

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

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Data Irregularities
(see Sections 2.1 and 6.1.1)*

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SECTION 1 BACKGROUND AND PURPOSE OF THE NATIONAL CANCER INSTITUTE'S MONITORING 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 visit team should use the opportunity to share with the local staff good clinical practice 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 Clinical 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) 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 Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases, and Clinical 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 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.

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

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 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. To assure consistency in the conduct of on-site audits, CTMB staff or its designee may attend certain on-site audits.

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 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 regarding 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

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 Monitoring Program

The specific purposes of the monitoring 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

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 CCOP components adhere to GCP. A CCOP may have a Cooperative Group or a Cancer Center serve as its research base. A CCOP may have affiliates and/or components, however, in this document and in the CTMB-AIS they are referred to as 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 as long as they meet the minimum requirements established by the NCI.

2.4 CTSU

The CTSU will facilitate coordination by incorporating audits of CTSU enrolled patient cases into the current Cooperative Group and CCOP Research Base audit mechanisms. CTSU in conjunction with the Group, will determine if additional reviewers are needed to augment the team, and will coordinate the supply of audit materials. For high accruing CTSU institutions that are aligned with a Cooperative Group, the CTSU may supplement the Group audit team to review CTSU patient cases. The CTSU alone will conduct single

site audits at institutions that do not belong to Cooperative Groups, but are part of the CTSU Independent Clinical Research Sites (CICRS) that have enrolled CTSU patients. “Non-members” that do not belong to a Cooperative Group are known as CICRS. The CTSU will operate in accordance with the Guidelines and the Standard Operating Procedures (SOPs) developed and updated annually by the CTSU. (See Appendix 1) Annual CTSU updates may be accessed at: <https://members.ctsu.org/EducationTraining>.

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 thirty-six months but may be selected for audit at any time.

The following definition will be used to determine which institutions are to be listed on the Group roster:

Any institution **MUST** be listed on the Group roster if it satisfies both of the following criteria:

1. Has an IRB that reviews Group protocols or is covered by a written OHRP approved IRB agreement and
2. Consents patients for Group protocols

3.1 Cooperative Group Membership Type

Investigators participating in Cooperative Group research may come from a wide variety of academic and practice settings. Categorization of membership type is based on policies determined by each Cooperative Group. For auditing purposes, all participants should 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 sites may also be private physician's offices or community clinics.
- CCOPs/CCOP Components: Funded through the Division of Cancer Prevention, 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. Since their accrual counts towards the CCOP, these participating sites must be included in the roster and are held to the same standards as all other clinical trial participants.

3.2 CTSU

Participants are funded through Cooperative Group Subcontracts. CTSU physician participants are composed of members of Cooperative Groups as well as non-members. Physicians may use the CTSU to register patients onto studies that they have not previously had access to, or studies that were not open in their Cooperative Group. “Non-members” that do not belong to a Cooperative Group are known as CICRS.

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.

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 Components/Affiliates

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

- 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.
- 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 CTSU Participants

CTSU enrolled patients may be audited by a Cooperative Group auditor at the time of an audit at a participating institution or by a supplemental CTSU audit team. It is the responsibility of the CTSU to conduct audits at CICRS. In all cases, the audit should be conducted in accordance with the established NCI audit guidelines.

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, the 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 should focus on institutions that had large accrual to 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) audits 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 should be entered into the CTMB Audit Information System at least six to ten weeks in advance of the scheduled audit. It 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 institution should 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 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 site should 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 minimum number of cases equivalent to 10 % of patients accrued since the last audit will be reviewed. The 10 % of cases reviewed apply to each participating site being audited. For selection purposes, the 10 % of chosen cases will always 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% Group/CCOP cases, 2) 10% of Group/CCOP “endorsed” cases, and 3) 10% of “non-endorsed” credited to the Group or CCOP. 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 unannounced cases will be reviewed, if the total accruals warrant 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%.

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 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 integral 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.

SECTION 5 CONDUCTING THE QUALITY ASSURANCE AUDIT

During the audit, the auditors review specific data related to research and regulatory requirements as described in this section. Source documents should 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 content and IRB documentation may be reviewed prior to the conduct of the on-site audit. Findings from these reviews must be included in the Preliminary Report, discussed at the Exit Interview, and included in the Final Audit Report. It should be stated in the final report that these 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 corrective action plan to the Cooperative Group, CCOP Research Base or CTSU. A copy of the written response/corrective action plan, along with an assessment of adequacy by the Cooperative Group, CCOP Research Base or CTSU of the response/corrective action 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 (3-5 patients).

5.2 Review of IRB Documentation and Informed Consent Content

5.2.1 IRB Documentation

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 site. Since the local IRB has assumed responsibility through facilitated review, these documents (hard copy) must be present at the time of the audit.

For each protocol selected for an audit, the following should be the minimum items to be reviewed:

- Documentation of full initial IRB approval of each protocol
- Documentation of full IRB annual reapproval of each protocol
- Documentation of IRB approval for protocol amendments that affect 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 (e.g., letter from IRB, IRB minutes, etc.).
- 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 2, Table A, and Appendix 3).
- Other: Issues with amendments/revisions/updates not described above.

Amendments must be approved by the IRB of record within 90 days of the Group's notification. Each Group, CCOP or CTSU has its own methods for notifying their

institutions. Amendments that are editorial in nature are exempt from the 90 day requirement.

External safety reports for adverse events that are unexpected and \geq Grade 3 (attribution of possible, probable or definite) must be submitted to the local IRB within 90 days of the Group's notification (unless the institution's policy does not require such events to be reported and documentation of the institution's policy on external safety report review can be provided at the time of the audit). For each protocol selected for an audit, a random sample of at least 10% of external safety reports should be reviewed.

The following are examples of major and lesser deficiencies to be considered in assessing IRB compliance (see Appendix 2, 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 3)
- Registration and/or treatment of patient prior to full IRB approval
- Reapproval delayed more than 30 days, but less than one year
- Registration of patient on protocol during a period of delayed reapproval
- Missing reapproval
- Expired reapproval
- Internal reportable adverse events reported late or not reported to the IRB
- Lack of documentation of full IRB approval of a protocol amendment that affects more than minimal risk or IRB approval is greater than 90 days after Group's notification
- Failure to submit or submitted after 90 days, any external safety reports to the IRB for unexpected \geq grade 3 events with an attribution of possible, probable or definite, unless the local IRB policy does not mandate reporting of external safety reports

Lesser IRB deficiencies may include but are not limited to:

- Protocol reapproval delayed 30 days or less
- Delayed reapprovals for protocols closed to accrual for which all patients have completed therapy

5.2.2 Informed Consent Content

The content of the local informed consent document for at least three protocols, if the number of protocols allows, should be reviewed to be sure the consent contains the elements required by Federal Regulations (see Appendix 3). In addition, each of the three informed consent documents should be checked to ensure they contain the risks and alternatives listed in the model informed consent document approved by the NCI. If CTSU case(s) are reviewed at least one local informed consent document should be reviewed for content.

The following are examples of major deficiencies related to informed consent content (see Appendix 2, Table B). 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 informed consent updates or failure to revise an informed consent in response to an NCI warning letter regarding risks that require a change to the informed consent
- Omission of one or more required informed consent elements per the Federal regulations
- 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
- Major deficiencies identified during the audit that were addressed and/or corrected **prior to** the audit for which documentation exists and no further action is required by the Cooperative Group, CCOP Research Base CTSU, the institution, or the principal investigator

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 corrective action plan to the Cooperative Group, CCOP Research Base or CTSU. A copy of the written response/corrective action plan, along with an assessment of adequacy by the Cooperative Group, CCOP Research Base, or CTSU of the response/corrective action plan, must be forwarded to CTMB within 45 days of the date the final audit report is submitted in the CTMB Audit Information System. I 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 CTEP, DCTD, NCI policy. Because of 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 Appendix 4).

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 2, Table C):

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 should be 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 (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, or other institution receives a multiple day or overnight storage supply of CTEP supplied investigational agents, satellite accountability records must be maintained for each satellite location and copies must be available for review by site auditors.

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
- Electronic DARFs do not contain all information required on NCI DARF; paper printout is not identical to the NCI DARF
- Incorrect agent, dose, route of administration, or dates documented on DARF
- 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 and initialed
- Agent has been transferred to an investigator who is not registered with PMB, DCTD, and NCI
- CTEP supplied investigational agents are repackaged and/or reshipped to other investigators or locations by mail or express carrier

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, etc)

SATELLITE RECORDS

Compliance

- DARF used at each location where agents are stored and/or dispensed, e.g., main pharmacy, satellite pharmacy, physician's office, or other dispensing areas

Non-Compliance

- 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: agent returns, broken vials, etc.
- Inter-institutional transfer of DCTD investigational agents 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 faxed documentation from PMB of approval for transfer of agent
- No satellite NCI DARF

RETURN OF DRUG TO NCI

Compliance

- Return to DCTD/DCP agents (a) that are outdated; and (b) that are damaged or unfit for use
- For studies that are completed or discontinued, return DCTD/DCP agents to the NCI or appropriately transfer to another NCI protocol
- Return to DCTD/DCP agents within 90 days of study closure
- Patient returns of IND supplied agents are not be recorded on DARFs unless agents are supplied as double blinded

Non-Compliance

- DCTD/DCP agent not returned to NCI or transferred to an appropriate NCI protocol
- Not using the transfer form when transferring a DCTD/DCP supplied agent to an approved NCI protocol
- DCTD/DCP agents not returned for patients in follow-up when no DCTD/DCP agent is being administered
- Patient returns of IND supplied agents are recorded on the DARF for non-double blinded studies

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 (refrigerator, freezer, etc.) 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

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

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

- Compliance found for all categories
- All non-compliant items identified during the audit that were addressed and/or corrected **prior to** audit for which documentation exists and no further action is required by the Cooperative Group, CTSU, the institution, or the principal investigator

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

If this component is rated as **Acceptable Needs Follow-up** or **Unacceptable**, the institution will be required to submit a written response and/or corrective action plan to the Cooperative Group, CCOP Research Base or CTSU. A copy of the written response/corrective action plan, along with an assessment of adequacy by the Cooperative Group, CCOP Research Base, or CTSU of the response/corrective action 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 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 patients have been accrued (3-5 patients).

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 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. 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 also Appendix 2, Table D).

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 was not 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

Eligibility

- Review of documentation available at the time of the audit confirms patient did not meet all eligibility criteria 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 doses incorrectly administered, calculated or 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 according to protocol
- Protocol-directed response criteria not followed
- Claimed response (PR, CR, etc) cannot be verified
- 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 the 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 a adverse event that would require filing an Expedited Adverse Event Report (AER)
- Recurrent under- or over-reporting of adverse events

General Data Management Quality

- Recurrent missing documentation e.g., charts
- Protocol-specified laboratory tests not reported or not documented
- Protocol-specified diagnostic studies not reported or not documented
- 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. Disregard or untimely data reporting per Group, CCOP 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 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 Patient Case Records 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 deficiencies identified during the audit that were addressed and/or corrected **prior to** the audit for which documentation exists and no further action is required by the Cooperative Group, CTSU, the institution, or the principal investigator

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 corrective action plan to the Cooperative Group, CCOP Research Base or CTSU. A copy of the written response/corrective action plan, along with an assessment of adequacy by the Cooperative Group, CCOP Research Base, or CTSU of the response/corrective action 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 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 patients have been accrued (3-5 patients).

5.5 Role of the Investigator during the Audit

The responsible investigator or designee and his/her research staff should 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 responsible investigator(s) and 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 Audit Information System. This pre-populated report contains all of the identifying information about the institution to be audited.

6.1.1 Submission

The Preliminary Report (Appendix 5) must be faxed to CTMB [(301) 480-2642] within one working 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** (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 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.

A revised Preliminary Report may be faxed if it is within 10 working days of the audit. Any revision to the Preliminary Report should be explained in the Final Report.

6.1.2 Content

Any major deficiencies related to the following categories must be described in the Preliminary Report of Audit Findings (see Appendix 5).

- 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 should be given for each category listed on the Preliminary Report of Audit Findings. Issues addressed and briefly described in the Preliminary Report must be included in the Final Report or an explanation of why the issue is not addressed. If the problem had been resolved or clarified this must be commented upon in the Final Report.

6.2 Final Audit Report

6.2.1 Submission

Within 70 calendar days of the date of the audit, the final report must be submitted in the CTMB Audit Information System. 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.

6.2.2 Content

The following information should be included in the final audit report (see Appendix 6).

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 site during the period covered by this audit
- Indicate **Compliant, Non-compliant, or NR (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
- 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 NR (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 corrective action plan to the Cooperative Group, CCOP Research Base or CTSU. A copy of the written response/corrective action plan, along with an assessment of adequacy by the Cooperative Group, CCOP Research Base, or CTSU of the response/corrective action 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 or CTSU, for any component rated as **Unacceptable**. **Copies of source documentation should NOT be sent to CTMB**. A reaudit should be done no later than one year after an Unacceptable audit or when sufficient patients have been accrued (3-5 patients).

6.3.1 Suspension of Participating Institutions

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

- The Group will provide written notice to the Principal Investigator at the institution that the response/corrective action plan is overdue and a five working day grace period will be granted for the submission of the response/corrective action plan.
- If follow-up or a corrective action plan is not received by the Group during the five day grace period, the Group will immediately suspended patient registrations from that institution.
- If the audited institution is an affiliate of a Main Member institution or a component of a CCOP, or a CTSU, 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 corrective plan is not submitted during the 5 working 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/corrective action plan to the Group and the response/corrective action 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/corrective action plan may result in permanent termination from participation in NCI sponsored clinical trials through the Cooperative Group, CCOP or CTSU mechanisms.

6.3.2 Probation of Participating Institutions

If a participating institution is deemed unacceptable for the same audit component(s) 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 should address key infrastructural issues contributing to poor performance. A copy of the plan is to be submitted to CTMB within 45 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 from the Group, CCOP or CTSU, this 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 Re-audit

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 re-audit be conducted on-site. Depending on the nature of the deficiency or deficiencies which resulted in the **Unacceptable** rating, the re-audit could be done as an off-site review. This is left to 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 (3-5 patients). For tracking purposes, off-site re-audits must be scheduled and reported in the CTMB Audit Information System.

6.5 Clinical Trials Monitoring Branch Audit Information System

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>