



NCI GUIDELINES FOR AUDITING CLINICAL TRIALS FOR THE NCI NATIONAL CLINICAL TRIALS NETWORK (NCTN) PROGRAM INCLUDING NCI COMMUNITY ONCOLOGY RESEARCH PROGRAM (NCORP) AND NCORP RESEARCH BASES

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

Revised: January 2021
Effective: 15 February 2021

Approving Officials

CTMB Branch Chief

Date

CTEP Associate Director

Date

TABLE OF CONTENTS

LIST OF APPENDICES	vi
LIST OF ACRONYMS	vii
CTMB-AIS DEFINITIONS	viii
SECTION 1 BACKGROUND AND PURPOSE OF THE AUDITING PROGRAM FOR THE NCI NETWORK GROUPS AND NCORP RESEARCH BASES	1
1.1 Introduction	1
1.2 Background	1
1.3 Purpose and Objectives	3
SECTION 2 ROLES AND RESPONSIBILITIES FOR THE CONDUCT OF QUALITY ASSURANCE PROGRAMS	4
2.1 Clinical Trials Monitoring Branch (CTMB).....	4
2.2 Network Groups	5
2.2.1 Quality Control	5
2.2.2 Quality Assurance	5
2.2.2.1 Study Monitoring	5
2.2.2.2 Data and Safety Monitoring Board (DSMB)	6
2.2.2.3 Auditing Program	6
2.2.2.4 CTMB – Audit Information System (AIS).....	6
2.3 NCI Community Oncology Research Program (NCORP)	7
2.3.1 NCORP Research Bases of the Network Groups	7
2.3.2 NCORP Research Bases.....	7
2.4 Cancer Trials Support Unit (CTSU).....	7
2.4.1 Auditing Patient Cases for Studies in Medidata Rave	7
2.4.2 Auditing Patient Cases Utilizing the Source Document Portal (SDP)	7
SECTION 3 AUDITS	9
3.1 Network Group Membership Type	9
3.1.1 Network Institutions/Lead Participating Organizations	11
3.1.1.1 Main Members	11
3.1.1.2 Affiliates	11
3.1.2 DCP’s NCI Community Oncology Research Program (NCORP)	11
3.1.2.1 NCORPs	11
3.1.2.2 NCORP Affiliates.....	11
3.1.3 NCORP Research Base (NCORP-RB).....	12

3.1.4	Network Lead Academic Participating Sites (LAPS)	12
3.1.4.1	Lead Academic Participating Main Members (LAPS MM)	12
3.1.4.2	Lead Academic Participating Site Integrated Components (LAPS IC)	12
3.1.4.3	Lead Academic Participating Site Affiliates (LAPS A)	12
3.1.4.4	Lead Academic Participating Site Aligned Affiliates (LAPS AA)	13
3.1.4.5	Main Member Sub Affiliates/NCORP Sub Affiliates	13
3.1.4.6	NCTN Pediatric Network Group Members	14
3.1.4.7	Non-Member Collaborators	14
3.2	Crediting of Accrual	15
3.3	Auditable and Non-Auditable Institutions	15
3.4	Grouping of Membership Types	16
3.5	Network Group Main Member Institutions	17
3.6	Network Affiliate, LAPS Affiliate and LAPS Aligned Affiliates Institutions	17
3.7	NCORP and NCORP Affiliates	17
3.8	NCORP Research Bases	18
3.9	Lead Academic Participating Sites (LAPS)	18
3.10	Special Protocols	18
3.11	Auditing of Withdrawn or No Longer Funded (NLF) Institutions	19
3.12	Off-cycle Audits	19
SECTION 4	PREPARATIONS FOR CONDUCTING THE AUDIT	20
4.1	CTMB-AIS Generated Notifications/Emails	20
4.2	Arranging the Audit	20
4.3	Off-site/Remote Audit	20
4.4	Selection of Protocols and Patient Cases for On-site or Off-site Audits	21
4.5	Selection of the Audit Team	22
4.5.1	Network Group and NCORP Research Base	22
4.5.2	National Cancer Institute	22
4.6	Institution Responsibilities	22
SECTION 5	CONDUCTING THE AUDIT	24
5.1	Assessing Audit Findings	24
5.2	Review of the Regulatory Documentation	25
5.2.1	Review of the NCI Central Institutional Review Board (CIRB) - IRB of Record	25
5.2.2	Review of the Local Institutional Review Board (IRB) - IRB of Record	25

5.2.3	Listing of IRB Deficiency Types	26
5.2.3.1	CIRB – IRB of Record	26
5.2.3.2	Local IRB – IRB of Record	27
5.2.4	Review of Informed Consent Content (ICC)	28
5.2.5	Review of the Delegation of Tasks Log (if applicable)	30
5.2.6	Assessment of the Regulatory Documentation Review	30
5.3	Review of Accountability of Investigational Agents and Pharmacy Operations	32
5.3.1	Control Dispensing Area/Pharmacy	32
5.3.2	Satellite Dispensing Area/Pharmacy	32
5.3.3	Imaging Studies/Cancer Control	33
5.3.4	Guidelines for Conducting the Pharmacy Review	33
5.4	Review of Patient Case Records	39
5.4.1	Deficiency Type by Category	40
5.4.2	Assessing the Findings from the Patient Case Review	43
5.5	Role of the Investigator During the Audit	44
5.6	Exit Interview	44
SECTION 6	REPORTING OF AUDIT FINDINGS AND FOLLOW-UP	45
6.1	CTMB-AIS Generated Notifications/Emails	45
6.2	Preliminary Report of Audit Findings	45
6.2.1	Submission	45
6.2.2	Content	46
6.3	Final Audit Report	46
6.3.1	Submission	46
6.3.2	Content of Final Audit Report	47
6.3.2.1	General Information	47
6.3.2.2	Regulatory Documentation	47
6.3.2.3	Accountability of Investigational Agents and Pharmacy Operations	47
6.3.2.4	Patient Cases	48
6.3.2.5	Audit Procedures	48
6.3.2.6	General Comments	48
6.3.2.7	Exit Interview	48
6.4	Corrective and Preventative Action (CAPA) Plan / Response	49
6.5	Re-audits	49

6.6	For Cause (Off-cycle) Audits	49
6.7	Probation of a Clinical Investigator	49
6.8	Probation of a Participating Institution	50
6.9	Suspension of a Clinical Investigator and/or Participating Institution	50
6.10	Withdraw of a Participating Institution.....	51

LIST OF APPENDICES

Appendix 1 Audit Worksheet for Regulatory Documentation Review

Appendix 2 Audit Worksheet for Pharmacy Review

Appendix 3 Audit Worksheet for Patient Case Review

LIST OF ACRONYMS

AE	Adverse Event
CAPA	Corrective and Preventative Action
CCOP	Community Clinical Oncology Program
NCCCP	NCI Community Cancer Center Program
CFR	Code of Federal Regulations
CIP	Cancer Imaging Program
CIRB	Central Institutional Review Board
CLASS	Compliance, Learning, and SOP Solutions
COI	Conflict of Interest
CTEP	Cancer Therapy Evaluation Program
CTMB	Clinical Trials Monitoring Branch
CTMB-AIS	Clinical Trials Monitoring Branch-Audit Information System
CTMS	Clinical Trial Monitoring Service
CTSU	Cancer Trials Support Unit
DARF	Drug Accountability Record Form
eDARF	Electronic Drug Accountability Record Form
EMR	Electronic Medical Record
DCP	Division of Cancer Prevention
DCTD	Division of Cancer Treatment and Diagnosis
DSMB	Data and Safety Monitoring Board
DTL	Delegation of Tasks Log
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IAM	Identity and Access Management
ICC	Informed Consent Content
IND	Investigational New Drug
IRB	Institutional Review Board
LAPS	Lead Academic Participating Site
LIRB	Local Institutional Review Board
LPO	Lead Participating Organization
MU	Minority Underserved
NCORP	National Community Oncology Research Program
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NLF	No Longer Funded
PII	Personally Identifiable Information
RCR	Registration and Credential Repository
RSS	Regulatory Support System
SDV	Source Data Verification
SDP	Source Document Portal
SOP	Standard Operating Procedure

CTMB-AIS DEFINITIONS

Auditable Flag: a designation in the CTMB-AIS that indicates how an institution will be audited.

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

Audit Type: Routine, Re-audit 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 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 an active 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 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/NCORP package. This term NLF is only used in CTMB-AIS. In the RSS, the corresponding term is 'Follow-up'.

Membership Status Date: Status date is when the Group makes changes to an institution's record such as status change (e.g., active, withdrawn) or other changes to the membership type/role (e.g., Main Member, 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), NCORP, NCORP Affiliate, NCORP Sub Affiliate, 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 institution 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.

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 (e.g., POG, SELECT); no changes will be made to the roster record (i.e., 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 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 qualified 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 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 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 regulatory support, assistance with audit activities, patient enrollment, 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 in CTEP's Quality Assurance program is constantly evolving, currently their activities primarily include:

- Establishing the ability to electronically capture Source Data Verification (SDV) activity as part of the auditing of patient cases
- Provision of IT system integrations to support roster and limited audit activities
- Posting of regulatory documentation in RSS (Regulatory Support System)
- Assisting with teleconferences or meetings between NCI and Network Group staff to discuss new policies and procedures

In 2014, the Community Clinical Oncology Program (CCOP) was restructured and combined with the NCI Community Cancer Center Program (NCCCCP) to create the NCI Community Oncology Research Program (NCORP). The NCORP community site is defined as a consortium of community hospitals, oncology practices, or community-based integrated healthcare systems. This community-based network supports a wide range of clinical research, including cancer prevention/control, screening/post-treatment surveillance, imaging trials, NCTN supported cancer treatment, 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 when ACRIN joined with ECOG to form the ECOG-ACRIN Network Group in 2014.

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 NCORP programs (i.e., member institutions participating in cancer trials were designated as having NCTN membership or NCORP membership) for uniformity when applying NCI policies and guidelines.

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. This document, the 'NCI Guidelines for Auditing Clinical Trials for the NCI National Clinical Trials Network (NCTN) Program Including NCI Community Oncology Research Program (NCORP) and NCORP Research Bases' requires all institutions to be audited at least once every 36 months. To ensure the Group's compliance with this requirement, CTMB annually reviews all current membership institutions for each Group. This includes review of all Main Members, Affiliates, Sub Affiliates, LAPS Main Members, LAPS Affiliates, LAPS Sub Affiliates, LAPS Integrated Components, LAPS Aligned Affiliates, LAPS Aligned Sub Affiliates, NCORPs, NCORP Affiliates, and NCORP Sub Affiliates and audit activity for each.

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 and the NCORP 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 studies in all phases, creation and updating of the informed consent form template for all NCI-sponsored clinical trials, setting standards for criteria when evaluating data timeliness and query for data resolution, implementation of 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 and the NCORP Research Bases. It is recognized that there may be inherent differences in the methodologies and processes utilized by the Network Groups/NCORP Research Bases when auditing. Groups/NCORP Research Bases may establish additional policies and procedures specific to their Group/NCORP Research Base.

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

CTMB staff also serve 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 or CTMS member) 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. 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 component (Regulatory Documentation, 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 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 CTMB 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 several 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 Board (DSMB)

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 an 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/NCORP Research Bases. Specifically, each Group/NCORP Research Base will verify investigator compliance with the protocol, applicable regulatory requirements, and adherence to Group policies and procedures. If necessary, the Group/NCORP Research Base may provide institution staff with resources for a more thorough understanding of the regulatory requirements, good clinical practices (GCPs), data collection and data management practices.

2.2.2.4 CTMB – Audit Information System (AIS)

The CTMB has designed an information system which permits the on-line submission and collection of all data related to audits and audit findings. This includes scheduling and tracking audits, transmission of final audit reports, collection and tracking of follow-up responses to audit findings, and capturing documentation for the review of preliminary reports, final audit reports and follow-up responses. The system allows restricted access to the stored data and will keep a record of any data changes. The CTMB-AIS can be accessed after obtaining: an Identity and Access Management (IAM) account, appropriate documented training, and providing a username and password at: <https://ctepcore.nci.nih.gov/CTMBWeb/>

2.3 NCI Community Oncology Research Program (NCORP)

The 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, NCORP Affiliates, and NCORP Sub Affiliates adhere to the federal regulations, GCP and the CTMB audit guidelines. A NCORP may have a Network Group or a Cancer Center serve as its Research Base.

2.3.1 NCORP Research Bases of the Network Groups

All Group members including all institutions as part of the NCORPs must follow the same mechanisms and processes as the other Group member institutions (i.e., LAPS, Main Members, Affiliates, etc.). monitoring procedures. They must be audited per the CTMB audit guidelines.

2.3.2 NCORP Research Bases

Cancer Centers that serve as 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 audit per the CTMB audit guidelines including scheduling audits, auditing, generating and uploading final audit reports and obtaining and uploading Corrective and Preventative Action (CAPA) plans into the CTMB-AIS.

2.4 Cancer Trials Support Unit (CTSU)

The CTSU provides an array of support including roster management, regulatory support, patient enrollment, data collection, and posting on CTSU website. Services specifically tailored to auditing activities are:

2.4.1 Auditing Patient Cases for Studies in Medidata Rave

A system is utilized by auditors reviewing patient records to electronically record Source Data Verification (SDV) activity directly in Medidata Rave (Rave) for those studies using Rave to manage patient clinical data. A process has also been developed to provide a unified framework, to create a consistent workflow to facilitate pre- and post-SDV activities, and to provide transparency for the site auditing process to meet regulatory requirements.

A comprehensive auditor's guide detailing this process for auditors can be found at: <https://www.ctsu.org/readfile.aspx?fname=Public/CTSU-SAR-Auditors-UserGuide.pdf>.

In addition, the CTSU Members' Website Site Audit Portal will provide a gateway into the process for Network Groups/NCORPs and auditors, see link: <https://www.ctsu.org/RAVE/SiteAudit.aspx>

2.4.2 Auditing Patient Cases Utilizing the Source Document Portal (SDP)

This approach is an alternative to auditing patient cases when access to the EMRs cannot be obtained, or in some circumstances may also be used in combination with other approaches. The process of auditing utilizing this approach is currently only applicable to review of the Patient Cases. Review of the Regulatory Documentation and Pharmacy is conducted separately.

The following instructions are available when conducting Remote Audits utilizing the Source Document Portal.

Remote Auditing Instructions for Auditors (*Note: Links below require log-in to the CTSU website*)

<https://www.ctsu.org/master/simplepage.aspx?ckey=HELP-REMOTE-AUDITING-AUDITORS#Introduction>

Remote Auditing Instructions for Site Staff:

<https://www.ctsu.org/master/simplepage.aspx?ckey=HELP-REMOTE-AUDITING-SITES#Introduction>

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, NCORPs, NCORP Affiliates, and NCORP Sub Affiliates) that accrue patients to the Network Group and 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 NCORP Research Base roster in the CTSU-RSS (CTSU-Regulatory Support System) and the CTMB-AIS. Each Network Group and 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 (90 days) from the date the change was made.

Storefronts are administrative sites that do not accrue or treat patients. All NCORP and LAPS are storefronts. The NCORP storefronts handle the regulatory, registration, data management and financial aspects for their Affiliates. 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.

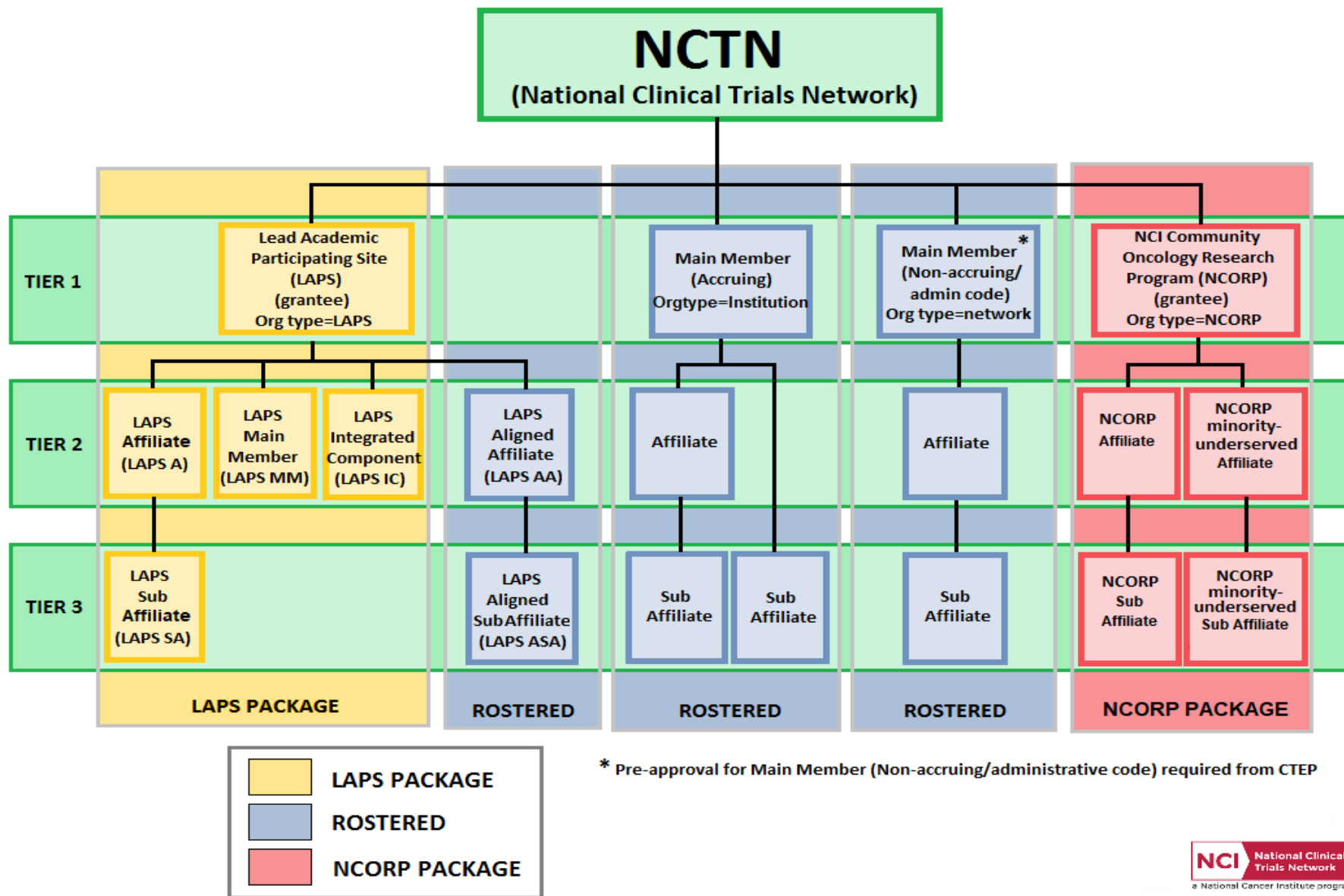
Main Members and Affiliates are expected to enroll patients and provide significant accrual to the NCTN program. CTEP may consider a limited number of Main Members to be designated as storefronts. A Network Group may request that a Main Member be a storefront which handles the administrative aspects of their associated institutions. These institutions cannot be included in a 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 Network Group may include an international collaborator as a full member. This request must also be approved by CTEP before it can be included on the Global Membership Roster for the Network Group making the request. If an international collaborator has a formal structure in place that handles the administrative aspects as described above, they may be listed as storefront. These international collaborators may be asked by the Network Group to conduct audits of their international members.

3.1 Network Group Membership Type

Clinical 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 funding and accrual purposes (see Figure 1).

Figure 1 Organizational Chart for the NCI National Clinical Trials Network (NCTN) Including NCORPs



3.1.1 Network Institutions/Lead Participating Organizations

Main Members and Affiliates are determined by the Network Group/Lead Participating Organization (LPO) 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's offices or community clinics.

3.1.2 DCP's NCI Community Oncology Research Program (NCORP)

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 (HMOs), groups of practicing physicians, consortiums, or other healthcare organizations which agree to work with a principal investigator through a single administrative unit. Minority-underserved (MU) NCORPs may include the institutions above in addition to public hospitals or medical centers. MU NCORPs have a patient population comprising of at least 30% racial/ethnic minorities or rural residents.

3.1.2.1 NCORPs

Administrative sites handle financial, regulatory, registration and data management for the Affiliates within the NCORP. An individual 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 NCORP Affiliates

All hospitals, clinics, HMOs, etc. are approved by DCP as part of a 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 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 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 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 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 Groups. For instance, 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 an NCORP.

3.1.4.5 Main Member Sub Affiliates/NCORP Sub Affiliates

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

Main Member Sub Affiliates/NCORP Sub Affiliates **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 Main Member Sub Affiliates/NCORP Sub Affiliates:

- LAPS Sub Affiliates (LAPS SA) must be listed on a LAPS grant
- LAPS Aligned Affiliates (LAPS AA) and LAPS Aligned Sub Affiliates (LAPS ASA) are **not** listed on a LAPS grant
- NCORP Sub Affiliates (NCORP SA) and NCORP minority-underserved (NCORP MU) Sub Affiliates must be listed on a NCORP grant

Requirements of Main Member Sub Affiliates/NCORP Sub Affiliates:

- 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 Sub Affiliate is 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
 - Ongoing assessment of regulatory, pharmacy and patient/study participant data
 - Compliance of the pharmacy operations (procedures, storage and security) with NCI policies and federal regulations
 - The review of the appropriateness of the Sub Affiliate's 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

Main Member Sub Affiliates/NCORP Sub Affiliates (non-auditable sites) 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. Selecting 10% of patient cases from each Sub Affiliate is not required. Under certain circumstances, CTMB may mandate an independent audit of any institution.

3.1.4.6 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 NCORP grant but they have the option to select which NCORP Affiliate they accept as their member. Therefore, their institution's membership type (role) may differ from the other Network Groups who participate with the LAPS or NCORP grants.

3.1.4.7 Non-Member Collaborators

There may be domestic or international institutions that collaborate with a Network Group on a particular trial (i.e., enroll patients on a Network Group trial) which are not members of the Network Group. These collaborating

institutions do not receive NCI funding for their participation from DCTD or DCP. These sites must be approved by DCTD/CTEP (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 submitted for review by CTMB.

3.2 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.

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 NCORP Research Bases that was credited with the registration/enrollment.

3.3 Auditable and Non-Auditable Institutions

An 'Auditable' institution refers to an institution when an audit is scheduled and conducted as a single institution audit and the audit report will consist of findings only for that specific institution being audited (one final audit report by CTEP Site Code). A Preliminary Report of Audit Findings form is uploaded in the CTMB-AIS by the Group/NCORP Research Base for each audited site(s).

Characteristics of an Auditable Institution:

- The audit flag for the institution (by Group) is 'Yes' in the CTMB-AIS
- Usually these types of audits are conducted on-site. On occasion, an audit can be conducted off-site if, for instance, the Network Group/NCORP Research Base is conducting a re-audit of only the regulatory documentation. In this scenario, the audited institution will be required to provide the appropriate documentation to the Group/NCORP Research Base location for review. This scenario would also apply to audits being conducted entirely off-site/remotely.
- Auditable institutions may include NCORPs, Main Members, Affiliates, LAPS Main Members and LAPS Affiliates.

A 'Non-Auditable' institution refers to an institution when an audit is comprised of more than one institution and a single final audit report consists of findings for all the institutions audited (one final audit report for multiple CTEP Site Codes). One Preliminary Report of Audit Findings form is submitted for the institutions audited 'as a whole' (combined).

Characteristics of a Non-Auditable Institution:

- The audit flag for the institution (by Group) is 'No' in the CTMB-AIS
- Usually these types of audits are scheduled and conducted at the parent site (see Figure 1 on page 10) and corresponding Tier 2 (and Tier 3) sites being conducted off-site. The scheduling and auditing of multiple sites at a single visit is considered an audit 'as a whole' (or combined). This scenario would not apply to audits being conducted entirely off-site/remotely.
- The final audit report is generated for the parent site and includes all audited sites under the parent. All audited sites are listed by CTEP Site Code and institution name.

Other Items Related to the Audit Flag:

- The Network Group/NCORP Research Base is responsible for designating and/or changing the audit flag for Tier 1 and Tier 2 sites, where applicable.
- The audit flag for a Tier 1 and Tier 2 institution within the same NCORP cannot be both set to 'No' for an audit to be scheduled correctly. This rule applies to NCORPs and NCORP Affiliates.
- The audit flag for Tier 3 institutions must be set to 'No' in the CTMB-AIS. The CTMB (in consultation with the Group/NCORP Research Base) may request an on-site audit (and separate final audit report) of a Tier 3 site if there are reasons for concern. In this scenario, the audit flag would need to temporarily change from 'No' to 'Yes' for the audit to be scheduled appropriately. This scenario would not apply to audits being conducted entirely off-site/remotely.
- For audits that include non-auditable institutions, when there are separate IRBs or pharmacies (i.e., receives drug directly from PMB or other sponsors), each IRB and pharmacy must be identified in the final audit report by CTEP site code, IRB name, and pharmacy location(s). Protocols and patient cases must be selected for review from the parent and each non-auditable institution being audited.

Note: Section 3.3 does not apply to Special Protocol designations, Pediatric Oncology Group institutions, and other instances when approved by CTEP.

3.4 Grouping of Membership Types

The membership type designated by DCTD in relation to a LAPS grant or designated by DCP in relation to a 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 NCORP grant:

- A LAPS Main Member or NCORP
- A LAPS Integrated Component, LAPS Affiliate, or NCORP Affiliate
- Sub Affiliate under a NCORP grant or a LAPS Sub Affiliate under a LAPS grant

- An institution can only be listed on one grant package (i.e., LAPS or 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

3.5 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 audit should be conducted sooner than 18 months. Following the initial audit, Main Member institutions and Affiliates 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.

The 18-month rule does not apply to an institution that has been previously audited by the same Group. This rule also does not apply if a Main Member institution moves to a new location which requires a new CTEP site code and/or a decision is made by CTEP to change to a new site code.

3.6 Network Affiliate, LAPS Affiliate and LAPS Aligned Affiliates Institutions

An audit of an Affiliate may be conducted by the Network Group on-site. Alternatively, it 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. This scenario would not apply to audits being conducted entirely off-site/remotely.

3.7 NCORP and NCORP Affiliates

NCORP institutions will be audited within 18 months after entry of the first patient/study participant. If the NCORP accrues rapidly, the initial audit should be conducted sooner than 18 months. Following the initial audit, NCORP institutions must be audited at least once every 36 months. For high accruing NCORPs and NCORP Affiliates, 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/NCORP Research Base may utilize one of three audit methods to conduct an audit of its NCORPs, NCORP Affiliates, and NCORP Sub Affiliates:

Method 1: A separate audit may be conducted for each NCORP and NCORP Affiliate (including NCORP Sub Affiliates). A separate Preliminary of Audit Findings form and a separate final audit report is generated for each institution audited as part of the NCORP.

Method 2: One audit may be conducted for the NCORP 'as a whole'. All NCORP Affiliate institutions (including their Sub Affiliates) that have accrued patients since the previous audit may be selected and scheduled to be audited under the NCORP. One Preliminary of Audit Findings form and one final audit report is generated to include findings from all audited institutions within the NCORP.

Method 3: A combination of the two above audit methods may be utilized. For example, one or more NCORP Affiliates that are considered high accruing institutions can be audited separately (Method 1) and the remaining NCORP Affiliates audited 'as a whole' (Method 2).

3.8 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 NCORP, NCORP Affiliate, or Main Member/Affiliate.

3.9 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 audit should be conducted sooner than 18 months. The 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 form and final audit report must be submitted for each LAPS Main Member, LAPS IC, LAPS A and LAPS AA.

However, the audit flag for a LAPS IC may be changed from 'yes' to 'no' so that an audit can be combined with the LAPS Main Member and audited 'as a whole'. One preliminary form 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 (i.e., receives drug directly from PMB or other sponsors), each IRB or pharmacy must be audited. The final audit report must identify the relevant regulatory documentation, pharmacy and patient cases by the LAPS Main Member and each LAPS IC.

3.10 Special Protocols

The auditing policy generally requires that the Network Group credited with the enrollment is responsible for conducting the audit. An exception to this may occur for registration studies, where the Lead Network Group has pre-determined to audit a protocol more

frequently, a higher percentage of cases are selected for audit, and access across all institutions without regards to which Network Group is credited. In these circumstances, a Special Protocol status can be designated within the CTMB-AIS to allow the Lead Network Group access to all patients regardless of which Group is credited with the enrollment. If special circumstances exist to warrant this type of approach, the Network Group may submit a request to CTMB for review and approval.

3.11 Auditing of Withdrawn or No Longer Funded (NLF) Institutions

If an institution's membership or participation in a Network Group or 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 NCORP is "defunded" by DCP, or the LAPS is no longer funded by CTEP, their membership status will be set to 'NLF' in the CTMB-AIS until the patients/study participants are off treatment/study intervention, the patient case(s) are transferred to another investigator/ institution and/or follow-up 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 withdrawing them. The Group remains responsible for auditing the NCORP Affiliate, NCORP Sub Affiliate, LAPS Main Member, LAPS Integrated Component, LAPS Affiliates/Aligned Affiliates, and LAPS Affiliates/Aligned Sub Affiliates.

For NCORPs and LAPS in NLF or withdrawn status, a close-out audit should be considered by the Network Group/NCORP Research Base. The decision whether to conduct an audit is based on the following:

- The number of patient cases enrolled since the previous audit.
- The number of active protocols with emphasis on registration or pivotal trials.
- If there is a high number of patients/study participants in follow-up.
- Site performance is not meeting acceptable quality standards for audit and/or submitting follow-up data.

If there is accrual and the institution has never been audited, it must have a close out audit conducted. A decision not to audit these institutions must first be discussed with CTMB.

3.12 Off-cycle Audits

Audits may be entered as an 'off-cycle' audit in the CTMB-AIS for the following scenarios:

- A Response Audit may be conducted when there are promising preliminary findings that warrant verification of findings. CTEP, a Network Group or a sponsor may request this review type.
- A For-Cause Audit may be warranted when there are concerns or irregularities found through quality control procedures or when allegations of possible scientific misconduct are made.
- More frequent auditing may also be scheduled, if requested by CTEP/CTMB due to the nature of the study (Special Protocols, registration trials, etc.).

SECTION 4 PREPARATIONS FOR CONDUCTING THE AUDIT

A Network Group/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 CTMB-AIS Generated Notifications/Emails

The Group/NCORP Research Base Audit Coordinator/designee assigned in the CTMB-AIS receives AIS generated emails related to audits that have not been scheduled per the audit guidelines. The Group/NCORP Research Base Audit Coordinator/designee must provide a response/explanation in writing within 5 business days of receiving the notification. The Group/NCORP Research Base response should be directed to the appropriate CTMB liaison.

4.2 Arranging the Audit

An audit date must be entered into the CTMB-AIS at least six weeks in advance of the scheduled routine audit or re-audit. This will ensure sufficient notification to the institution and will allow CTMB staff to decide which audits they or their designee will attend. The Group/NCORP Research Base must contact CTMB for approval prior to scheduling any audit within six weeks. At the time of contacting CTMB, the Group/NCORP Research Base must forward written documentation to CTMB from the institution to be audited (routine or re-audit) 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 four but no more than six weeks prior to the audit. This will allow the institution staff sufficient time to collect, prepare, assemble and label the required materials.

If the Group/NCORP Research Base needs to cancel an audit within three business days prior to the audit for unforeseen circumstances, they must notify the CTMB liaison. If a Clinical Trials Monitoring Service (CTMS) co-site visitor was assigned to the audit, the Group/NCORP Research Base must also contact CTMS.

4.3 Off-site/Remote Audit

For continued oversight of patient safety, there may be circumstances when remote auditing (i.e., off-site) is necessary. To the extent possible, this approach should include remote access to the site's Electronic Medical Records (EMRs) system. Due to logistical issues and unfamiliarity with the site's EMR system related to conducting remote audits, it may require extending the audit duration (i.e., # of days). Use of the Source Document Portal (SDP) as described under Section 2.4.2 is an alternative and may also be used in combination with other approaches.

The use of the above approaches is primarily intended for review of Patient Cases. It is at the discretion of the Network Group/Research Base on how the review of the Regulatory and Pharmacy documentation are provided and reviewed.

Sites should not request the auditors to disclose any Personally Identifiable Information (PII) other than the auditor's name. Examples of what should not be provided are birthdate, copy of auditor's driver's license, social security number, etc. Their IAM account number may be used in lieu of these identifiers. Furthermore, auditors are not Business Associates as defined in the HIPAA (Health Insurance Portability and Accountability Act) Privacy Rule.

4.4 Selection of Protocols and Patient Cases for On-site or Off-site Audits

These audit guidelines predominantly focus on intervention trials involving more than minimal risk. The statistical, operations, or data management office for the Network Group/NCORP Research Base selects the protocols for review. A minimum of four protocols representing studies conducted at the institution must be selected, when applicable. Emphasis should be given to the following types of studies: registration trials, IND, multi-modality, advanced imaging studies, and prevention/cancer control trials, as well as those with high accrual.

Specific trials (e.g., 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 of 10% of the patient case accrued since the last audit will be reviewed by the Network Group/NCORP Research Base. For Tier 1 and Tier 2 sites, patient cases accrued must be selected from each accruing institution. For Tier 3 sites, a representative sampling is to be audited at the 'parent' institution. For selection purposes, the 10% of chosen cases must be rounded up (e.g., if 12 patient cases are eligible for audit selection, at least two cases must be audited). In summary, when selecting the patient cases for audit, the following selection process applies, where appropriate:

- Select 10% of treatment cases where the auditing Group is the protocol lead or credited with the enrollment; and
- Select 10% of patient cases from protocols with advanced imaging studies/imaging studies embedded in treatment protocols; and
- Select 10% of patient cases enrolled onto DCP cancer control/prevention trials.

In addition to the above criteria, a patient case from every registration trial must be selected for audit. This includes patients enrolled onto a registration trial for every site being audited. Depending on the volume of patients enrolled onto a registration trial, auditing additional patient cases may be required.

While most cases will be selected from patients accrued since the previous audit, any patient case may be audited at any time. In addition, the Network Group/NCORP Research Base must select at least one or more unannounced cases to be reviewed, if the total accrual warrants selection of unannounced cases. The audited institution(s) may learn of the unannounced case(s) the day before or the day of the audit. These cases may have a limited review consisting of minimally reviewing the patient informed consent document and patient eligibility to be counted as part of the selection process noted above. Note: If unannounced cases receive a limited review, these patient cases do not count towards the required minimum of 10% to be reviewed. Selection of unannounced cases for review does not apply when conducting an off-site/remote audit.

In the event of a patient case transfer, the receiving/accepting institution should ensure that complete documentation is provided as part of the transfer process. Any audit taking place after the date of transfer will occur in its entirety at the receiving/accepting institution. This is because only the accepting institution will have access to the subject's information after the transfer takes place.

4.5 Selection of the Audit Team

Selection of the audit team should receive special consideration. Auditors should be selected based on auditing experience, knowledge of the federal regulations, GCPs, NCI guidelines and other procedural documents. It is expected that each auditor also be cognizant of the audit guidelines and procedures of the Network Group/Research Base they are affiliated with. All auditors must be registered minimally as an Associate Plus (AP) level in the Registration and Credential Repository (RCR). All auditors must also have completed the required CTMB Auditor Training via the CLASS (Compliance, Learning, and SOP Solutions) training system.

It is the responsibility of the Network Group/NCORP Research Base scheduling an audit to ensure there is no 'Conflict of Interest (COI)', or potential COI, between the auditor(s) and the institution(s) being audited. Documentation such as an "Auditor Confidentiality Agreement" must be maintained by the Group and readily accessible, if requested.

4.5.1 Network Group and NCORP Research Base

The audit team should include Network Group/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 responsible Clinical Investigator and institution staff. The auditors must be knowledgeable about clinical trial methodology, NCI policies, and federal regulations.

4.5.2 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 NCORP Research Base operations office of the audits the observers will attend. If CTMB staff or NCI designees 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 designees must be included in all exit interview discussions.

4.6 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, NCORP, LAPS Main Member or if the entire audit is conducted remotely, the following requested records must be available during of the audit:

- IRB documents, copies of the locally utilized informed consent documents, Delegation of Tasks Logs (DTLs) and 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) of patient cases selected for audit
- 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 above-mentioned documents must be made available the day of the audit or sooner, if requested by the Network Group/NCORP Research Base. The location of the audit may be at the institution being audited, the linked-parent (per the CTMB-AIS) or at the Network Group/NCORP Research Base conducting the audit. It is also recommended that a representative from each of the audited institutions be present at the audit (if applicable) 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, informed consent form documents, etc. The Network Group/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 navigating through the system.

For audits conducted off-site/remotely, the circumstances vary depending on the approach used to review the documentation. Regardless, the above bulleted items must be made available as requested. A designated site staff member must also be available to contact and assist with navigating through the site's EMR system, when necessary.

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:

- Regulatory Documentation (IRB of record documents, informed consent documents, and Delegation of Tasks Logs, if applicable)
- 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 and discharge summaries
- Study flow sheets and other research records that are signed and dated on a real-time basis by the health care practitioner evaluating the patient/study participant
- For advanced imaging studies, source documentation worksheets would include the acquisition, processing, quality assurance documentation, reader's interpretation, record of imaging administration, patient/study participant monitoring (vital signs, monitoring of contrast reactions, etc.), and log of staff signatures and imaging responsibilities
- Protocol or study roadmaps
- Registration/enrollment tracking sheets
- Patient diaries/calendars

At the discretion of the Network Group or NCORP Research Base, certain documents such as regulatory documentation, DARFs, and informed consent documents may be reviewed prior to the audit, if the audit is conducted on-site. These documents must be made available to the Group/NCORP Research Base auditors, if requested. Findings from off-site/remote reviews must be included in the Preliminary Report, discussed at the Exit Interview, and described in the Final Audit Report.

5.1 Assessing Audit Findings

An audit consists of reviewing and evaluating the following components:(1) Regulatory Documentation including conformance to IRB regulations and guidelines, informed consent form requirements, and maintenance of a delegation of tasks log (if applicable), (2) Pharmacy operations and use of NCI DARFs or NCI approved drug accountability logs, and (3) individual Patient Cases. An Audit Worksheet for each of these components can be found under Appendix 1, 2, and 3.

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 NCORP Research Bases will use a common set of terms or examples of Critical, Major and Lesser deficiencies. A common system is utilized for assessing each component of an audit, resulting in a standard format for final audit reports generated in the Clinical Trials Monitoring Branch - Audit Information System (CTMB-AIS). See definitions below:

Critical Deficiency

Any condition, practice, process or pattern that adversely affect the rights, safety or well-being of the patient/study participant and/or the quality and integrity of the data; includes serious violation of safeguards in place to ensure safety of a patient/study participant and/or manipulation and intentional misrepresentation of data (see http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500178525.pdf).

Major Deficiency

A variance from protocol-specified procedures or practices that makes the resulting data questionable.

Lesser Deficiency

Finding does not have 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 assigned as a major deficiency when determining the final assessment of an audit component.

5.2 Review of the Regulatory Documentation

5.2.1 Review of the NCI Central Institutional Review Board (CIRB) - IRB of Record

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

- Annual Institution Worksheet approval letter from CIRB to the Principal Investigator (PI) for study specific worksheet (local context)
- Documentation that CIRB approval was obtained prior to patient registration
- Unanticipated problems, serious non-compliance and/or continuing non-compliance problems as defined by OHRP are reported (see <https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html>)

5.2.2 Review of the Local Institutional Review Board (IRB) - IRB of Record

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

- Documentation of full-board initial IRB approval
- Documentation of full-board IRB annual reapproval
- Documentation of timely IRB approval (or disapproval) of protocol amendments that affect more than minimal risk
- Documentation of IRB approval or reapproval prior to patient registration

- Documentation of expedited review done appropriately
- Documentation of internal safety reports submitted timely
- Documentation of external safety reports (when required by the local IRB) submitted timely

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 greater than one year
- Missing reapproval: Missing documentation of protocol reapproval (e.g., no letter from IRB stating reapproval granted, IRB minutes not available)
- Expedited review: Expedited review conducted instead of full-board review. See OHRP guidance (<https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-expedited-review-procedures/index.html>)
- Other: Any regulatory concern not described above

Amendments (addendums or updates) must be approved (or disapproved) by the IRB of record within 90 calendar days of the Group's notification. Each Group/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 soon as possible with further instructions, as necessary.

Amendments that are editorial or administrative in nature are exempt from the 90 calendar day requirement and may be deemed a lesser deficiency. 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 OHRP (see OHRP guidance: <https://www.hhs.gov/ohrp/sites/default/files/ohrp/policy/advevntguid.pdf>) including external safety reports must be reported to the IRB within 90 calendar days of the Group's notification. A random sample of at least 10% of external safety reports reportable per OHRP policy must be reviewed for each protocol selected for an audit.

5.2.3 Listing of IRB Deficiency Types

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

5.2.3.1 CIRB – IRB of Record

Critical CIRB Deficiency

- Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1)

Major CIRB Deficiencies

- Unanticipated problems, Serious Non-Compliance and/or Continuing Non-Compliance (per OHRP) problems not reported
- Institution enrolls under an incorrect CTEP site code and the institution or institution CTEP site code is not covered by the CIRB
- Other (explain)

Lesser CIRB Deficiencies

- Copy of CIRB approval letter/study worksheet is not available or accessible at the time of the audit
- Other (explain)

5.2.3.2 Local IRB – IRB of Record

Critical IRB Deficiency

- Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1)

Major IRB Deficiencies

- Initial approval by expedited review instead of full-board 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 calendar days, but less than one year
- Registration of patient on protocol during a period of delayed reapproval or during a temporary suspension (i.e., 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 calendar 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 calendar days, any reportable external safety report to the IRB that is considered an unanticipated problem as defined by OHRP, unless there is a local IRB policy that does not mandate reporting of external safety reports
- Other (explain)

Lesser IRB Deficiencies

- Protocol reapproval delayed 30 calendar days or less
- Delayed reapproval for protocol closed to accrual for which all study participants have completed therapy
- Amendment/Investigator Brochure editorial revision or administrative in nature or other Network Group/NCORP Research Base specific document not submitted or not submitted timely to the local IRB
- Other (explain)

5.2.4 Review of Informed Consent Content (ICC)

The content of the local informed consent documents for at least four protocols (if there are four or more protocols) must be reviewed for content regardless of patient registration/enrollment to ensure the informed consent documents contain the elements required by federal regulations. If there are a variety of protocols, at least one informed consent document must be reviewed for CIRB or local IRB approval for a Treatment, Advanced Imaging and DCP protocol.

For each CIRB and local IRB approved informed consent document selected to be audited, the following items should be reviewed:

- Omission of one or more required informed consent elements as listed in the model approved by the NCI and required per the federal regulations
- Omission of one or more risks/side effects as listed in the model informed consent document
- Omission of any revision 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
- Changes made to the informed consent document not approved by the IRB of record; for CIRB-approved consent form documents, the only change allowed is the incorporation of the CIRB-approved boilerplate (local context)
- Multiple cumulative effects of lessers for a given informed consent document

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

Critical ICC Deficiency

- Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1)

Major ICC deficiencies

- Missing any of the following statements or language specific to the elements required per the federal regulations, when appropriate:
 - Involves research, purposes; duration of participation; description of procedures; identification of experimental procedures

- Description of foreseeable risks or discomforts
- Description of any benefits to subjects or others
- Disclosure of alternative procedures or treatments
- Description of the extent of confidentiality of records
- Explanation regarding compensation and/or whether treatments are available if injury occurs, including who to contact if injury occurs.
- Explanation of whom to contact for answers to pertinent questions about the research and whom to contact for questions related to research subject's rights
- Statement that participation is voluntary; refusal to participate involves no penalty or loss of benefits; subject may discontinue participation at any time
- Unforeseeable risks to subject, embryo or fetus
- Statement that circumstances in which subject's participation may be terminated by the investigator without subject consent
- Statement of additional costs to subject that may result from participation in the study
- Statement of consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- Statement that significant new findings which may be related to subject's willingness to continue participation will be provided to subject
- Disclosure of approximate number of subjects involved in the study
- Statement: "A description of this clinical trial will be available on www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time"
- Statement that a copy of the informed consent form will be given to the subject
- Failure to revise the informed consent document in response to an NCI Action Letter regarding risks
- Significant or substantial changes to the consent form document deviating from the CIRB-approved boilerplate (other than local context) not approved by the CIRB
- Consent form document contains changes not approved by the local IRB, including changes to questions that do not match the model consent form
- Multiple cumulative effect of lesser deficiencies for a given consent form
- Other (explain)

Lesser ICC Deficiencies

- Failure to have the informed consent document (after CIRB amendment approval) locally implemented within 30 calendar days of notification (posted on the CTSU website)
- Language/text is missing or added that is administrative or editorial in nature (e.g., 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)
- IRB approved informed consent document with incorrect version date
- Other (explain)

5.2.5 Review of the Delegation of Tasks Log (if applicable)

A Clinical Investigator is held responsible for the conduct of a clinical trial and ultimately the safety and well-being of the patients/study participants. Due to the nature and complexity of conducting clinical research, the Clinical Investigator may delegate activities/duties associated with the clinical trial to his/her staff.

To evaluate the roles and responsibilities of the individuals contributing efforts to a clinical trial, a Delegation of Tasks Log (DTL) must be maintained. The DTL is to list anyone who contributes significant trial-related duties. This log is generated and maintained by institution and by protocol, by the responsible Clinical Investigator.

If applicable, the auditor will request the DTLs for the protocols being audited (for one or more institutions). The auditor will review the log to evaluate appropriate implementation and maintenance.

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

Critical DTL Deficiency

- Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1)

Major DTL Deficiencies

- Performing tasks not assigned to individual
- Failure to keep DTL current
- Individual performing study-related activities not listed on DTL
- Other (explain)

Lesser DTL Deficiencies

- Other (explain)

5.2.6 Assessment of the Regulatory Documentation Review

Each item reviewed as part of the audit can be found to be Critical, Major, Lesser, OK, or Not Reviewed. If an item that was planned to be reviewed as part of the audit

was not reviewed for any reason (e.g., insufficient time for auditor to review, etc.), this must be explained in the Regulatory Documentation section of final audit report.

One of the following designations must be used when assigning a final assessment to this component of the audit:

Acceptable

- No deficiencies identified and no follow-up being requested
- Few lesser deficiencies identified
- Any major deficiency identified during the audit that was addressed and/or corrected prior to being notified of 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, NCORP Research Base, the institution, or the clinical 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 uploaded into the CTMB-AIS or by the date follow-up is due.

Acceptable Needs Follow-up

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

Unacceptable

- A single critical deficiency
- Multiple major deficiencies identified
- Multiple lesser deficiencies of a recurring nature found in most of the protocols or informed consent documents reviewed

If the Regulatory Documentation Review 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 NCORP Research Base. A copy of the written CAPA plan/response, along with an assessment of adequacy by the Network Group or NCORP Research Base, must be uploaded into the CTMB-AIS (for CTMB review) by the Network Group/NCORP Research Base. The CAPA plan/ Response must be received by CTMB within 45 calendar days from the date the final audit report was uploaded into the CTMB-AIS. Network Group or 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 NCORP Research Base for any audit component rated as Unacceptable. A re-audit should be conducted no later than a year after an Unacceptable audit.

5.3 Review of Accountability of Investigational Agents and Pharmacy Operations

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

The NCI does not endorse any electronic DARF (eDARF) pharmacy software package. Institutions that choose to use an electronic accountability system must ensure the database can produce a paper printout that is identical to the NCI DARF. Electronic accountability system database limitations are not valid reasons for improper accountability documentation per NCI policy.

5.3.1 Control Dispensing Area/Pharmacy

The Control Dispensing Area for each investigator is identified as the shipping address receiving the study-supplied agent from the supplier.

The Control Dispensing Area is responsible for:

- Direct receipt of study-supplied agent from the supplier
- Appropriate storage, accountability and security of study-supplied agent
- Dispensing study-supplied agent to patients/study participants as prescribed by authorized, study-eligible physician investigators with an active investigator registration status with CTEP and as dictated by the protocol
- Overall agent accountability and inventory control (including provision of agent to authorized, eligible physician for a study with an active investigator registration status at satellite dispensing areas, as applicable, oversight of satellite dispensing areas, and dissemination of agent stock recovery information)
- Timely return of final disposition of non-dispensed study-supplied agents (e.g., returns, authorized transfers or authorized local destructions)
- Physical destruction of patient returned study-supplied agents per applicable regulations and institutional policies and procedures

5.3.2 Satellite Dispensing Area/Pharmacy

The Satellite Dispensing Area receives study-supplied agent from a Control Dispensing Area. The Satellite Dispensing Area is under the direct responsibility and oversight of the Control Dispensing Area.

The Satellite Dispensing Area is responsible for:

- Receiving study-supplied agent from the Control Dispensing Area
- Appropriate storage, accountability and security of study-supplied agent
- Dispensing study-supplied agent to patients/study participants as prescribed by authorized, study-eligible physician investigators with an active investigator registration status and as dictated by the protocol
- Timely return of non-dispensed study-supplied agent to the Control Dispensing Area for further or final disposition

- Physical destruction of patient returned study-supplied agents per applicable regulations and institutional policies and procedures

5.3.3 Imaging Studies/Cancer Control

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 abide by the same NCI/CTEP policies. It is strongly suggested that NCI DARFs be utilized to track these study agents. 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 a deficiency as critical, major or lesser for the pharmacy component of the audit. As a result, the auditors for the Network Group/NCORP Research Base determine the rating based on identified non-compliance items. The auditor will review: drug accountability, proper use of NCI DARFs, adherence to appropriate storage and security measures and ensure required pharmacy procedures are being followed for NCI-sponsored and/or funded trials using NCI-supplied study agents, including cancer control/ prevention and imaging agents. DARFs are audited by protocol and study agent. When capturing the number of DARFs reviewed on the final audit report, it is the number of study agents (including different 'strengths'), not the number of DARF pages. Cancer control/ prevention and imaging agents may be supplied by other vendors.

Findings such as any condition, practice, process or pattern that adversely affect the rights, safety or well-being of the patient/study participant and/or the quality and integrity of the data; includes serious violation of safeguards in place to ensure safety of a patient/study participant and/or manipulation and intentional misrepresentation of data should be cited as a **Critical-Non-Compliance**.

The following pages outline the various types of descriptions to assess overall **Compliance** and **Non-Compliance**:

NCI DARFs COMPLETELY AND CORRECTLY FILLED OUT

Compliance

- Maintain complete, accurate and timely records of agent disposition of all study-supplied agents using NCI Investigational Agent (Drug) Accountability Record Forms (DARFs)
- Oral study-supplied agents are documented on the Oral DARF
- NCI DARFs are utilized to track cancer control/imaging study-supplied 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
- Agent was dispensed to a registered patient/study participant and documented on the appropriate DARF
- Appropriate documentation of multi-dose vial agent dispensing to multiple patients/study participants on separate lines of the DARF
- Patient/study participant returns of oral study-supplied agents are documented on the oral DARF
- Patient/study participant returns of non-oral, non-patient-specific agent supplies are *not* documented on the DARF
- Patient/study participant returns of non-oral, patient-specific agent supplies are documented on the DARF
- [For NCI-sponsored Study] 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 repackage) NCI-supplied study agent to the institution's Satellite Dispensing Areas
- [For NCI-sponsored Study] Study Agent has been transferred to an authorized investigator and/or protocol with CTEP approval

Non-Compliance

- NCI DARF not maintained or not maintained completely, accurately or on a timely basis
- Oral NCI DARF not maintained for oral study-supplied agents, not maintained completely, accurately or on a timely basis
- Lack of a DARF(s) to verify cancer control/imaging study supplied agents are administered to patients/study participants
- 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
- Study-supplied agent dispensed to a registered patient/study participant and not recorded on the appropriate DARF
- Multiple dose vials not used for more than one patient/study participant and/or doses not documented correctly on separate lines of the DARF
- Dispensing of study-supplied agent to a non-registered patient/study participant recorded on the DARF
- Patient/study participant returns of oral study-supplied study agents not documented on the Oral DARF
- Patient/study participant returns of non-oral, non-patient-specific agent supplies are documented on the DARF
- Patient/study participant returns of non-oral, patient-specific agent supplies are not documented on the DARF
- [For NCI-sponsored Study] NCI-supplied study agents are repackaged and/or reshipped to other investigators, patients, or locations by mail or express carrier
- [For NCI-sponsored Study] Study agent has been transferred to an unauthorized investigator or protocol without CTEP approval

DARFs PROTOCOL AND STUDY AGENT SPECIFIC

Compliance

- Only study-supplied agents used to treat patients/study participants and study-supplied agents not used for other purposes
- Protocol using multiple study-supplied agents have a separate DARF for each agent
- Separate DARFs are maintained by protocol, study agent, strength, 'dosage form' (e.g., oral, injectable), and by ordering investigator
- A separate patient-specific DARF is maintained for each patient/study participant on a patient-specific supply study, as directed by the protocol

Non-Compliance

- Substitution of any study-supplied agent, with non-study supplied study agent, including commercial agents
- 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 agent strengths, dosage forms, or ordering investigators
- Single DARF used for multiple patients/study participants on study when patient-specific DARF should be maintained
- Study-supplied agent used for pre-clinical or laboratory studies without written approval by NCI

SATELLITE RECORDS OF DISPENSING AREA

Compliance

- Satellite Dispensing Area DARF is used at each location where study-supplied agent is received from the Control dispensing area and is 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 and un-dispensed study-supplied agent is documented on Satellite Dispensing Area DARF as returned to Control for disposition (i.e., 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 and un-dispensed study-supplied agent is not documented as returned to Control dispensing area; Satellite Dispensing Area is inappropriately transferring and/or locally destroying study-supplied agent

NCI DARFs KEPT AS PRIMARY TRANSACTION RECORD

Compliance

- Study-supplied agent order receipts/documentation (paper or electronic) are retained and available for review
- Documentation on Control DARF of study-supplied agent transactions such as agent returns, authorized agent transfers or authorized agent local destruction
- Balance on DARF matches physical inventory
- [For NCI-sponsored Study] Written documentation of NCI authorization for transfer of study-supplied agent between investigators, protocols or institutions or for local destruction of unused/un-dispensed NCI-supplied study agent is maintained (paper or electronic)

Non-Compliance

- Study-supplied agent order receipts/documentation are not retained or not available for review
- Lack of documentation on Control DARF of study-supplied agent transactions and local destruction
- Quantities not accounted for in physical inventory; quantity does not match DARF
- [For NCI-sponsored Study] No written documentation of NCI authorization of transfer or local destruction of NCI-supplied study agent maintained

RETURN OF STUDY AGENT [NCI-Sponsored Studies]

Compliance

- Return of unused/un-dispensed 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
- Return of unused/un-dispensed NCI-supplied study agent to NCI or locally destroyed with NCI authorization or transferred to another NCI protocol (with NCI approval), when studies are complete or discontinued. Return Form or local destruction authorization is maintained
- NCI-supplied study agent is returned, transferred or locally destroyed within 90 calendar 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
- [For Non-NCI sponsored Study] Study agent final disposition of inventory is documented on DARF

Non-Compliance

- Unused/un-dispensed NCI-supplied study agent is not returned, not transferred to an appropriate NCI protocol or not destroyed within 90 calendar days of notification from NCI; NCI-supplied study agent is locally destroyed without NCI authorization or not locally destroyed per local institution's destruction policy
- Agent returned to PMB that should have been destroyed on-site or agent returned to PMB that was not supplied by PMB
- Failure to maintain Return Form or documentation of authorized local destruction; no written NCI authorization for transfer or local destruction
- Unused/un-dispensed NCI-supplied study agents not returned, transferred or locally destroyed within 90 calendar days when patients/study participants are in follow-up and no NCI-supplied study agent is being administered
- [For Non-NCI sponsored Study] Study agent final disposition of inventory is not documented on DARF

STUDY AGENT STORAGE

Compliance

- Each study-supplied agent is stored separately by protocol, strength, 'dosage form' (e.g., oral, injectable) and by ordering investigator
- Study-supplied agent is stored under proper conditions (i.e., refrigeration, freezer or room temperature) with appropriate documentation and maintenance of temperature monitoring

Non-Compliance

- Study-supplied agent is not stored separately by protocol, strength, 'dosage form' (e.g., oral, injectable) and/or by ordering investigator
- Study-supplied agent not stored under proper temperature conditions; temperature monitoring documentation not maintained

ADEQUATE SECURITY

Compliance

- Study-supplied 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

- Study-supplied agent is stored in an unsecured area
- Unauthorized individuals have access to a secure area without supervision

AUTHORIZED PRESCRIPTION(S)

Compliance

- [For NCI sponsored Study] Investigator prescribing or cosigning a prescription for study-supplied agent has an active investigator registration with CTEP and is an authorized prescriber for the protocol
- [For NCI sponsored Study] An order for a study-supplied agent is signed or co-signed by an active, authorized registered CTEP investigator 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 study-supplied agent is an authorized prescriber

Non-Compliance

- [For NCI sponsored Study] Investigator prescribing or co-signing an order for study supplied agent does not have an active investigator registration with CTEP or is not an authorized prescriber for the protocol
- [For NCI sponsored Study] An order for a study-supplied agent is not signed or co-signed by an authorized and registered investigator prior to study agent dispensing and administration
- Pharmacy does not have procedures in place to ensure person prescribing or cosigning prescriptions for study-supplied agent is an authorized prescriber

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 and/or funded clinical trials, and the number of open protocols reviewed should be considered in the evaluation.

Items audited under the pharmacy component must be assessed as one of the following:

- Critical-Non-Compliant*
- Non-Compliant
- Compliant
- Not Reviewed

* Any finding identified before or during an audit that is suspected to be fraudulent activity should be cited as Critical-Non-Compliant (see definition for critical under Section 5.1)

If an item that was planned to be reviewed as part of the audit was not reviewed for any reason, it must be explained in the pharmacy narrative of the final audit report. One of the following designations must be used when assigning a final assessment to this component of the audit:

Acceptable

- Compliance in all categories and no follow-up being requested
- Any Non-Compliance item identified during the audit that was addressed and/or corrected prior to being notified of 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, NCORP Research Base, the institution, or clinical investigator because no similar Not Compliant issue has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a Not Compliant item 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 uploaded into the CTMB-AIS or by the date follow-up is due.

Acceptable Needs Follow-up

- Any non-compliance identified during the audit that requires follow-up

Unacceptable

- A single Critical-Non-Compliance
- Multiple Non-Compliance items
- Inability to track the 'chain-of-custody' of a study-supplied agent(s)

No Assessment Required

- No study-supplied agent in stock or in-use for the timeframe being reviewed/audited
- This designation applies under the following two conditions:
 - The review of the pharmacy consists of only security, storage and review of pharmacy procedures to ensure investigator has an active PMB registration.
 - Review of security, storage and pharmacy procedures (described above) were found to be 'compliant'.

Limited Review Needs Follow-up (On-site or Virtual Pharmacy Visits Only)

- Non-compliance identified under Pharmacy Review and the audit was limited to review of storage, security and/or pharmacy procedures; and CAPA plan or follow-up response is requested.

If the Pharmacy Review is rated as Limited Review Needs Follow-up, 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 NCORP Research Base. A copy of the written response/CAPA plan, along with an assessment of adequacy by the Network Group or NCORP Research Base, must be uploaded into the CTMB-AIS (for CTMB review) by the Network Group. This response/CAPA plan must be uploaded into the CTMB-AIS within 45 calendar days from the date the final audit report was uploaded into the CTMB-AIS. Network Group or 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 NCORP Research Base for any audit component rated as Unacceptable. A re-audit should be conducted 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 re-audit due to non-compliance related to storage and/or security, the re-audit must be conducted on-site or via a virtual visit. For other routine pharmacy audits, the Groups/NCORP Research Base can use their own discretion to determine if/when an on-site or virtual visit of the pharmacy should be conducted.

5.4 Review of Patient Case Records

Each patient case must be reviewed to determine if there are any critical, major, or lesser deficiencies in each of the following categories:

- Properly signed and dated informed consent document, including consent process
- Eligibility of a patient/study participant
- Correct treatment and treatment sequence
- Evaluation of disease outcome/tumor response
- Assessment and reporting of 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. Source documentation of each patient case requested by the audit team for review that is identified as missing at the time of the audit and must be supplied to the Network Group/NCORP Research Base within 10 business days of the audit date.

5.4.1 Deficiency Type by Category

The following examples of deficiencies do not represent an all-inclusive list of possible 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 – Critical Deficiencies

- Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1)
- Consent form document not signed and dated by the patient/study participant (or parent/legally authorized representative, if applicable)
- Patient/study participant signature cannot be corroborated
- Consent form not protocol specific

Informed Consent – Major Deficiencies

- Failure to document the informed consent process with the study participant
- Patient/study participant signs consent form document containing changes not approved by the CIRB/IRB
- Consent form document missing
- Translated consent, short form or other form of translation not available or signed/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 most current IRB-approved version at the time of patient registration
- Consent form does not include updates or information required by IRB
- Re-consent not obtained as required
- Consent for ancillary/advanced imaging studies not executed properly
- Other (explain)

Eligibility – Critical Deficiency

- Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1)

Eligibility – Major Deficiencies

- 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.]
- Other (explain)

Treatment – Critical Deficiencies

- Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1)
- Incorrect agent/treatment/intervention used

Treatment – Major Deficiencies

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

Disease Outcome/Response – Critical Deficiency

- Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1)

Disease Outcome/Response – Major Deficiencies

- Inaccurate documentation of initial sites of involvement
- Tumor measurements/evaluation of 'status of disease' not performed, not reported, or not documented per protocol
- Protocol-directed response criteria not followed
- Claimed response (i.e., partial response, complete response, stable) 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
- Other (explain)

Adverse Events – Critical Deficiency

- Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1)

Adverse Events – Major Deficiencies

- 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
- Adverse events not assessed by the investigator in a timely manner (per protocol)
- 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
- Recurrent under- or over-reporting of adverse events
- Other (explain)

General Data Management Quality – Critical Deficiency

- Any finding identified before or during an audit that is suspected to be fraudulent activity (see definition for Critical under Section 5.1)

General Data Management Quality – Major Deficiencies

- Recurrent missing documentation in the patient/study participant records
- Protocol-specified laboratory tests or other parameters (Quality of Life forms, collection of research samples, etc.) not done, 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; data cannot be verified
- Delinquent data submission (> 6 months delinquent is considered a major deficiency; a 3-6 month delinquency is considered a lesser deficiency)
- Other (explain)

The Groups and 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 NCORP Research Base guidelines may be rated as a major deficiency.

Assigning Lesser Deficiencies

As defined under Section 5.1, a lesser deficiency may be assigned under each of the above categories if it 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 an audit component.

5.4.2 Assessing the Findings from the Patient Case Review

Each category (Informed Consent, Eligibility, Treatment, Disease Outcome/ Disease Response, Adverse Event, General Data Management Quality) for each patient case audited can be found to be Critical, Major, Lesser, OK or Not Reviewed. If one or more categories is not reviewed for any reason (e.g., subject did not receive treatment, insufficient time for auditor to review, etc.) or the patient chart was designated as the Unannounced case, this must be explained in the patient case review section of final audit report.

One of the following designations must be used when assigning a final assessment to this component of the audit.

Acceptable

- No deficiencies identified and no follow-up being requested
- Few lesser deficiencies identified and no follow-up being requested
- Any major deficiency identified during the audit that was addressed and/or corrected prior to being notified of 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, NCORP Research Base, the institution, or the clinical 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 uploaded into the CTMB-AIS or by the date follow-up is due.

Acceptable, Needs Follow-up

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

Unacceptable

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

If the Patient Case Review 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 NCORP Research Base. A copy of the written response/CAPA plan, along with an assessment of adequacy by the Network Group or NCORP Research Base, must be uploaded into the CTMB-AIS (for CTMB review) by the

Network Group. This response/CAPA plan must be uploaded into the CTMB-AIS within 45 calendar days from the date the final audit report was uploaded into the CTMB-AIS. Network Group or 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 NCORP Research Base for any audit component rated as Unacceptable.

A re-audit should be conducted no later than a year after an Unacceptable audit or when sufficient new patients/study participants have accrued. If sufficient new patients/study participants have not accrued within a year from the previous audit, further discussion with CTMB is necessary prior to requesting an extension of the re-audit timeline in the CTMB-AIS.

5.5 Role of the Investigator During the Audit

The Clinical 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 responsible Clinical Investigator and designated staff be present at the exit interview. During the exit interview the audit team will review with the institution, the preliminary findings, including items reviewed off-site, and discuss any recommendations from the audit team. If applicable, the auditors should mention the expectation of providing a response/CAPA plan to the audit findings and clarify approximate timeframe of when the institution will need to submit their response(s). The exit interview should be an opportunity for education, immediate dialogue, feedback, and clarification for both the institution staff and the auditor(s).

SECTION 6 REPORTING OF AUDIT FINDINGS AND FOLLOW-UP

6.1 CTMB-AIS Generated Notifications/Emails

The Group/Research Base Audit Coordinator/designee assigned in the CTMB-AIS receives AIS generated emails related to overdue follow-up/CAPA plans per the audit guidelines. The Group/Research Base Audit Coordinator/designee must provide a response/explanation in writing within 5 business days of receiving the notification. The response should include when the follow-up/CAPA plan is expected to be submitted and/or what actions have been taken so that the follow-up/CAPA plan is uploaded in the CTMB-AIS as soon as possible. The Group/NCORP Research Base response should be directed to the appropriate CTMB liaison.

6.2 Preliminary Report of Audit Findings

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

6.2.1 Submission

The Preliminary Report of Audit Findings Form must be uploaded into the CTMB-AIS 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. 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 component (Regulatory Documentation, Pharmacy, and Patient Case Review) 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 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 CTMB notification. It is also essential that involved individual(s) and/or institutions follow their own institutional scientific misconduct procedures in these matters.

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 generated.

A Co-site Visitor (CTMB or CTMS staff) may be assigned to an audit by CTMB. If one is assigned, a Co-site Preliminary Report of Audit Findings must also be uploaded into the CTMB-AIS within the same timeframe required by the Network Groups.

Regulatory Documentation Section – Briefly describe all deficiencies identified; and label as critical or major.

Pharmacy Section - Briefly describe all non-compliance items identified; label as critical-non-compliance or non-compliance. If pharmacy was a limited review (i.e., review of storage, security and/or pharmacy procedures to ensure investigator has an active CTEP registration, state 'limited review', and describe the non-compliance, if any. If the pharmacy is not reviewed, the pharmacy section should state 'No NCI-supplied drug in use during this audit period', if this applies. Or state, 'Not Reviewed' and mention why it was not reviewed in this section. In the latter two scenarios, the 'yes' or 'no' designation should not be circled on the form.

Patient Case Section - Briefly describe all deficiencies identified, and appropriately label each deficiency as critical or major. If not an unannounced case, explain if and why any patient case was not reviewed in full.

A revised preliminary report may be uploaded into the CTMB-AIS if it is within ten business days of Day 1 of the audit. Deficiencies identified and briefly described in the Preliminary Report must be included in the Final Audit Report. Any revisions to the Preliminary Form must also be explained before uploading into the CTMB-AIS.

6.2.2 Content

Critical and major deficiencies must be identified and described under the appropriate audit component in the Preliminary Report of Audit Findings.

- Regulatory Documentation
- Pharmacy (Accountability of Investigational Agents and Pharmacy Operations)
- Patient Cases

The total number of cases with any critical and major deficiencies and the total number of patient cases reviewed must be provided for each category listed in the Preliminary Report of Audit Findings.

6.3 Final Audit Report

6.3.1 Submission

The Final Audit Report must be uploaded into 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 by the auditors from the Network Group or NCORP Research Base should be noted in the General Comments or Exit Interview sections of the final audit report.

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.

If a co-site visitor (CTMB or CTMS staff) 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.

Final Audit Reports that are returned to the Group/Research Base/CTMS for a correction or clarification must be returned (uploaded in the CTMB-AIS) within two

weeks. Also, all corrections or clarifications made should be explained in the General Comments section of the report.

6.3.2 Content of Final Audit Report

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

6.3.2.1 General Information

- Front page of the final audit report, include information specific to the institution such as number of cases audited, average annual accrual, and institutional staff present at the audit
- List the members of the audit team; indicating title and affiliation
- List Co-site visitor(s) and affiliation, if applicable

6.3.2.2 Regulatory Documentation

- The CTMB-AIS will populate each protocol title for protocols audited and list the number patient cases selected for audit, the IND drugs, treatment modalities used and the disease(s) studied in each protocol (if drug is NCI-supplied study agent)
- The CTMB-AIS will populate for each protocol selected for audit whether utilizing the NCI CIRB or a local IRB
- Designate whether critical, major, or lesser deficiencies were identified under CIRB/IRB and ICC and describe each critical, major or lesser deficiency; otherwise indicate OK
- Designate whether major or lesser deficiencies were identified for review of the Delegation of Tasks – Log, if so, describe; otherwise indicate OK
- Indicate if any portion of the Regulatory Documentation review was audited off-site
- Provide an overall assessment for this component and indicate if a re-audit is required, including timeframe

6.3.2.3 Accountability of Investigational Agents and Pharmacy Operations

- Indicate the number of DARFs reviewed (i.e., number of study agents reviewed), and the number of patients' cross-checked against the DARF, if applicable
- For each item identified as Critical-Non-Compliance and/or Non-Compliance, select the appropriate Not Compliant description or descriptions; otherwise indicate OK or Not Reviewed
- Summarize in the pharmacy narrative any items that require a response, any items not reviewed and explain why they were not reviewed (see Section 5.3.5); include guidance or recommendations provided to the institution. [Other examples of information that may be included under the pharmacy narrative may include descriptions of

non-compliance issues not outlined in the audit guidelines; review of temperature logs and excursions; rationale of why IND or study-supplied agents were not selected for review, etc.]

- For a full review of the pharmacy component, provide an overall assessment (Acceptable, Acceptable needs F/U, or Unacceptable), and indicate if a re-audit is required, including timeframe
- For a limited review of the pharmacy, indicate which items were reviewed (i.e., storage, security, and/or pharmacy procedures). If follow-up is required when conducting a limited review, describe the non-compliance finding(s). The overall assessment for a 'limited review' of the pharmacy should be: 'No Assessment Required' or 'Limited Review Needs Follow-up' (details on page 40)

6.3.2.4 Patient Cases

- For each category, indicate if critical, major or lesser deficiencies were found and describe; otherwise indicate OK or Not Reviewed (explain if not reviewed)
- The CTMB-AIS pre-populates and summarizes the deficiencies for each patient/study participant and category in a table; this table calculates the total number of critical, major and lesser deficiencies for the total patient cases reviewed
- All patient cases including those registered/enrolled under each Sub Affiliate/NCORP Sub Affiliate are identified by institution (CTEP site code)
- Provide an overall assessment for this component and indicate if a re-audit is required, including timeframe

6.3.2.5 Audit Procedures

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

6.3.2.6 General Comments

This section may be used to indicate if any data or correspondence was 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.

6.3.2.7 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 (in advance of the audit), the findings of that review should be discussed at the exit interview.

6.4 Corrective and Preventative Action (CAPA) Plan / Response

If an audit component is rated as Limited Review with Follow-up, Acceptable Needs Follow-up or Unacceptable, each audited institution will be required to submit a written CAPA plan/response to the Network Group/NCORP Research Base. The CAPA plan/response must be uploaded into the CTMB-AIS by the appropriate Network Group/NCORP Research Base within 45 calendar days from the date the final audit report was uploaded into the CTMB-AIS. In addition to the CAPA plan, the Group/NCORP Research Base may upload any pertinent correspondence/emails related to the audit. All documentation uploaded to the Document Management tab in the CTMB-AIS must be by Group/NCORP Research Base and corresponding audit date.

6.5 Re-audits

A re-audit is mandatory for any audit component rated as Unacceptable if the institution continues to participate in the Group or NCORP Research Base. A re-audit should be conducted no later than a year after an Unacceptable audit or when sufficient patients/study participants have been accrued.

A re-audit requirement remains linked to the institution regardless of its status (i.e., active or withdrawn). If the institution is being withdrawn, the re-audit timeline on the final audit report for the applicable audit components are to be designated 'No Re-audit'. If the institution rejoins the same Group/NCORP Research Base at a later date, the re-audit must be conducted within 12 months from the first new accrual. The 'No Re-audit' timeline allows the Group/NCORP Research Base and CTMB to track these institutions that require a re-audit, if reactivated. For tracking purposes, any off-site/remote audit or re-audit must also be scheduled and reported in the CTMB-AIS.

6.6 For Cause (Off-cycle) Audits

A 'for cause' audit may be warranted when there are concerns or irregularities found through quality control procedures or when there are allegations of possible scientific misconduct. It is the responsibility of the Network Group/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 NCORP Research Base coordinate the for cause audit. Selection of auditors to conduct For Cause on-site audit will be made jointly by the NCI, Network Group, or 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.

6.7 Probation of a Clinical Investigator

If there are concerns that appear to be investigator specific identified before, during or after an audit, mentoring and retraining will be the primary focus, if appropriate. After further evaluation by CTMB in collaboration with the NCTN Program Director the investigator may be taken off probation if documentation exists that support the specific actions were taken.

Repeated and deliberate failure to comply with the federal regulations, GCP and/or these audit guidelines may result in one or more of the following actions:

- Replacing Clinical Investigator
- Re-analyzing or retract published results

- Requesting a formal investigation by the Office of Research Integrity
- Revoking the Investigator's FDA Form 1572
- Terminating privileges for participating on any NCI sponsored clinical trial

6.8 Probation of a Participating Institution

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/NCORP Research Base 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/NCORP Research Base. The Group/NCORP Research Base 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.

6.9 Suspension of a Clinical Investigator and/or Participating Institution

If a critical deficiency is cited it will result in suspension of the clinical investigator and/or participating institution. Additionally, 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/NCORP Research Base.

- The Network Group/NCORP Research Base will provide written notice to the Clinical Investigator at the institution that the response/CAPA plan is overdue and a 5 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 Network Group/NCORP Research Base during the 5 business day grace period, the Group/NCORP Research Base 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 NCORP, all new patient registrations will be suspended from both the Network Group Main Member, LAPS Main Member, or NCORP and the corresponding Network Group Affiliate, LAPS Integrated Components and LAPS Affiliates, or NCORP Affiliates (as well as any associated Sub Affiliates).
- No registrations will be accepted by the Network Group/NCORP Research Base 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 Clinical Investigator detailing the reason for the delay must be included. Suspension of patient registration will not be lifted until the institution submits the response/CAPA plan to the Group/Research Base and the

response/CAPA plan is reviewed and approved 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 NCORP Research Base mechanisms.

6.10 Withdraw of a Participating Institution

If improved performance is not documented at the time of the second re-audit, the institution may be withdrawn by the Network Group or 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.