staff. During this exit interview, the preliminary findings, items reviewed ‘off-site’, and any recommendations from the audit team should be discussed. This interview provides opportunity for education, immediate dialogue, feedback, and clarification.

SECTION 6 REPORT OF AUDIT FINDINGS AND FOLLOW UP

6.1 Preliminary Report of Audit Findings

A pre-populated Preliminary Report of Audit Findings is available to the audit team once an audit has been scheduled in the CTMB-AIS. This pre-populated report contains all of the identifying information about the institution to be audited.

6.1.1 Submission

The Preliminary Report of Audit Findings form (see Appendix 8) must be faxed to CTMB (301) 480-2642 or sent by email to: NCICTMBPrelimForms@mail.nih.gov within one business day of completing the audit. 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 (301) 496-0510 of any findings suspicious and/or suggestive of intentional misrepresentation of data and/or disregard for regulatory safeguards for **any of the three components** (regulatory, pharmacy and patient cases) 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 Cooperative Group, CCOP Research Base or CTSU to **immediately** notify CTMB when they learn of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their research program. It should be emphasized that 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 institutions follow their own institutional misconduct procedures in these matters.

Deficiencies identified and briefly described in the Preliminary Report must be included in the Final Report. A revised Preliminary Report may be submitted if it is within 10 business days of the audit. Any revision to the Preliminary Report must be explained in the Final Report.

6.1.2 Content

Any major deficiency related to the following components must be described in the Preliminary Report.

- IRB and Informed Consent Content
- Accountability of Investigational Agents and Pharmacy Operations
- Patient Case Records

The total number of cases with major deficiencies and the total number of patient cases reviewed must be provided for each category listed on the Preliminary Report.

6.2 Final Audit Report

6.2.1 Submission

The Final Report (Appendix 9) must be submitted in the CTMB-AIS within 70 calendar days of day one of the audit. This institution-specific report should summarize the findings at the time of the audit for each of the three components of the audit. Recommendations from the Cooperative Group, CCOP Research Base, or CTSU should be noted in the General Comments or Exit Interview sections.

If a co-site visitor/auditor is assigned to an audit, the co-site auditor will also generate a final audit report summarizing the findings of the audit and the overall audit process.

6.2.2 Content

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

6.2.2.1 General Information

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

6.2.2.2 IRB and Informed Consent

- Provide the title of each protocol audited and list the number of patients 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’
- Provide an overall assessment for this component and indicate if a re-audit is required and the time frame

6.2.2.3 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 **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
- For off-site audits, indicate 'Not Reviewed' for return of drug (unless verified by returned receipt from PMB/sponsor), storage, and security
- Provide an overall assessment for this component and indicate if a re-audit is required and the time frame

6.2.2.4 Patient Cases

- For each category, indicate if **major or lesser** deficiencies were found and describe, otherwise, put **OK** or **Not Reviewed**
- The CTMB Audit Information System pre-populates and summarizes the deficiencies for each patient and category in a table; this table identifies the total number of major and lesser deficiencies for the total patient cases reviewed
- Provide an overall assessment for this component and indicate if a re-audit is required and the time frame

6.2.2.5 Audit Procedures

This section may indicate audit participants, how the audit was conducted, items reviewed 'off-site', and other pertinent information.

6.2.2.6 General Comments

This section may be used to indicate if any data or correspondence were submitted by the institution following the audit which affects the information reported on the Preliminary Report of Audit Findings. Indicate which categories were affected and how.

6.2.2.7 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.

6.3 Follow-up Information

If this component is rated as **Acceptable Needs Follow-up** or **Unacceptable**, the institution will be required to submit a written response and/or CAPA plan to the Cooperative Group, CCOP Research Base or CTSU. A copy of the written response/CAPA plan, along with an assessment of adequacy by the Cooperative Group, CCOP Research Base, or CTSU of the response/CAPA plan, must be forwarded to CTMB by the Cooperative Group within 45 calendar days of the date the final audit report is submitted in the CTMB-AIS. Cooperative Group, CCOP Research Base, or CTSU policies and procedures may recommend and/or require additional actions or sanctions. A re-audit is mandatory, if an institution continues to participate in the Group, CCOP Research Base or CTSU, for any component rated as **Unacceptable**. A reaudit should be done no later than one year after an Unacceptable audit or when sufficient patients have been accrued.

6.3.1 Suspension of Participating Institutions

If an audited institution fails to provide a Corrective and Preventive Action (CAPA) plan for one or more audit components rated as acceptable needs follow-up or unacceptable within the required 45 calendar day time limit, the following actions will be imposed by the Group (or CTSU for non-Group aligned institutions).

- The Group will provide written notice to the Principal Investigator at the institution that the response/CAPA plan is overdue and a five business day grace period will be granted for the submission of the response/CAPA plan.
- If follow-up or a CAPA plan is not received by the Group during the five day grace period, the Group will immediately suspend patient registrations from that institution.
- If the audited institution is an affiliate of a Main Member or a component of a CCOP, all new patient registrations will be suspended from both the Main Member/CCOP and the affiliate/CCOP component.
- No registrations will be accepted by the Group through any mechanism.
- If follow-up or a CAPA plan is not submitted during the 5 business day grace period, a written explanation from the Principal Investigator detailing the reason for the delay must be included. Patient registration will not be lifted until the institution submits the response/CAPA plan to the Group and the response/CAPA plan is forwarded to and reviewed by CTMB. CTMB must receive written notification of the suspension and of the reinstatement (if applicable) of the institution.
- On subsequent audits the failure to submit a timely response/CAPA plan may result in permanent termination from participation in NCI sponsored clinical trials through the Cooperative Group, CCOP Research Base or CTSU mechanisms.

6.3.2 Probation of Participating Institutions

If a participating institution is deemed unacceptable for the same audit component on two consecutive audits, the institution will be placed on probation. During the probationary period, accrual will be closely monitored by the Group with increased utilization of quality control procedures at the time of patient registration and timely review of data submission. The institution may also be assigned a mentor by the Group. The Group may be involved in the development of the site improvement plan in conjunction with the institution. The institution site improvement plan must address key infrastructural issues contributing to poor performance. A copy of the site improvement plan is to be submitted to CTMB within 45 calendar days of the second unacceptable audit.

6.3.3 Termination of Participating Institutions

If improved performance is not documented at the time of the second re-audit, the institution may be permanently terminated by the Group, CCOP Research Base or CTSU. Any such action will be done in consultation with CTMB. A 'for cause' audit may take place if patient safety or scientific misconduct is suspected.

6.4 Reaudits

A re-audit is mandatory for any component rated as **Unacceptable** if the institution continues to participate in the Group, CCOP Research Base or CTSU. It is not necessary that the reaudit be conducted on-site. Depending on the nature of the deficiency or deficiencies which resulted in the **Unacceptable** rating, the reaudit could be done as an off-site review, unless the pharmacy requires a reaudit due to non-compliance related to storage and/or security. This is at the discretion of the Cooperative Group, CCOP Research Base, or CTSU. A reaudit should be done no later than a year after an Unacceptable audit or when sufficient patients have been accrued.

If the institution is being terminated or withdrawn, the reaudit timeline on the final report for the applicable audit components are to be designated 'No Reaudit'. This allows the Group and CTMB to track these institutions that require a reaudit if reactivated. For tracking purposes, off-site reaudits must also be scheduled and reported in the CTMB-AIS.

6.5 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. This includes submission of audit schedules, acknowledgment of preliminary reports, transmission of final audit reports, and tracking of follow-up responses to audit findings. The system allows restricted access to the stored data and will keep a record of any data changes. Documentation of the CTMB Audit Information System can be accessed after providing a username and password at:

https://webapps.ctep.nci.nih.gov/ctmbais/ctmbaislogin.startup