

**NCI GUIDELINES FOR AUDITING CLINICAL TRIALS
FOR THE NCI NATIONAL CLINICAL TRIALS NETWORK
(NCTN) PROGRAM, COMMUNITY CLINICAL ONCOLOGY
PROGRAM (CCOP) / NCI COMMUNITY ONCOLOGY
RESEARCH PROGRAM (NCORP) AND RESEARCH BASES**

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CTMB-AIS DEFINITIONS

Auditable Flag: This is a designation that indicates how an institution will be audited. This flag is changeable for the CCOP/NCORP, CCOP/NCORP components, LAPS integrated components, sub affiliates and sub components. The default for the auditable flag for these institutions is ~~y~~esq (ie, institution is audited separately). The auditable flag for all other institutions cannot be changed.

Audit Category: A type of protocol being audited, this includes: Treatment, Prevention, or Combined (Prevention and Treatment).

Audit Type: Routine, Reaudit or Off-cycle

Membership Start Date: Date institution first joined Group (either through the Cooperative Group or through the NCTN program), this date does not change. The roster history indicates changes over time regarding participation in the Group.

Membership Status: Active, Withdrawn, Follow-up or No Longer Funded (NLF)

- Active is when an institution is an actively participating member of a Group(s).
- Withdrawn is when an institution is no longer a member of a Group, this action may either be initiated by the institution or by the Group.
- No Longer Funded (NLF) indicates that a LAPS or CCOP/NCORP package is no longer being funded. The institution is in a transition phase with their patients/study participants still in treatment and/or in follow-up until data submission is no longer required. Once the transition phase is completed, each Group will change the package status to withdrawn. The NLF status would allow a Group to request a new membership type/role for an individual institution in the LAPS/CCOP/NCORP package. This term NLF is only used in CTMB-AIS. In the RSS, the corresponding term is ~~f~~ollow-upq

Membership Status Date: Status date is when the Group makes changes to an institution's record such as status change (eg, active, withdrawn) or other changes to the membership type/role (eg, Main Member, CCOP/NCORP), name, or audit flag. The Group determines when the change is effective.

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

Membership Type: Main Member, Affiliate, Sub affiliate, Lead Academic Participating Site Main Member (LAPS MM), LAPS integrated component (LAPS IC), LAPS affiliate (LAPS A), LAPS aligned affiliate (LAPS AA), LAPS sub affiliate (LAPS SA), LAPS aligned sub affiliate (LAPS ASA), CCOP/NCORP, CCOP/NCORP component, NCORP sub components, or *Non-member collaborator.

** For the NCTN, a Non-member collaborator is not a "membership type" and would not appear on the Global Membership Roster for the NCTN. The Non-member designation for the NCTN would designate a CTEP-approved collaboration with an outside organization or site for an NCTN clinical trial led by one of the NCTN Groups that requires an auditing report by the Lead NCTN Group for the trial.*

Record: A roster entry of an institution per Group and membership study type.

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

Record Status: Active or Inactive

- Active is the current roster entry.
- Inactive is the past record entry.

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

Roster Types: Active or Legacy

- Active is the ongoing Group roster.
- Legacy is a Group and/or Membership Type roster that has been closed or made inactive (eg, POG, SELECT); no changes will be made to the roster record (ie, institution name, CTEP site code, dates and/or status); it will remain the same (frozen) at the time the roster was closed or made inactive.

SECTION 1 BACKGROUND AND PURPOSE OF THE AUDITING PROGRAM FOR THE NCI NETWORK GROUPS AND CCOP/NCORP RESEARCH BASES

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. The integrity of a data set is a function of the entire process of data recording, collection, analysis, and reporting. 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 Meinert¹ 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 should use the results of the on-site audit to identify operational areas where improvements can be made.

1.2 Background

As one of the world's largest publicly-funded sponsors 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 initial Cooperative Group Program in 1955. 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.

¹ Curtis Meinert, PhD, is a professor of epidemiology and founding director of the Center for Clinical Trials at the Johns Hopkins Bloomberg School of Public Health, May 2012.

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 NCI's Cancer Trials Support Unit (CTSU) was implemented in 1999. 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. The functions include a regulatory support unit, assistance with audit activities, development of a clinical trials informatics support system, and the development and conduct of education and training in the CTSU website.

In 2014, as recommended by the Institute of Medicine (IOM), the Cooperative Group Program was replaced by a new program, the NCI National Clinical Trials Network (NCTN) program with funding of four U.S. adult Network Groups, one pediatric Network Group and one Canadian Collaborating Clinical Trials Network Group. The NCTN program facilitates prioritization of clinical research and provides greater incentives for conducting comprehensive, multi-disciplinary, clinical treatment and advanced imaging research trials across a broad range of diseases and diverse patient populations. The CTSU's role with auditing was also modified with the implementation of the NCI NCTN. Its auditing activities are primarily limited to:

- Provision of qualified auditors for non-endorsed accrual for legacy trials that may have transitioned from the former Cooperative Group program to the new NCTN (until approximately 2016).
- Provision of IT system integrations to support roster and limited audit activities.
- Assisting with teleconferences or meetings between NCI and Network Group staff to discuss new policies and procedures to improve auditing activities.

In 2014, the Community Clinical Oncology Program (CCOP) combined with the NCI Community Cancer Center Program (NCCCP) to create the NCI Community Oncology Research Program (NCORP). The NCORP community site is defined as a consortium of community hospitals, oncology practices, or a community based integrated healthcare systems. This community based network will support a wide range of clinical research, including cancer prevention/control, screening/post-treatment surveillance, NCTN supported cancer treatment, imaging trials, quality of life studies, and cancer care delivery research studies.

In 1998, the Cancer Imaging Program (CIP) established the American College of Radiology Imaging Network (ACRIN). This organization conducts and coordinates clinical research in cancer imaging science and is dedicated to performing clinical trials for prevention, early detection, diagnosis, treatment, patient-centered outcomes, associated correlative science and the development of cancer-related imaging biomarkers. This program was also phased out with the implementation of the NCTN program.

With the implementation of the NCTN, a global membership roster was created for the entire program and it was constructed in conjunction with the Division of Cancer Prevention to harmonize the membership status of institutions in the NCTN and CCOP/NCORP programs (ie, member institutions participating in cancer trials were designated as having NCTN membership or CCOP/NCORP membership per standard policies).

1.3 Purpose and Objectives

As a sponsor and 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 Network 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 Network 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 Network 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 auditing of clinical trials for the Network Groups and CCOP/NCORP Research Bases 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 Network Group must conduct a comprehensive review of all its current membership. This includes all main members, affiliates, sub affiliates, CCOP/NCORPs, CCOP/NCORP components, NCORP sub components, LAPS main members, LAPS IC, LAPS A, LAPS AA, LAPS SA, and LAPS ASA; and their audit activity. A listing of all institutions, regardless of membership type and their CTEP site code must be provided in tabular format by each Network Group in the competing or non-competing continuation application. A separate table must be provided for each Membership Study Type (eg, Treatment, Prevention). This table must include: (1) start date of affiliation or withdrawn date with the Group; (2) membership role, (3) parent CTEP site code of each institution, (4) auditable flag, (5) status of institution, (6) date of the institution's last audit date, (7) the projected accrual for the upcoming year; (8) accrual for the immediate preceding 48 months (4 years) broken down by year; and (9) the projected date (month/year) of the next proposed audit. This requirement is part of the NCI National Clinical Trials Network Group Program guidelines. A template of the Roster and Auditing Activity can be found under Appendix 1.

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

The Clinical Trials Monitoring Branch (CTMB) within the Cancer Therapy Evaluation Program (CTEP) has direct oversight responsibilities for the quality assurance and auditing programs used by the Network Groups, CCOPs/NCORPs and the Research Bases. CTEP staff with representatives from other NCI programs, have worked closely with the Network Groups to design, implement, and evaluate their quality assurance programs. Working together we have implemented policies and procedures to standardize processes across all Groups. For example: the establishment of the CIRB for Phase 3 and Phase 2 studies; creation of the informed consent form template for all NCI-sponsored clinical trials; standardized criteria for evaluating data timeliness and query for data resolution; developed and implemented RAVE (a common data capture system) and RAVE audit templates; and the ongoing modifications of the CTMB audit guidelines.

The CTMB audit guidelines are used by the Network Groups, CCOPs/NCORPs and the Research Bases. Although efforts have been made to standardize procedures used in conducting the audits, it is recognized that there may be inherent differences in the methodologies and processes utilized for clinical trials by the Groups and CCOP/NCORP Research Bases. However, while the Groups and CCOPs/NCORPs and the Research Bases must meet the standards of the CTMB audit guidelines, more stringent policies and procedures may be established and enforced by the Groups and CCOP/NCORP Research Bases.

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 Network Groups and CCOP/NCORP Research Bases with the NCI/CTMB auditing guidelines. Compliance with applicable federal regulations and GCP is also monitored by CTMB.

CTMB staff also 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 and preventative actions. A co-site visitor (CTMB, CTMS or other designee) may also be present at an audit to observe the audit process of the Network Group.

Any data irregularities identified through quality control procedures or through the audit program that raise any suspicion of intentional misrepresentation of data must be immediately reported to CTMB, CTEP, NCI. The CTMB must be notified immediately by telephone (240) 276-6545 of any findings suspicious and/or suggestive of intentional misrepresentation of data and/or disregard for regulatory safeguards for any of the three (regulatory, pharmacy and patient case) components of an audit. Similarly, any data irregularities identified through other quality control procedures suspicious and/or suggestive of intentional misrepresentation of data must be immediately reported to CTMB. It is the responsibility of the Network Group or the CCOP/NCORP Research Base 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 regarding these matters.

2.2 Network Groups

The multi-center and multi-modality nature of the Network 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 Network 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 Network Group. Generalization concerning optimal quality control is not possible. Cost and benefit are important factors in this assessment. The Network 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, imaging, advanced imaging and administration of investigational agents
- Educational functions which address data collection, data management, and overall data quality
- Credentialing of investigators or other staff when specialized training and/or expertise is required for a research study

2.2.2 Quality Assurance

Quality assurance is the mechanism in which research clinical trials are conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and applicable regulatory requirements. It is a continuous process that can be conducted on-site or off-site, and involves oversight of all patients/study participants on a trial.

2.2.2.1 Study Monitoring

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

- Precise tracking of patient/study participant accrual
- Ongoing assessment of patient/study participant eligibility and evaluability
- Adequate measures to ensure timely submission of study data

- Adequate measures to ensure timely medical review and assessment of data for each patient/study participant
- Rapid reporting of adverse events and treatment-related morbidity information
- Periodic evaluation of outcome measures and patient safety information

2.2.2.2 Data and Safety Monitoring

For Phase 3 clinical trials, Network Groups are required to establish Data and Safety Monitoring Boards (DSMBs) 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 DSMBs are to:

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

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

2.2.2.3 Auditing Program

Auditing is a systematic and independent examination of trial related activities and documents. It determines whether the evaluated trial related activities were conducted, dates recorded, analyzed and accurately reported according to the protocol, sponsor's SOPs, 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/study participants on a trial.

The specific purposes of the auditing program are to document the accuracy of data submitted from the participating institution to the Network Groups. Specifically, each Group will verify investigator compliance with the protocol, applicable regulatory requirements, and adherence to Group policies and procedures. If necessary, provide institution staff with resources for a more thorough understanding of the regulatory requirements, good clinical practices (GCPs), data collection and data management practices.

2.3 Community Clinical Oncology Program (CCOP)/NCI Community Oncology Research Program (NCORP)

The CCOP/NCORP utilizes the same quality assurance programs as those used by the Network Groups. The overall purpose is to ensure that clinical trials conducted by the NCORP and NCORP components adhere to the federal regulations, GCP and the CTMB audit guidelines. A CCOP/NCORP may have a Network Group or a Cancer Center serve as its Research Base. A CCOP may have affiliates and components, however in this document and in the CTMB-AIS, they are referred to as CCOP components. An NCORP will have components and sub components per the Division of Cancer Prevention (DCP).

2.3.1 Network Groups

Network Groups follow the same monitoring procedures for CCOP/NCORPs and CCOP/NCORP components as they follow for their other members.

2.3.2 CCOP/NCORP Research Bases

Cancer Centers that serve as CCOP/NCORP Research Bases must develop their own quality assurance and monitoring programs that meet the minimum requirements established by the NCI. These Research Bases must be audited per the CTMB audit guidelines including scheduling audits and submitting audit reports in the CTMB-AIS.

2.4 CTSU

The CTSU shall provide qualified auditors for non-endorsed accrual for trials in the Endorsement Program under the former NCI Cooperative Group Clinical Trials Program. This program ended July 31, 2013. To accommodate the three year audit cycle, the CTSU provides qualified auditors to assist with auditing non-endorsed cases in legacy trials transitioned to the new NCTN program which is expected to last through 2016.

SECTION 3 AUDITS

All institutions (main members, affiliates, sub affiliates, LAPS main members, LAPS integrated components, LAPS affiliates, LAPS aligned affiliates, LAPS sub affiliates and LAPS aligned sub affiliates, CCOP/NCORPs, CCOP/NCORP components, and NCORP sub components) that accrue patients to the Network Group, CCOP/NCORP Research Base and other multi-institutional organizations onto NCI clinical trials are eligible for an audit at least once every 36 months. However, an institution is at risk for an audit at any time.

All institutions must be listed on a Network Group or CCOP/NCORP Research Base roster in the CTSU-RSS (CTSU-Regulatory Support System) and the CTMB-AIS database. Each Network Group and CCOP/NCORP Research Base is responsible for timely and accurate maintenance of their roster in the CTMB-AIS. Changes to the roster must be requested within three months from the date the change was made.

Storefronts are administrative sites that do not accrue or treat patients. All CCOP/NCORP and LAPS are storefronts. The CCOP/NCORP storefronts handle the regulatory, registration, data management and financial aspects for their components. The LAPS storefronts designate the grant institution responsible for grant related activities, including distribution of funding to the enrolling institution(s) within a LAPS grant.

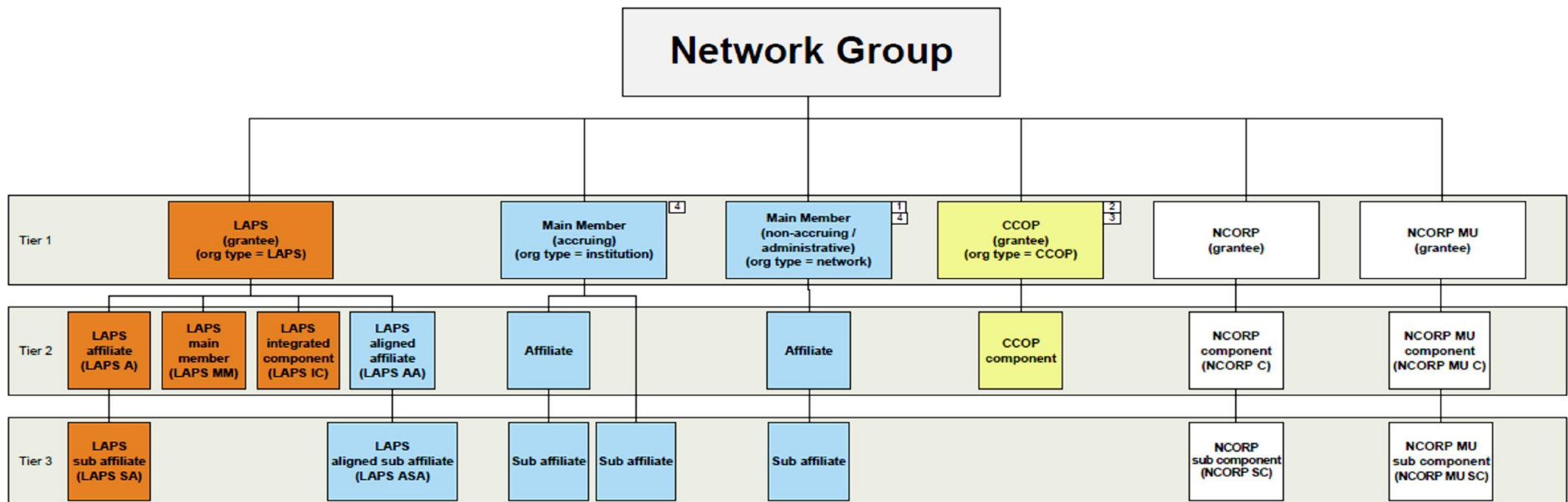
LAPS main members, Network main members and affiliates cannot be a storefront as they are expected to enroll patients and provide significant accrual to the NCTN program. CTEP may consider a limited number of main members to be designated as storefronts. A Network Group may request that a main member be a storefront which handles the administrative aspects of their associated institutions. These institutions cannot be included in a CCOP/NCORPs or LAPS grant. This type of designation must be approved by CTEP before it can be included on the Global Membership Roster for that Network Group.

A Group may include an international Group/institution as a full member. This request must also be approved by CTEP before it can be included on the Global Membership Roster for the Group making the request. If an international Group has a formal structure in place that handles the administrative aspects as described above, they may be listed as storefront. These international Groups may be asked by the Network Group to conduct audits of their international members.

3.1 Network Group Membership Type

Investigators participating in Network Group research come from a wide variety of academic and/or community practice settings. All institutions must be a member of at least one Network Group to participate in CTEP-sponsored clinical trials. Categorization of membership type is based on the NCTN Program Guidelines and the policies determined by each Network Group. All institutions must be recognized across the entire NCTN Network as one of the following mutually exclusive membership type for the purpose of funding and accrual (see Figure 1).

Figure 1 NCI National Clinical Trials Network (NCTN) Organizational Chart



- LAPS Package
- Rostered
- CCOP Package
- NCORP Package

1	Pre-approval for Main Member (non-accruing / administrative) code required from CTEP
2	Attribute for MB CCOP provided by DCP and viewable in RSS
3	Attribute for PEDS ONLY provided by DCP and viewable in RSS
4	International Sites will not have Tier 3

3.1.1 Network Institutions

Main members and affiliates are determined by the Network Group and may vary from Group to Group.

3.1.1.1 Main Members

These institutions 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.

3.1.1.2 Affiliates

Institutions that 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 Network Group through their main member institution. Affiliate institutions may also be private physician offices or community clinics.

3.1.2 DCP's CCOPs/NCORPs Program

CCOPs/NCORPs are designated by and funded through the Division of Cancer Prevention (DCP), NCORPs function as an outreach initiative to expand access of clinical trials to community physicians. NCORPs are comprised of any of the following: hospitals, clinics, Health Maintenance Organizations (HMO), groups of practicing physicians, a consortium, or other healthcare organizations which agree to work with a principal investigator through a single administrative unit. Minority-underserved (MU) CCOP/NCORP may include the institutions above in addition to public hospitals or medical centers. MU CCOP/NCORP has a patient population comprising of at least 30% racial/ethnic minorities or rural residents.

3.1.2.1 CCOP/NCORPs

Administrative sites handle financial, regulatory, registration and data management for the components within the CCOP/NCORP. An individual CCOP/NCORP is an administrative site, known as a storefront which is a site that does not actively accrue or treat patients.

3.1.2.2 CCOP/NCORP Components

All hospitals, clinics, HMOs, etc. are approved by DCP as part of a CCOP/NCORP grant award. These institutions enroll patients on a regular and ongoing basis to NCI-approved cancer prevention, cancer control and cancer treatment clinical trials. Their accrual contributes towards the total accrual of the CCOP/NCORP, therefore these institutions must be included in the roster and are held to the same standards as all other institutions conducting clinical trials.

3.1.3 CCOP/NCORP Research Base (NCORP-RB)

A Network Group or NCI-designated Cancer Center that designs, develops, and conducts cancer prevention and control clinical trials. Network CCOP/NCORP Research Bases may also provide cancer treatment clinical trials.

3.1.4 Network Lead Academic Participating Sites (LAPS)

Network Lead Academic Participating Sites (LAPS) are designated by and funded through a grant from the Division of Cancer Treatment and Diagnosis (DCTD) for their participation in the NCTN treatment program and advanced imaging clinical trials for adult cancer patients. A LAPS grantee consists of a main academic institution, LAPS IC (integrated component), LAPS A (affiliate), LAPS SA (sub affiliate), as well as associated institutions not included in the LAPS grant, which include the LAPS AA (aligned affiliate) and the LAPS ASA (aligned sub affiliate).

LAPS maintain this grouping of institutions across all the adult Network Groups. There are no pediatric LAPS as only one pediatric Network Group is currently part of the NCTN program. The institutions in the LAPS grant cannot be part of a CCOP/NCORP grant.

3.1.4.1 Lead Academic Participating Main Members (LAPS MM)

The LAPS main members or lead academic institutions provide direct medical care to patients/study participants and have a comprehensive medical training program, as well as preclinical laboratories that perform basic research. These institutions have oversight of their LAPS IC, LAPS A, LAPS AA, LAPS SA, and LAPS ASA, as listed on their grant.

3.1.4.2 Lead Academic Participating Site Integrated Components (LAPS IC)

LAPS ICs are essential or integrated components (hospitals and/or clinics) of the LAPS academic medical center and are under the same/single financial management system and governance structure of the academic center but are located at a different geographic location. LAPS ICs have separate CTEP site codes for registration/enrollment of patients at their geographic location and are explicitly designated integrated components and maintain this membership type across all the adult Network Groups.

3.1.4.3 Lead Academic Participating Site Affiliates (LAPS A)

LAPS affiliates are other organizations that are associated with a LAPS academic center (e.g., VA Hospitals), but they are not under the same financial management and governance structure as the LAPS main academic center. LAPS affiliates however, are included in the LAPS grant because the LAPS main academic center provides complete management services for the affiliate institution related to enrollment of patients to NCTN treatment and advanced imaging clinical trials for adult cancer patients, with the exception of IRB services as those services may or may not be provided by the LAPS main academic center. These institutions are explicitly designated as LAPS affiliates by DCTD as part of the LAPS grant. LAPS affiliates maintain this membership type across all the adult Network Groups.

3.1.4.4 Lead Academic Participating Site Aligned Affiliates (LAPS AA)

LAPS aligned affiliates are other organizations that are associated with the LAPS main academic center; however, they are not included in the LAPS grant as the LAPS main academic center does not provide complete management services for the aligned affiliate. Since these institutions are not part of the LAPS grant, they can have different membership types (roles) within different adult Network Group. They may be a LAPS aligned affiliate for one Network Group but may be a main member or affiliate in another Network Group. However, LAPS aligned affiliates cannot be part of a CCOP/NCORP.

3.1.5 Other Membership Types

3.1.5.1 NCTN Pediatric Network Group Members

There is only one pediatric Network Group in the NCTN program. This Network Group does not participate with the LAPS grant. They do participate with the CCOP/NCORP grant but they have the option to select which CCOP/NCORP component they accept as their member. Therefore, their institutions membership type (role) may differ from the other Network Groups who participate with the LAPS or CCOP/NCORP grants.

3.1.5.2 Sub affiliates/Sub components

Sub affiliates and sub components are defined as healthcare practice locations for example, clinics, physician offices or treatment locations. These locations which are used by registered investigators to consent, register/enroll and treat (including study agents) as allowed by protocol or specific conditions listed below.

Sub affiliates/Sub components **MUST** be on the Group roster if:

- Consenting and/or registering (enrolling) patients, either directly or through a central registration with their linked LAPS, Network Group main member, affiliate, NCORP, or
- Receiving investigational agent(s) or investigational imaging agent(s) or supplied agent(s) directly from NCI (Pharmaceutical Management Branch, DCP or a contractor) and/or IDE for a device used with treatment/intervention at the local institution

Classification of Sub affiliates/Sub components:

- LAPS sub affiliates (LAPS SA) must be listed on a LAPS grant
- NCORP sub component (NCORP SC) or NCORP minority-underserved (NCORP MU) must be listed on a NCORP grant
- Main member sub affiliates (MM SA), affiliate sub affiliates (ASA) and LAPS aligned affiliate sub affiliates (LAPS AASA) are **not** listed on a LAPS or NCORP grant

Requirements of Sub affiliates/Sub components:

- Can only be listed once on a NCTN Group roster
- Must be covered by an IRB
- Must be linked to a parent
 - Can only have one parent within a Network Group (within the same membership study type)
 - If part of a LAPS or NCORP package, the parent must be the same across all Groups.
 - If participating in more than one Group, the parent may be different across the Groups

The Principal Investigator at the linked-parent (all institutions) is responsible for:

- Overseeing protocol-related activities
 - Ensuring that they have IRB oversight
 - Ensuring the study treatment/interventions are administered in accordance with the IRB-approved protocol
 - Ensuring appropriate arrangements are made for reporting protocol-related data and any unexpected adverse events
- Monitoring the conduct of research
 - Responsible for ongoing assessment of regulatory, pharmacy and patient/study participant data
 - Responsible for the compliance of the pharmacy operations (procedures, storage and security) with NCI policies and federal regulations
 - Responsible for the review of the appropriateness of the sub affiliate/sub components corrective and preventative action (CAPA) plan and its implementation that addresses:
 - Any concern related to the conduct of the research
 - Any findings as a result of a Group audit

In General:

- Sub affiliate/sub component institutions credit their accrual to their parent per Group being credited. This accrual must be captured twice:
 - At the sub affiliate/sub component where registration/enrollment occurred, and
 - At the parent and the Group level who is credited with the accrual.
- Sub affiliate/sub component institutions are at risk for an audit when a Group schedules an audit of the parent institution. The Group is expected to select a representative sampling from each sub affiliate/

sub component. Selecting 10% of patient cases from of each sub affiliate/sub component is not required. Under certain circumstances, CTMB may mandate an independent audit of any institution.

- CTMB is responsible for changing the audit flag for the NCORP Sub components and Sub affiliates, if necessary.

3.1.6 Non-member Collaborators

There may be domestic or international institutions that collaborate with a Network Group on a particular trial (ie, enroll patients on a Network Group trial) but which are not members of the Network Group. These collaborating institutions members do not receive NCI funding for their participation from DCTD or DCP. These participant(s) must be approved by CTEP/DCTD (or DCP) and CTMB prior to designation as a collaborating institution for a particular trial and before they can register/enroll patients on that trial. There are specific limitations for these collaborating institutions set by DCTD (or DCP) and CTMB as well as the Network Group. These institutions are not to be listed on the NCTN global roster; they will be listed on a separate non-member roster.

As part of the approval process for these collaborating institutions on a particular trial, appropriate arrangements for an acceptable auditing plan must be in place with CTMB.

3.2 Grouping of Membership Types

The membership type designated by DCTD in relation to a LAPS grant or designated by DCP in relation to a CCOP/NCORP grant must be the same across the adult Network Groups. Only the Network Main Member, Network Affiliate, and LAPS aligned affiliates (and their associated sub affiliates) may differ between adult Network Groups.

Across all adult Network Groups, an institution can only have one of the following designations if it is funded by a DCTD LAPS grant or a DCP CCOP/NCORP grant:

- A LAPS main member or CCOP/NCORP
- A LAPS integrated component, LAPS affiliate, or CCOP/NCORP component
- Sub component under a NCORP grant or a LAPS sub affiliate under a LAPS grant
- An institution can only be listed on one grant package (ie, LAPS or CCOP/NCORP)

Between adult Network Groups, an institution can be:

- A main member, affiliate, or sub affiliate in different Groups
- An aligned affiliate associated with a LAPS main member, an affiliate or sub affiliate in different Groups

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

- Both a Network Group main member and affiliate or sub affiliate

- Both a LAPS aligned affiliate and a Network Group main member or affiliate or sub affiliate
- Both a LAPS aligned sub affiliate and a Network Group main member or affiliate or sub affiliate

3.3 Crediting of Accrual

Enrollment/accrual is a patient/study participant that has been consented, registered/enrolled to a study and assigned a patient ID number.

Accrual must be credited to the individual institution regardless of their membership type/role that identified a patient/study participant to be consented and registered/enrolled. Accrual credit for that identified patient/study participant may not be rolled up or credited to another institution that is registering this patient/study participant through a central registration or by a LAPS main member, Network Group Main Member, CCOP/NCORP, or any affiliate or CCOP/NCORP component registering for other institutions. Only sub affiliates and sub components may roll their accrual up to their linked-parent. For sub affiliate and sub components, registration/enrollment and the institution credited for the accrual must be captured.

The general policy for crediting by institutions in the NCTN is governed by the NCTN guidelines. Institutions should follow the guidelines regarding general policy for accrual crediting. The CTSU will also post the general policy and any CTEP-specific changes for accrual crediting for the NCTN in conjunction with the OPEN system. The audit responsibility for an institution falls to the Network Group or CCOP/NCORP Research Bases that was credited with the registration/enrollment.

3.4 Network Group Main Member Institutions

Network Group main member institutions will be audited within 18 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 high accruing main member institutions, it may be appropriate for the Network Group to audit these institutions on a more frequent interval given the high number of cases for review.

If a main member institution moves to a new location which requires a new CTEP site code and/or a decision is made by the NCI Site Code Committee to change the CTEP site code to a new CTEP site code, the 18 month rule does not apply as long as the institution has been previously audited by the same Group or legacy Group.

3.5 Network Affiliate, LAPS Affiliate and LAPS Aligned Affiliates Institutions

For affiliates, an on-site audit may be conducted by the Network Group. Alternatively, these affiliates may be audited off-site (at the main member/LAPS main member) when the Network Group conducts the on-site audit of the Main Member/LAPS main member.

3.6 CCOP/NCORP and CCOP/NCORP Components

CCOP/NCORP institutions will be audited within 18 months after entry of the first patient/study participant. If the CCOP/NCORP accrues rapidly, the initial on-site audit

should be done sooner than 18 months. Following the initial audit, CCOP/NCORP institutions must be audited at least once every 36 months. For high accruing CCOP/NCORPs and NCORP components, it may be appropriate for the Network Group to audit these institutions on a more frequent interval given the high number of cases for review.

A Network Group may utilize one of three audit methods to conduct an audit of its CCOPs/NCORPs, CCOP/NCORP components, and NCORP Sub components:

- A separate audit may be conducted for each CCOP/NCORP and CCOP/NCORP component (including NCORP sub components). Separate preliminary and final audit reports must be submitted for the CCOP/NCORP and each CCOP/NCORP component.
- One audit may be conducted for the CCOP/NCORP as a whole. Protocols and patient cases must be selected for review from the CCOP/NCORP and each component that has accrual. If the CCOP/NCORP is audited as one entity, only one preliminary and final audit report is required.
- A combination of the two above audit methods may be utilized.

For combined audits in instances when there are separate IRBs or pharmacies (ie, receives drug directly from PMB or other sponsors), each IRB or pharmacy must be audited and identified (by CTEP site code, IRB name, and pharmacy location) in the final audit report. The final audit report must also identify the patient cases by institution by entering the applicable CTEP site code for any non-auditable institution (ie, CCOP/NCORP component, NCORP sub component).

An ~~audit~~ audit+(yes) or ~~no~~ no-audit+(no) flag is included in the CTMB-AIS roster to determine the method chosen by the Network Group or CCOP/NCORP Research Base. The default for this auditable flag is ~~yes~~ yes (ie, each institution audited separately). The Network Group is responsible for changes to the audit flag for the CCOP/NCORP and CCOP/NCORP components.

3.7 CCOP/NCORP Research Bases

A Research Base may be a Network Group or an NCI-designated cancer center which is funded by Division of Cancer Prevention (DCP) to develop and conduct cancer control or cancer prevention studies. They may also provide cancer treatment based on an NCI clinical study. The Research Base will audit their members based on the membership role, either as a CCOP/NCORP, CCOP/NCORP component, or main member/affiliate.

3.8 Lead Academic Participating Sites (LAPS)

A LAPS main member will be audited within 18 months after entry of the first patient. If the LAPS main member accrues rapidly, the initial on-site audit should be done sooner than 18 months. This 18 month rule does not apply as long as the LAPS main member has been previously audited. Following the initial audit, the LAPS main member must be audited at least once every 36 months. For high accruing LAPS, it may be appropriate for the Network Group to audit these institutions on a more frequent interval given the high number of patient cases for review. The LAPS integrated component (LAPS IC), LAPS Affiliate (LAPS A), and LAPS Aligned Affiliate (LAPS AA) must be audited at least every 36 months if there is accrual.

A separate audit will be conducted for the LAPS main member, each LAPS IC, LAPS A and LAPS AA. A preliminary and final audit report must be submitted for each the LAPS main member, LAPS IC, LAPS A and LAPS AA.

CTMB may change the audit flag for a LAPS IC to ~~noq~~ If the audit flag is changed, a CTMB-AIS generated email notification will be sent to the audit coordinator at the Network Group indicating this LAPS IC will be combined with the LAPS main member audit. One audit may be conducted for the LAPS main member and LAPS IC(s) as a whole. Only one preliminary and one final audit report will be required. Protocols and patient cases must be selected for review from the LAPS main member and each non-auditable LAPS IC(s). If there are separate IRBs or pharmacies (ie, receives drug directly from PMB or other sponsors), each IRB or pharmacy must be audited. The final audit report must identify the IRB/ICC, pharmacy and patient cases by the LAPS main member and each LAPS IC.

3.9 Non-Auditable Institutions

Non-auditable institutions may include CCOP/NCORP components, LAPS IC(s), sub affiliates, and sub components. An audit conducted for a parent and their non-auditable institutions is considered an audit ~~as~~ as a whole (combined). For these types of audits, when there are separate IRBs or pharmacies (ie, receives drug directly from PMB or other sponsors), each IRB or pharmacy must be audited. The CTEP site code, IRB name, and pharmacy location(s) must be captured on the final audit report. Protocols and patient cases must be selected for review from the parent and each non-auditable institution being audited. A single preliminary and single final audit report is required for audits conducted ~~as~~ as a whole.

3.10 Withdrawn/No Longer Funded (NLF) Institutions

If an institution's membership or participation in a Network Group or CCOP/NCORP Research Base is withdrawn, continued long-term follow-up of registered/enrolled patients and the collection of good quality data according to the study schedule are required. Therefore, these institutions remain eligible for an audit.

If the CCOP/NCORP is ~~not~~ defunded by DCP or the LAPS by CTEP, their status will be set to ~~NLF~~ NLF in the CTMB-AIS until the patients/study participants are off treatment/study intervention, the patient case is transferred to another investigator/institution and/or F/U is no longer required. The LAPS aligned affiliate is not part of the LAPS grant. The Group will need to change the aligned affiliate by either assigning a new main member, changing their role (to a main member) or withdraw them. The Group remains responsible for auditing the CCOP/NCORP component, NCORP sub component, and the LAPS main member, LAPS integrated component, LAPS affiliates/aligned affiliates, and LAPS sub affiliates/aligned sub affiliates.

For CCOP/NCORPs and LAPS in NLF or withdrawn institutions, a close-out audit should be considered by the Network Group/Research Base. The decision whether to audit should be based on the number of total patient cases and protocols with emphasis on important or pivotal trials, have a high number of patients/study participants in follow-up, or are not meeting acceptable quality standards for audit and/or follow-up data. If the

institution has never been audited, it must have a close out audit. A decision not to audit these institutions must first be discussed with CTMB.

3.11 Special Audits/'For Cause' Audits

Special audits may be conducted when there are promising preliminary findings that warrant verification of findings. CTEP, a Network Group or a sponsor may request a special audit (Response Audit) and CTEP determines if a special audit is warranted.

~~F~~or cause audits may be warranted when there are concerns or irregularities found through quality control procedures or when allegations of possible scientific misconduct are made. It is the responsibility of the Network Group or CCOP/NCORP Research Base 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 or CCOP/NCORP Research Base coordinate the special audits/~~f~~or cause' audits. Selection of auditors to conduct special/~~f~~or cause on-site audits will be made jointly by the NCI, Group, or CCOP/NCORP Research Base, and a joint course of action will be planned. Other federal agencies or offices may be invited to participate in an audit at the discretion of the NCI.

SECTION 4 PREPARATIONS FOR CONDUCTING THE AUDIT

A Network Group or CCOP/NCORP Research Base 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 protocols and patient cases for review.

4.1 Arranging the Audit

The audit date must be entered into the CTMB-AIS database at least six 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. The Group must contact CTMB for approval prior to scheduling any audit within six 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 six 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.

If an audit needs to be canceled within three business days prior to the audit, the Group must notify CTMB. If a Clinical Trials Monitoring Service (CTMS) co-site visitor was assigned to the audit, the Group must contact CTMS.

4.2 Selection of Protocols and Patient Cases

The statistical, operations, or data management office for the Network Group or CCOP/NCORP Research Base 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, advanced imaging studies, prevention/cancer control trials and potential licensing trials, as well as those with high accrual.

Specific trials (eg, prevention, screening trials, etc) with very high accrual may be audited under a different mechanism with CTMB approval. 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. Ten percent of patient cases accrued must be selected from each participating institution (Network Group Main Member, Network Group Affiliate, CCOP/NCORP, each individual CCOP/NCORP component, LAPS main member, LAPS IC, LAPS A and LAPS AA. A representative sampling from the sub affiliates/sub components is to be audited at the parent institution. For selection purposes, the 10% of chosen cases must be rounded up (eg, if 12 patient cases are eligible for audit selection, at least two cases must be audited). When selecting patient cases the following applies, where appropriate:

- 10% of treatment cases where the auditing Group is the protocol lead and/or a participant on a protocol; and

Note: Until approximately 2016, the audit must include 10% of endorsed and 10% of non-endorsed cases of Legacy protocols credited to the Group.

- 10% from protocols with advanced imaging studies/imaging studies embedded in treatment protocols; and
- 10% of DCP cancer control/prevention cases.

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 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 audit report.

4.3 Selection of On-site Audit Team

Selection of the on-site audit team should receive special consideration. Auditors should be chosen based on their knowledge of the protocol(s) to be reviewed and of Network Group and CCOP/NCORP Research Base audit guidelines and procedures.

4.3.1 Network Group and NCORP Research Base

The audit team should include Network Group or CCOP/NCORP Research Base 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 staff. The auditors must be knowledgeable about clinical trial 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 Network Group or the CCOP/NCORP Research Base 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 and NCI staff or designee must be included in all exit interview discussions.

4.4 Institution Responsibilities

The institution is responsible for ensuring that all relevant materials are available for review at the time of the audit. If an institution is audited off-site at the Network Main Member, CCOP/NCORP, or LAPS main member, the following records must be available the day of the audit:

- IRB documents, copies of the locally utilized informed consent forms, other regulatory documentation, if applicable
- NCI Drug Accountability Record Forms (DARFs) for control and satellite pharmacies, shipping receipts, etc. and/or log for imaging/radiopharmaceutical agents

- Complete medical records (or copies)
- Dictated report of all imaging studies (X-rays, scans, MRIs, PET, etc.)
- For imaging studies: source documents/worksheets used for imaging acquisition, processing, quality assurance documentation, reader's interpretation, record of imaging administration, patient/study participant monitoring (vital signs, monitoring of contrast reactions, etc.), and log of staff signatures and imaging responsibilities
- Other relevant source documents or information

These documents must be available at the main member institution the day of the audit or earlier if determined by the Network Group. The linked-parent (affiliate or Main Member) of the sub affiliate/sub component is responsible for obtaining the above mentioned documents by the day of their audit. It is recommended that a representative from each of the audited institutions be present to address questions during the audit.

To facilitate the review process, it is recommended that institution staff label all documents such as hospital/clinic records, research notes, on-study labs, scans and imaging studies, consent forms, etc. The Network Group or CCOP/NCORP Research Base 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:

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

At the discretion of the Network Group or CCOP/NCORP Research Base, 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. An audit tool/checklist for each of the components can be found under Appendix 2.

5.1 Assessing Audit Findings

An audit consists of reviewing and evaluating: (1) documentation and conformance to IRB and informed consent requirements, (2) pharmacy operations and use of NCI DARFs, or NCI approved drug logs, and (3) individual patient cases. During the audit, each of these three components will independently be assigned an assessment of either Acceptable; 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 Network Groups, and CCOP/NCORP Research Bases 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 Preventative Action (CAPA) plan to the Network Group or CCOP/NCORP Research Base. A copy of the written response/CAPA plan, along with an assessment of adequacy by the Network Group or CCOP/NCORP Research Base of the response/CAPA plan, must be forwarded to CTMB within 45 calendar days of the date the final audit report is submitted in the CTMB-AIS. Network Group or the CCOP/NCORP Research Base 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 or CCOP/NCORP Research Base 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 experienced members of the IRB of research which involves no more than minimal risk or involves minor changes in previously approved research (see OHRP guidance <http://www.hhs.gov/ohrp/policy/exprev.pdf>)
- Other: Any regulatory concern not described above

Amendments (addendums or updates) must be approved (or disapproved) by the IRB of record within 90 days of the Group's notification. Each Group or CCOP/NCORP Research Base 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 the Office of Human Research Protections (OHRP) [see OHRP guidance <http://www.hhs.gov/ohrp/policy/advevntguid.pdf>] including external safety reports must be reported to the IRB within 90 days of the Group's notification. This does not apply if the CIRB is the IRB of record for the institution/protocol. 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.

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

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

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

The following are examples of major and lesser deficiencies to be considered when assessing IRB compliance. This list does not represent an all inclusive list of major and lesser deficiencies that may be found during an audit.

Major IRB deficiencies may include but are not limited to:

- Protocol never approved by IRB
- Initial IRB approval documentation missing
- Initial approval by expedited review
- Expedited reapproval for situations other than approved exceptions
- Registration and/or treatment of patient prior to full IRB approval
- Reapproval delayed greater than 30 days, but less than one year
- Registration of patient on protocol during a period of delayed reapproval or during a temporary suspension (ie, Request for Rapid Amendment)
- Missing reapproval
- Expired reapproval
- Internal reportable adverse events reported late or not reported to the IRB

- Lack of documentation of IRB approval of a protocol amendment that affects more than minimal risk or IRB approval is greater than 90 days after Network Group's notification; this includes a Request for Rapid Amendment (RRA) resulting from an Action Letter indicating temporary suspension of accrual with expedited review permitted
- Failure to submit or submitted after 90 days, any reportable external safety report to the IRB that is considered an unanticipated problem as defined by OHRP

Lesser IRB deficiencies may include but are not limited to:

- Protocol reapproval delayed 30 days or less
- Delayed reapproval for protocol closed to accrual for which all patients/study participants have completed therapy

5.2.2 Informed Consent Content

The content of the local informed consent documents for at least three protocols (if there are three or more protocols) must be reviewed for content regardless of patient registration/enrollment to ensure the informed consent forms contain the elements required by federal regulations. If there are a variety of protocols, at least one informed consent document must be reviewed for a treatment, advanced imaging and DCP protocol.

Each of the informed consent documents selected for audit must be reviewed to ensure they contain the risks and alternatives listed in the model informed consent document approved by the NCI. For CIRB-approved consent forms, the only change allowed is the incorporation of the CIRB-approved boilerplate (local context).

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

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

5.2.3 Assessing the IRB and Informed Consent Content Findings

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

Acceptable

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

Acceptable Needs Follow-up

- 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 Network Group or CCOP/NCORP Research Base. A copy of the written response/CAPA plan, along with an assessment of adequacy by the Network Group or CCOP/NCORP Research Base of the response/CAPA plan, must be forwarded by the Network Group to CTMB within 45 calendar days from the date the final audit report is submitted in the CTMB-AIS. Network Group or CCOP/NCORP Research Base 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 Network Group or CCOP/NCORP Research Base for any component rated as Unacceptable. A re-audit should be done no later than a year after an Unacceptable audit. See Section 6.4 for more information related to reaudits.

5.3 Review of Accountability of Investigational Agents and Pharmacy Operations

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

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

The auditing of DARFs is by protocol and study agent. When capturing the number of DARFs pages entered on the final audit report, it is the number of study agents (including different strengths) reviewed, not the number of DARF pages.

A waiver statement allowing use of electronic DARFs (eDARFs) has not been issued by the NCI and the NCI does not endorse any eDARF pharmacy package. Institutions that choose to use an electronic accountability system must ensure the database is capable of producing a paper printout that is identical to the NCI DARF. Electronic accountability system database limitations are not valid reasons for improper accountability documentation according to NCI policy.

5.3.1 Control Dispensing Area/Pharmacy

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

The location is responsible for:

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

5.3.2 Satellite Dispensing Area/Pharmacy

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

responsibility of the Control Dispensing Area. The Satellite Dispensing Area is responsible for:

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

5.3.3 Cancer Control/Imaging Studies

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

5.3.4 Guidelines for Conducting the Pharmacy Review

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

NCI DARFs COMPLETELY AND CORRECTLY FILLED OUT

Compliance

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

Non-Compliance

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

DARFs PROTOCOL AND AGENT SPECIFIC

Compliance

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

Non-Compliance

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

SATELLITE RECORDS OF DISPENSING AREA

Compliance

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

Non-Compliance

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

NCI DARFs KEPT AS PRIMARY TRANSACTION RECORD

Compliance

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

Non-Compliance

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

RETURN OF STUDY AGENT

Compliance

- Return of NCI-supplied study agent to NCI or locally destroyed with NCI authorization when notified study agent is no longer suitable for clinical use; Return Form or local destruction authorization is maintained
- For studies that are completed or discontinued, return of NCI-supplied agent to the NCI, or locally destroyed upon NCI authorization or transferred to another NCI protocol (with NCI approval), and Return Form or local destruction authorization or transfer approval is maintained
- NCI-supplied study agent is returned, transferred or locally destroyed within 90 days of study completion, when requested by the NCI, or when patients/study participants are in follow-up and NCI-supplied agent is not being administered
- Patient/study participant returns of NCI-supplied study agents are recorded on the patient-specific DARF for patient-specific supply studies
- Patient/study participant returns of oral NCI-supplied study agents *are* documented appropriately on the oral DARF
- Patient/study participant returns of non-oral or non-patient-specific supplies *are not* recorded on the DARF

Non-Compliance

- NCI-supplied study agent is not returned, not transferred to an appropriate NCI protocol or not destroyed within 90 days; NCI-supplied study agent is destroyed without NCI authorization or not destroyed per local institution's destruction policy
- Failure to maintain Return Form or documentation of local destruction; no written NCI authorization for transfer or for local destruction
- NCI-supplied study agents not returned, transferred or destroyed when patients/study participants are in follow-up and no NCI-supplied study agent is being administered
- Patient/study participant returns of NCI-supplied study agents are not recorded on the patient-specific DARF for patient-specific supply studies
- Patient/study participant returns of oral NCI-supplied study agents *not* documented appropriately on the Oral DARF
- Patient/study participant returns of non-oral or non-patient-specific supplies *are* recorded on the DARF

STUDY AGENT STORAGE

Compliance

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

Non-Compliance

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

ADEQUATE SECURITY

Compliance

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

Non-Compliance

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

AUTHORIZED PRESCRIPTION(S)

Compliance

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

Non-Compliance

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

5.3.5 Assessing the Accountability of 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/study participants on NCI-sponsored clinical trials, and the number of open protocols reviewed should be considered in the evaluation.

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

Acceptable

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

Acceptable Needs Follow-up

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

Unacceptable

- Inability to track the disposition of NCI-supplied study drugs
- 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 Network Group or CCOP/NCORP Research Base. A copy of the written response/CAPA plan, along with an assessment of adequacy by the Network Group or CCOP/NCORP Research Base of the response/ CAPA plan, must be forwarded to CTMB by the Network Group within 45 calendar days from the date the final audit report is submitted in the CTMB-AIS. Network Group or CCOP/NCORP Research Base 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 or CCOP/NCORP Research Base 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 Preventative 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. See Section 6.4 for more information related to reaudits.

For institution audits that are performed off-site it is strongly recommended that an on-site visit be conducted every six years (every other routine audit or full reaudit). The audit may be conducted within 6 months prior to or on the day of the audit. An on-site pharmacy inspection can be done by the Network Group. The Network Group may designate this responsibility to the Main Member institution or the CCOP/NCORP. The pharmacy audit findings must be included in the final audit report of the affiliate or the CCOP/NCORP. 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 document
- Eligibility
- Correct treatment and treatment sequence
- Evaluation of disease outcome/tumor response
- Adverse events related to treatment
- General quality of the data collected

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

5.4.1 Examples of Major Deficiencies

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

Informed Consent

Failure to document properly obtained informed consent such as:

- Consent form document missing
- Consent form document not signed and dated by the patient/study participant

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

Eligibility

- Review of documentation available at the time of the audit confirms patient/study participant did not meet all eligibility criteria and/or eligibility requirements were not obtained within the timeframe as specified by the protocol
- Documentation missing; unable to confirm eligibility

Exception: Patients deemed ineligible based on laboratory/pathology reports following registration and changes based on central review of material.

Treatment

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

Disease Outcome/Response

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

- Inaccurate documentation of initial sites of involvement
- Tumor measurements/evaluation of status or disease not performed or not documented according to protocol
- Protocol-directed response criteria not followed
- Claimed response (PR, CR, etc.) cannot be verified or auditor could not verify the reported response

- Failure to detect cancer (as in a prevention study) or failure to identify cancer progression

Adverse Events

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

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

General Data Management Quality

- Recurrent missing documentation in the patient/study participant records
- Protocol-specified laboratory tests not reported or not documented
- Protocol-specified diagnostic studies including baseline assessments not done, not reported or not documented
- Protocol-specified research/advanced imaging studies not done or submitted appropriately
- Frequent data inaccuracies
- Errors in submitted data
- Delinquent data submission (> 6 month delinquency is considered a major deficiency; a 3-6 month delinquency is considered a lesser deficiency)

The Groups and CCOP/NCORP Research Bases have established guidelines and acceptability of the timeliness, completeness and accuracy of submitted data. A disregard of or untimely data reporting per Group or CCOP/NCORP Research Base 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 Preventative Action (CAPA) plan exists and no further action is required by the Network Group, CCOP/NCORP Research Base, the institution, or the principal investigator because no similar deficiency has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a deficiency is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, CTMB must receive a copy of the CAPA plan at the time the final audit report is submitted or by the date follow-up is due.

Acceptable, Needs Follow-up

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

Unacceptable

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

If this component is rated as Acceptable Needs Follow-up or Unacceptable, the institution will be required to submit a written response and/or CAPA plan to the Network Group or CCOP/NCORP Research Base. A copy of the written response/CAPA plan, along with an assessment of adequacy by the Network Group or CCOP/NCORP Research Base of the response/CAPA plan, must be forwarded to CTMB by the Network Group within 45 calendar days from the date the final audit report is submitted in the CTMB-AIS. Network Group or CCOP/NCORP Research Base 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 or CCOP/NCORP Research Base 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/study participants have been accrued. If sufficient new patients/study participants 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. See Section 6.4 for more information related to reaudits.

5.5 Role of the Investigator During the Audit

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

5.6 Exit Interview

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

SECTION 6 REPORTING 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. *If the preliminary report is submitted electronically by email, the 'subject line' must indicate the Group name and CTEP site code.*

6.1.1 Submission

The Preliminary Report of Audit Findings form (see Appendix 3) must be faxed to CTMB (240) 276-7891 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 (240) 276-6545 of any findings suspicious and/or suggestive of intentional misrepresentation of data and/or disregard for regulatory safeguards for any of the three 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 Network Group or CCOP/NCORP Research Base 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.

A co-site visitor may be assigned to an audit by CTMB. If one is assigned, they will also generate a Preliminary Report of Audit Findings summarizing the findings of the audit.

A separate Preliminary Report of Audit Findings is required for each audited institution. However, if the audit was conducted as a combined audit ~~as~~ a whole (parent and their non-auditable institutions), a single Preliminary Report is required.

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

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 Audit Report (Appendix 4) 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 Network Group or CCOP/NCORP Research Base should be noted in the General Comments or Exit Interview sections of the final audit report.

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

A separate Final Audit Report is required for each audited institution. However, if the audit was conducted as a combined audit as a whole (parent and their non-auditable institutions), a single final audit report is required.

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/study participants audited, the IND drugs, treatment modalities used and the disease(s) studied in each protocol
- For each protocol, indicate whether OK, major, or lesser deficiencies were found and describe each major and lesser deficiency
- Indicate Yes or No that informed consents were reviewed
 - If reviewed, identify any deficiencies
 - Indicate if the informed consent content was reviewed off site
- 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 the number of DARFs reviewed (ie, number of study agents reviewed)
- For off-site audits, indicate ~~Not Reviewed~~ for return of drug (unless verified by returned receipt from PMB/sponsor), storage, and security
- Indicate Compliant, Non-compliant, or Not Reviewed for maintaining accurate records, including primary transaction and satellite records, and specific regulations related to protocol and drugs, storage and security; for each item identified as non-compliant, select the appropriate non-compliant item or items
- The pharmacy narrative must provide an overall assessment for this component and can include guidance provided to the institution
- Examples of information that may be included under the pharmacy narrative are: descriptions of non-compliance issues not outlined in the audit guidelines; review of temperature logs and excursions; rationale of why IND or NCI-supplied study agents were not selected for review, etc.

6.2.2.4 Patient Cases

- For each category, indicate if major or lesser deficiencies were found and describe, otherwise indicate OK or Not Reviewed
- The CTMB Audit Information System (CTMB-AIS) pre-populates and summarizes the deficiencies for each patient/study participant and category in a table; this table identifies the total number of major and lesser deficiencies for the total patient cases reviewed
- Provide an overall assessment for this component and indicate if a re-audit is required and the time frame
- All patient cases including those registered/enrolled under each sub affiliate/sub component must be identified by institution.

6.2.2.5 Audit Procedures

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

6.2.2.6 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 and summarize the 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/Corrective and Preventative Action (CAPA) Plan

If a component is rated as Acceptable Needs Follow-up or Unacceptable, each audited institution will be required to submit a written response and/or CAPA plan to the Network Group or CCOP/NCORP Research Base. This written response must address the specific audit findings and be signed by the appropriate investigator at each audited institution. A copy of the written response/CAPA plan, along with an assessment of adequacy by the Network Group or CCOP/NCORP Research Base of the response/CAPA plan, must be forwarded to CTMB by the Network Group within 45 calendar days of the date the final audit report is submitted in the CTMB-AIS. Network Group or CCOP/NCORP Research Base 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 or CCOP/NCORP Research Base for any component rated as Unacceptable. A reaudit should be done no later than one year after an Unacceptable audit or when sufficient patients/study participants have been accrued.

6.3.1 Suspension of Participating Institutions

If an audited institution fails to provide a CAPA plan for one or more audit components rated as acceptable needs follow-up or unacceptable within the required 45 calendar day timeline, the following actions will be imposed by the Group.

- 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 Network Group Main Member or LAPS main member; or an integrated component of a LAPS or CCOP/NCORP, all new patient registrations will be suspended from both the Network Group Main Member, LAPS main member, or CCOP/NCORP and the corresponding Network Group affiliate, LAPS integrated components and LAPS affiliates, or CCOP/NCORP component (as well as any associated sub affiliates).
- 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 with the institution being prohibited to participate in NCI-sponsored clinical trials through the Network Group or CCOP/NCORP Research Base 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 Withdraw of Participating Institutions

If improved performance is not documented at the time of the second re-audit, the institution may be permanently withdrawn by the Group or CCOP/NCORP Research Base. 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 or CCOP/NCORP Research Base. 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 may be conducted 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 Network Group or CCOP/NCORP Research Base. A reaudit should be done no later than a year after an Unacceptable audit or when sufficient patients/study participants have been accrued.

A reaudit requirement remains linked to the institution regardless of its status (ie, active or withdrawn). If the institution is being withdrawn, the reaudit timeline on the final audit report for the applicable audit components are to be designated ~~No Reaudit~~. If the institution rejoins the same Group or CCOP/NCORP research base at a later date, the reaudit must be conducted within 12 months from the first new accrual. The ~~No Reaudit~~ timeline 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://eapps-ctep.nci.nih.gov/CTMBWeb>