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

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LIST OF ACRONYMS

AP	Associate Plus (as designated in RCR)
CAPA	Corrective and Preventative Action
CIRB	Central Institutional Review Board
CLASS	Compliance, Learning, and SOP Solutions
CRF	Case Report Form
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
DCP	Division of Cancer Prevention
DCTD	Division of Cancer Treatment and Diagnosis
DSMB	Data and Safety Monitoring Board
DTL	Delegation of Tasks Log
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IAM	Identity and Access Management
ICC	Informed Consent Content
ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
IVR	Physician Investigator (as designated in RCR)
LAPS	Lead Academic Participating Site
LPO	Lead Participating Organization
MU	Minority Underserved
NCI	National Cancer Institute
NCORP	National Community Oncology Research Program
NCTN	National Clinical Trials Network
NLF	No Longer Funded
NPIVR	Non-Physician Investigator (as designated in RCR)
OHRP	Office of Human Research Protections
PII	Personally Identifiable Information
RCR	Registration and Credential Repository
SDP	Source Document Portal
TSDV	Targeted Source Data Verification

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, Reaudit or Off-cycle

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

Membership Status: Active, Withdrawn or No Longer Funded (NLF)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- Withdrawn is when an institution is no longer an active member of a Group, this action may either be initiated by the institution or by the Group.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, NCORP package or single institution is no longer being funded. The institution is in a transition phase with their study participants still on-study and/or in follow-up until data submission is no longer required. Once the transition phase is completed, each Group will change the package/site 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 auditable 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 study participants 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 when conducting clinical trials since independent replication of most trials is not feasible.

Dr. Curtis Meinert[1] 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 potential concerns. 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 concerns 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 review and statistical methods should be implemented to detect certain types of issues, 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 study participants. In 1977, the FDA published proposed regulations on the responsibilities of sponsors and monitors of clinical trials.

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, study participant 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 study participant 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 and 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 (NCCCP) to create the NCI Community Oncology Research Program (NCORP). The NCORP community site is defined as a consortium of community hospitals, oncology practices, or 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 January 2025, FDA announced the adoption of "E6(R3) Guideline for Good Clinical Practice." The guidance was prepared under the auspices of the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use. This document is intended to improve clinical trial quality and efficiency, while maintaining

human subject protection and reliability of trial results. With new and updated regulations and guidances such as these, sponsors can improve and create more efficient approaches to clinical trial design, including conduct and oversight of their clinical trials.

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. This document is intended to supplement, not replace, regulatory obligations under FDA regulations and ICH Good Clinical Practice (GCP) guidelines. All participating institutions are expected to ensure compliance with these global standards.

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 AND QUALITY CONTROL 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 overseeing the scheduling of all audits, for reviewing audit reports and findings, and for reviewing and assessing the adequacy and acceptability of Corrective and Preventative Actions (CAPA) plans. A co-site visitor (CTMB or CTMS member) may also be present at an audit to observe the auditor and audit process of the Network Group/NCORP Research Base.

An audit consists of reviewing the below categories under the three components:

<u>Regulatory Documenation Component</u>:

- IRB of Record documentation;
- Informed Consent Content (ICC)
- Delegation of Tasks Log (DTL)

<u>Pharmacy Cmponent</u>:

- NCI DARFs Completely and Correctly Filled Out
- DARFs are Protocol and Study Agent Specific
- Satellite Records of Dispensing Area
- Agent Inventory and Accountability Documentation
- Return of Undispensed Study Agent (NCI sponsored study)

- Adequate Security
- Authorized Prescription(s)

Participant Case Component:

- Informed Consent
- Eligibility
- Treatment
- Disease Outcome/Response
- Adverse Event
- Correlative Studies, Tests, and Procedures
- General Data Management Quality

The CTMB must be notified immediately by telephone (240) 276-6545 and by email (ReportingResearchMisconductConcerns@nih.gov) of any findings suspicious and/or suggestive of intentional misrepresentation of data and/or disregard for regulatory safeguards for any component (Regulatory Documentation Review, Pharmacy Review and Participant 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 upon learning 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 essential that involved individual(s) and/or institution(s) follow their own institutional misconduct procedures regarding these matters. See 'Guidance for Allegations of Research Misconduct' under Appendix 1.

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 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), GCPs, and applicable regulatory requirements. It is a continuous process that can be conducted on-site or off-site, and involves oversight of all study participants on a trial.

2.2.1.1 Auditing Program

Auditing is a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, 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, and consists of reviewing a subset of study participants on a trial.

The purpose 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.

2.2.1.2 Monitoring Program

Monitoring is the act of overseeing the progress of a clinical trial. All clinical research carries with it the obligation to ensure optimal therapy for study participants and optimal conduct of the research such that participant 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 study participant accrual
- Ongoing assessment of 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 study participant
- Rapid reporting of adverse events and treatment-related morbidity information
- Periodic evaluation of outcome measures and study participant safety information including oversight by a DSMB for randomized studies

2.2.2 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
- Education and training 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

2.2.3 Data Safety Monitoring Board (DSMB)

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 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 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishment-and-operation-clinical-trial-data-monitoring-committees).

2.2.4 CTMB – Audit Information System (CTMB-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, study participant enrollment, data collection, and posting appropriate material on CTSU website. Services specifically tailored to auditing activities are:

2.4.1 Site Audit Portal (SAP)

The Site Audit Portal (SAP) is an application in the auditing area of the CTSU website that serves as the communications link between CTMB- AIS and Medidata Rave. The SAP seamlessly coordinates audit activities with Medidata using the visit information provided by CTMB-AIS. It displays visit information, tracks the visit process, and provides a direct link to study participants, visit-associated queries in Rave, Delegation of Tasks Logs (DTLs), and study participant-level source documentation uploaded to the Source Document Portal (SDP). Furthermore, it manages the invitation of volunteer auditors and cross-network auditors to studies in Rave for Targeted Source Data Verification (TSDV), which is described in the next section. *Note: SAP is not available to site staff.*

For auditor access to the SAP to view visit details and access study participant cases and other items go to (login required):
https://www.ctsu.org/RAVE/SiteAudit.aspx

For instructions on navigating the SAP (log-in required): https://www.ctsu.org/master/simplepage.aspx?ckey=HELP-AUDITING-NAVIGATION

2.4.2 Auditing Participant Cases for Studies in Medidata Rave

TSDV is a tool in Rave utilized by auditors reviewing study participant records to electronically record Source Data Verification (SDV) activity directly in Medidata Rave. A process exists to provide a unified framework, create a consistent workflow to facilitate pre- and post-SDV activities, and provide transparency for the site visit process to meet regulatory requirements. Please note that while the majority of studies in Rave are set up for TSDV, it is not used for all studies; its use is indicated at the protocol level in the SAP.

For instructions on the process for preparing, performing, and following up on TSDV in Rave, see: https://www.ctsu.org/master/simplepage.aspx?ckey=aHELP-AUDITING-USINGVERIFICATION

2.4.3 Auditing Participant Cases Utilizing the Source Document Portal (SDP)

The CTSU Source Document Portal (https://sdp.ctsu.org) is an application which allows site staff to identify and upload source documents for activities such as remote auditing, central monitoring, and the support of safety reporting in CTEP-AERS. Lead Protocol Organization (LPO) and other stakeholder staff with appropriate privileges are then able to access the documents within the application. In the case of remote auditing, the SDP provides an alternative for reviewing study participant cases when access to the EMRs cannot be obtained, or in some circumstances may also be used in combination with other approaches. This method

is currently only applicable to review of participant cases. Review of the Regulatory Documentation and Pharmacy is conducted separately.

The following instructions on conducting remote auditing using the SDP are available in both the SAP and the SDP (login required).

Remote/Off-site audit Instructions for Auditors: https://www.ctsu.org/master/simplepage.aspx?ckey=HELP-REMOTE-AUDITING-AUDITORS#Introduction

Remote/Off-site audit Instructions for Site Staff: https://www.ctsu.org/master/simplepage.aspx?ckey=HELP-REMOTE-AUDITING-SITES#Introduction

All auditors including volunteer auditors must complete the Source Document Portal (SDP) module under the Auditor and Monitor Training Course in the Compliance, Learning, and SOP Solutions (CLASS) system before they will be able to access documents in the SDP.

SECTION 3 MEMBERSHIP TYPES UNDER THE NCTN PROGRAM

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 study participants 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.

Storefronts are administrative sites that do not accrue or treat study participants. 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.

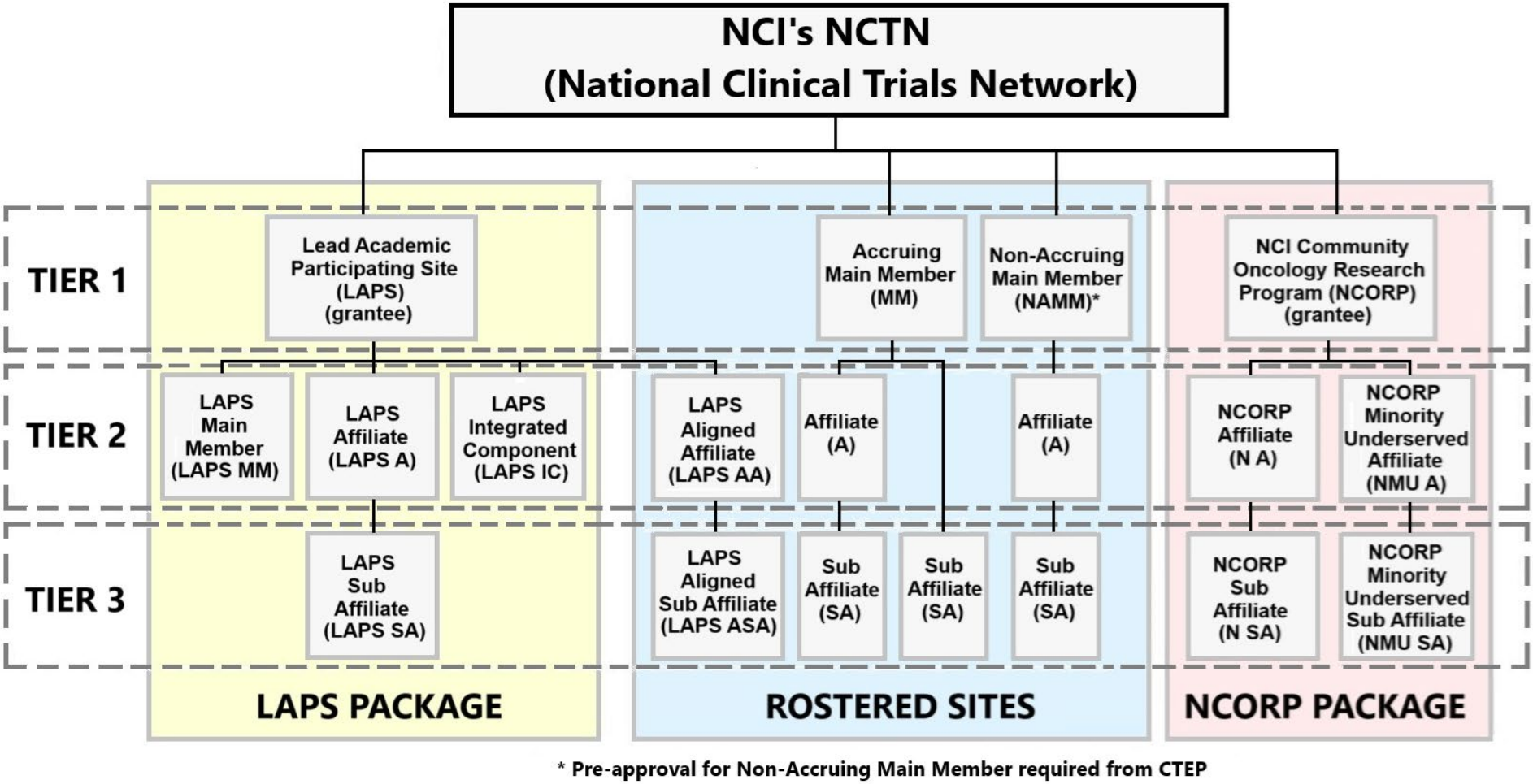
Main Members and Affiliates are expected to enroll study participants and provide significant accrual to the NCTN program. CTEP may consider a limited number of Main Members to be designated as storefronts. A Network Group may request that a Main Member be a storefront which handles the administrative 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, NCORP and LAPS Membership Type

Principal investigators participating in Network Group research, including NCORP and Lead Academic Participating Sites (LAPS), 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) by Membership Type



*** Pre-approval for Non-Accruing Main Member required from CTEP**

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.

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 study participants.

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 study participants 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 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 study participants 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 study participants to NCTN treatment and advanced imaging clinical trials for adult cancer study participants, 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.

3.1.5 Sub Affiliate(s) of a Main Member, NCORP or LAPS

Main Member Sub Affiliates, NCORP Sub Affiliates, and LAPS 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.

All Sub Affiliates must be on the Group roster if:

- Consenting and/or registering (enrolling) study participants, 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

<u>Classification of NCORP and LAPS Sub Affiliates</u>:

- NCORP Sub Affiliates (NCORP SA) and NCORP minority-underserved (NCORP MU) Sub Affiliates must be listed on a NCORP grant
- 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

<u>Requirements of all Sub Affiliates</u>:

- 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 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

3.1.6 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.

3.1.7 Non-Member Collaborators

There may be domestic or international institutions that collaborate with a Network Group on a particular trial (i.e., enroll study participants 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 study participants 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 study participant that has been consented, registered/ enrolled to a study and assigned a study participant ID number. Accrual must be credited to the individual institution regardless of their membership type/role that identified a 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 (auditable flag set to 'yes' in the CTMB-AIS) is an institution that is designated to be audited as stand-alone audit with its own preliminary report and final audit report. This 'auditable' designation is required for all enrolling LAPS and rostered sites categorized as Tier 1 and Tier 2 sites (see Figure 1). See exception for a LAPS Integrated Component sites under Section 3.9.

A 'non-auditable' institution (auditable flag set to 'no' in the CTMB-AIS) is an institution that is audited but in combination with other site(s). These types of audits are referred to auditing 'as a whole'. It is an audit comprised of more than one institution being reviewed and all information and audit findings incorporated into one preliminary report and one final audit report under the parent institution (consisting of multiple CTEP site codes).

For NCORP sites, the designation of the auditable flag may vary and is at the discretion of the Group/Research Base. For instance, the auditable flag can be set to 'no' for all NCORP components (Tier 2) but the NCORP (Tier 1) must then be set to yes. Note that the auditable flag for a Tier 1 and Tier 2 institutions within the same NCORP cannot be both set to 'No' for an audit to be scheduled correctly. See Section 3.7 for methods for setting the auditable flag for NCORP sites.

All institutions designated as a Sub Affiliate (Tier 3) site are listed with a non-auditable flag in the CTMB-AIS. The audits for these sites are scheduled to be in combination with the parent site. CTMB in consultation with the Group/NCORP Research Base may request to schedule a stand-alone audit of a Tier 3 site if there are reasons for concern. In this scenario, the auditable flag would need to temporarily change from 'No' to 'Yes' for the audit to be scheduled appropriately in CTMB-AIS.

For audits that include non-auditable institutions, when there are separate pharmacies (i.e., receives drug directly from NCI or other sponsors), the pharmacy must be identified in the final audit report by CTEP site code and pharmacy location(s). Protocols and study participant cases must be selected for review from the parent and each non-auditable institution being audited.

Note: This section does not apply to Special Protocol designations, Children's Oncology Group institutions, and other instances, when approved by CTEP.

3.4 Grouping of Membership Types

The membership type for the LAPS grant/package is designated by DCTD, and the NCORP grant/package is designated by DCP. The membership type 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 study participant. 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, NCORP Affiliates and NCORP Sub Affiliates

NCORP institutions will be audited within 18 months after entry of the first 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 study participants 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 study participant. 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 study participant 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 auditable 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 study participant

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 NCI or other sponsors), each IRB or pharmacy must be audited. The final audit report must identify the relevant regulatory documentation, pharmacy and participant 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 study participants 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.

SECTION 4 PREPARING FOR CONDUCTING THE AUDIT

The Network Group/NCORP Research Base must carefully plan for an audit months in advance.

4.1 Scheduling and Arranging the Audit

Audits are scheduled in the CTMB-AIS by the Group/NCORP Research Base. If there was a previous audit for the same institution for the same Group/NCORP Research Base in the CTMB-AIS, the prior audit must be considered complete (i.e., audit report and CAPA plan reviewed and acknowledged by CTMB in the CTMB-AIS) before a new audit can be scheduled.

The audit date must be entered into the CTMB-AIS at least six (6) weeks in advance. 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 obtain CTMB approval prior to scheduling any audit with less than six weeks of notice. The request should be directed to the appropriate CTMB liaison via the Email Notification Response Management module in the CTMB-AIS. The request to CTMB must include written documentation from the institution to be audited stating they are aware of the minimum six week requirement and agree with the proposed date.

The institution is to be provided with a list of protocols and study participant 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.

In the event of a for-cause audit, advance notice of the selection of protocols and/or study participant cases to be reviewed may be limited due to the nature of the review.

4.2 Audits Not Scheduled or Cancellation of an Audit

If the Group/NCORP Research Base Audit Coordinator/designee receives an AIS generated email related to an audit that has not been scheduled timely per the audit guidelines, the Audit Coordinator/designee must provide a response/explanation in writing within five (5) business days of receiving the notification. The response should be directed to the appropriate CTMB liaison via the Email Notification Response Management module in the CTMB-AIS.

If the Group/NCORP Research Base needs to cancel an audit for unforeseen circumstances and it is within three business days prior to the audit date, 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 Type of Audits in CTMB-AIS

Audits may be scheduled in the CTMB-AIS as a Routine, Reaudit or Off-cycle.

Routine audits are scheduled for routine reviews and can occur within 18 to 36 month intervals. The frequency of audits may depend on whether a particular site(s) is considered a high enrolling site or the rate of accrual is unusually high.

Reaudits are scheduled when there are concerns based on the prior audit (by component) and oversight is required usually within 12 months from the prior audit.

Off-cycle audits are scheduled based on the below circumstances:

- More frequent auditing may be warranted if requested by CTMB due to the nature of the study (registration trial, etc.), or
- A for-cause audit may be warranted when there are concerns or significant irregularities found through quality control procedures or if there are allegations of possible scientific misconduct.

If an audit at an institution is for a protocol designated as a Special Protocol, it can be scheduled in the CTMB-AIS database as an Initial, Semi-Annual or Annual review.

4.4 Audit Location

For continued oversight of study participant safety, there may be circumstances when off-site/remote auditing 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 2.4.1 is an alternative and may also be used in combination with other approaches. When scheduling the audit, below are location options to select in the CTMB-AIS. The location of the audit is at the discretion of the Network Group/Research Base.

- On-Site Review: conducted at the institution being audited
- Off-Site/Remote Review:
  - Review conducted at parent/affiliated site
  - Review conducted remotely at Network Group/Research Base

For on-site visits, institutions may require all entrants (including auditors) to display a government issued ID. For off-site/remote visits, institutions may require the auditor to display a government issued ID. However, Personally Identifiable Information (PII) should not be requested of the auditor. 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.

4.5 Selection of Protocols and Participant Cases for Audit

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. While most cases will be selected from study participants accrued since the previous audit, any study participant case may be audited at any time. A minimum of four (4) 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., registration, prevention, advance imaging, 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.

For Tier 1 and Tier 2 sites, a minimum of 10% of the participant cases accrued by site since the last audit will be reviewed by the Network Group/NCORP Research Base. For Tier 3 sites (Sub Affiliates), the Group is expected to select a representative sampling from each Sub Affiliate to audit under the parent institution. Selecting 10% of participant cases from each Sub Affiliate is not required. Under certain circumstances, CTMB may mandate an independent audit of any Sub Affiliate site.

For selection purposes, the 10% of chosen cases must be rounded up (e.g., if 12 participant cases are eligible for audit selection, at least two cases must be audited). In summary, when selecting the participant cases for audit, the following selection process applies, where appropriate:

- Select at least one participant case for every registration trial, at every institution selected for audit. Depending on volume of enrolled onto a registration trial, auditing additional participant cases may be required; and
- Select 10% of treatment cases where the auditing Group is the protocol lead or credited with the enrollment; and
- Select 10% of participant cases from protocols with advanced imaging studies/imaging studies embedded in treatment protocols; and
- Select 10% of participant cases enrolled onto DCP cancer control/prevention trials.

A participant case must not be counted towards the minimum 10% rule when:

- The participant case is only evaluated under a Screening Step of the study.
- No categories (i.e., Informed Consent, Eligibility, Treatment, etc.) were reviewed for a participant case at the time of the audit. In this scenario, the case must be removed from the audit report.

4.5.1 Selection of Unannounced Participant Case(s)

If the total accrual warrants selection of unannounced cases, the Group must select at least one unannounced participant case to review. The audited institution 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 participant informed consent and participant eligibility and cannot count towards the required 10% rule unless an unannounced case is reviewed in full (i.e., all categories reviewed). Selection of unannounced cases for review does not apply when conducting an off-site/remote audit due to system limitations.

4.5.2 Review of Transferred Participant Cases

In the event of a participant 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 at the receiving/accepting institution. This is because only the accepting institution will have access to the study participant’s information after the transfer takes place.

4.6 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 and Monitor Training Course 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.

4.6.1 Network Group and NCORP Research Base Auditors

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 Principal Investigator and institution staff. The auditors must be knowledgeable about clinical trial methodology, NCI policies, and federal regulations.

4.6.2 National Cancer Institute (NCI) or Other Representative(s)

Representatives from the NCI or their designee, and representatives from other federal regulatory agencies may participate in an audit. The CTMB or their representative will notify the Network Group/NCORP Research Base operations office of the audits the observers will attend. If NCI staff or their 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.

4.7 Institution Responsibilities

The institution is responsible for ensuring that all relevant materials are available for review at the time of the audit. 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 (off-site/remotely). Regardless, the following records must be available the day of the audit or sooner, if requested:

- 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 participant 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, study participant monitoring (vital signs, monitoring of contrast reactions, etc.), and log of staff signatures and imaging responsibilities
- Other relevant source documents or information

To facilitate the review process, it is advisable that institution staff label documents such as hospital/clinic records, research notes, on-study labs, scans, imaging reports, informed consent documents, etc. by participant case numnber. The Network Group/NCORP Research Base should provide guidance on how preparation of documents for the audit should be done. If multiple institutions with the same parent are being audited at the same time, it is recommended that a representative from each of the audited institutions be available at the time of the audit to address questions.

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. A site staff member must be available to assist with navigating through the EMR system.

For the audits conducted off-site/remotely, the circumstances vary depending on the approach used to review the documentation. A site staff member must also be available to contact and assist with questions.

4.8 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 participants 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 study participants are off treatment/study intervention, the participant 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 participant 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 study participants in follow-up
- Site performance is not meeting acceptable quality standards for 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.

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)
- NCI Drug Accountability Record Forms (DARFs) and/or log for imaging/ radiopharmaceutical agents, records of shipments/transfers/returns, stock recovery notices, etc.
- Inpatient and outpatient medical records
- Progress notes
- Dictated report of all imaging studies (X-rays, scans, MRIs, PET, etc.)
- Laboratory data
- Admission and discharge summaries
- Study flow sheets and other research records that are signed and dated in a real-time basis by the health care practitioner evaluating the study participant
- For advanced imaging studies, source documentation worksheets would include the acquisition, processing, quality assurance documentation, reader's interpretation, record of imaging administration, 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
- Medication diaries/calendars/adverse event logs

At the discretion of the Network Group/NCORP Research Base, certain documents such as regulatory documents, informed consent documents, delegation of tasks logs (DTLs), and DARFs may be reviewed prior to the audit date. These documents must be made available to the Group/NCORP Research Base auditors, if requested. Findings from the off-site/remote review 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, (2) Pharmacy, and (3) Study Participant Cases. An optional Review Worksheet for each of these components can be found under Appendices 2, 3, and 4, respectively.

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 CTMB-AIS. See definitions below:

Critical Deficiency

Any condition, practice, process or pattern that adversely affect the rights, safety or well-being of the study participant and/or the quality and integrity of the data; includes serious violation of safeguards in place to ensure safety of a study participant and/or manipulation and intentional misrepresentation of data (see: https://www.ema.europa.eu/en/documents/other/classification-and-analysis-good-clinical-practice-gcp-inspection-findings-gcp-inspections-conducted-request-chmp_en.pdf).

Note: See 'Guidance for Allegations of Research Misconduct' (Appendix 1) for reporting any allegation of research misconduct that is detected by site staff and/or review by a Network Group/NCORP Research Base outside of an audit (i.e., through internal quality assurance review procedures).

Major Deficiency

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

Lesser Deficiency

Finding does 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 or quantity of lesser deficiencies should be assigned as a major deficiency when determining the final assessment of a review component.

5.2 Review of the Regulatory Documentation

Protocols, informed consent documents and/or Delegation of Tasks Logs (DTLs) with no study participant enrollment are not required to be selected for review.

5.2.1 Review of the 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 participant registration
- Unanticipated problems, serious non-compliance and/or continuing non-compliance problems as defined by OHRP were reported (see https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html)

5.2.2 Review of the Local Institutional Review Board (LIRB) - 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 LIRB approval
- Documentation of full-board LIRB annual reapproval
- Documentation of timely LIRB approval (or disapproval) of protocol amendments that affect more than minimal risk
- Documentation of LIRB approval or reapproval prior to participant registration

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

The following descriptive terms should be used in assessing compliance:

- Delayed annual reapproval: Protocol reapproval by the LIRB delayed up to one year
- Expired annual reapproval: Protocol reapproval by the LIRB delayed for greater than one year
- Missing annual reapproval: Missing documentation of protocol reapproval (e.g., no letter from LIRB 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. For studies reviewed/conducted at sites outside of the U.S., amendments must be approved within 120 days to allow for local regulatory authority review, applicable translations, and review by the IRB of record. Each Group/NCORP Research Base has its own methods for notifying their institutions. Notification of temporary suspension of new participant registrations 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, serious non-compliance and/or continuing non-compliance problems as defined by OHRP (see https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html) 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 IRB compliance. This list does not represent an all-inclusive list of possible deficiencies that may be found during an audit as defined under Section 5.1.

5.2.3.1 CIRB – IRB of Record

Critical CIRB Deficiency

- Any finding identified before or during the review that meets the definition of a critical finding

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 review
- Other (explain)

5.2.3.2 Local IRB – IRB of Record

Critical LIRB Deficiency

- Any finding identified before or during the review that meets the definition of a critical finding

Major LIRB Deficiencies

- Initial approval by expedited review instead of full-board review
- Expedited reapproval for situations other than approved exceptions
- Registration and/or treatment of participant prior to full LIRB approval
- Annual reapproval delayed greater than 30 calendar days, but less than one year
- Registration of participant on protocol during a period of delayed reapproval or during a temporary suspension (i.e., Request for Rapid Amendment)
- Missing annual reapproval
- Expired annual reapproval
- Internal reportable adverse events reported late or not reported to the LIRB
- Lack of documentation of LIRB approval of a protocol amendment that affects more than minimal risk or LIRB approval is greater than 90 calendar days (or 120 calendar days for sites outside of the U.S.) after Network Group/NCORP Research Base 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 LIRB 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 LIRB Deficiencies

- Protocol annual reapproval delayed 30 calendar days or less
- Delayed annual reapproval for protocol closed to accrual for which all study participants have completed therapy
- Amendment editorial revision or administrative in nature or other Network Group/NCORP Research Base specific document not submitted or not submitted timely to the LIRB
- 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 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 as defined under Section 5.1.

Critical ICC Deficiency

- Any finding identified before or during the review that meets the definition of a critical finding

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 IRB of record, including changes to questions that do not match the model consent form
- Cumulative effect of multiple lesser deficiencies
- 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 (DTL)

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

To evaluate the roles and responsibilities of any individual contributing efforts to a clinical trial, a DTL must be maintained. The DTL is to list anyone who contributes significant trial-related duties. This log is generated and maintained by institution, by protocol and by the responsible Principal Investigator.

The auditor will review the DTL for each protocol selected for audit (by institution). The auditor will review the log to evaluate appropriate implementation and maintenance. If deficiencies are noted, additional DTLs may be reviewed at the auditor's discretion.

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 as defined under Section 5.1.

Critical DTL Deficiency

- Any finding identified before or during the review that meets the definition of a critical finding

Major DTL Deficiencies

- Performing tasks not assigned to individual
- Failure to sign DTL annually
- Individual performing study-related activities not listed on DTL
- Individual performing study-related activities with DTL unapproved greater than 30 calendar days
- Other (explain)

Lesser DTL Deficiencies

- Individual performing study-related activities with DTL unapproved 30 calendar days or less
- Other (explain)

5.2.6 Assessment of the Regulatory Documentation Review

The assessment of this component is based on the number and types of deficiencies (i.e., critical, major, lesser) across all protocols, informed consent documents and DTLs reviewed. One of the following designations is assigned as the assessment for the review of the Regulatory Documentation component:

Acceptable Rating

- No deficiencies identified, and no follow-up required
- Few lesser deficiencies identified, and no follow-up required
- Any major deficiency identified during the review 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 Principal Investigator because no similar deficiency has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a deficiency is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, the major deficiency(s) must still be cited and described in the audit report and 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 Rating

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

Unacceptable Rating

- 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 Corrective and Preventative Action (CAPA) plan and/or written response to the Network Group or NCORP Research Base. A copy of the 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 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 reaudit is mandatory if an institution continues to participate in the Network Group or NCORP Research Base for any audit component rated as Unacceptable. A reaudit should be conducted no later than a year after an Unacceptable rating.

5.3 Review of Pharmacy (Accountability of Investigational Agents and Pharmacy Operations)

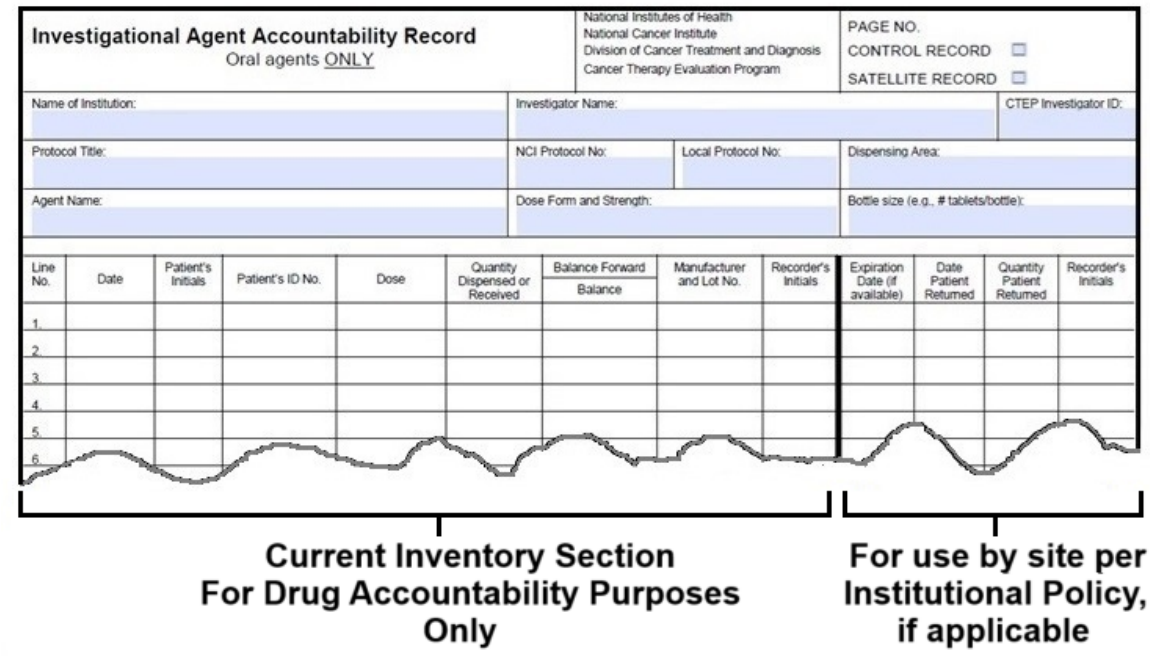
Agent accountability and storage procedures described in this section are required under federal regulations and NCI policy for NCI IND studies where agents are provided by CTEP. See CTEP policies under: https://dctd.cancer.gov/research/ctep-trials/for-sites/agent-management. Investigational agent accountability instructions for agents supplied under a non-NCI IND studies are available in the corresponding protocol.

The NCI does not endorse any commercial electronic accountability 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. NCI launched the electronic accountability module in AURORA, known as the eDARF on December 27, 2024.

A DARF is an inventory accountability log, not a study participant compliance document. For non-oral agents, study participant returns should therefore, not be documented on the DARF. Separate study participant compliance documentation may be maintained at the site if required by institutional policy.

For NCI Oral DARFs, study participant returns are considered waste pharmaceuticals and not part of agent accountability. The study participant return section of the DARF is for the convenience of the site (if required by site SOP) and is not part of study agent accountability for protocol auditing purposes (see Figure 2).

Figure 2 Example of NCI Oral DARF



Types of NCI DARFs:

- NCI DARF – paper or non-NCI eDARF that prints to match NCI DARF
- NCI Oral DARF – paper or non-NCI eDARF that prints to match NCI Oral DARF
- eDARF – AURORA accountability log

Site may choose which DARF type to use:

CTEP IND study - NCI supplied study agent	NCI DARF - *Required* (see above)
CTEP IND study – Study agent not directly supplied by NCI repository (including radiopharmaceuticals)	

Study utilizing non-CTEP IND agent and study agent not supplied by NCI	*NCI paper DARF (AURORA eDARF not available)
Study utilizing non-CTEP IND agent and study agent is supplied by NCI	

* The NCI DARF is not required to be the form used for drug accountability. Refer to protocol for specific drug accountability instructions.

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 agents to study participants as prescribed and verifying that investigator (IVR) or non-physician investigator (NPIVR) writing orders is an authorized, study-eligible person with an active registration status in the CTEP Registration and Credential Repository (RCR), and is qualified to write orders per institutional policy, their local, state laws and regulations or follow applicable international requirements
- Overall agent accountability and inventory control including provision of study agent to authorized, study-eligible physician investigator (IVR) with an active registration status in RCR at Satellite Dispensing Areas, as applicable, oversight of Satellite Dispensing Areas, and dissemination of study agent stock recovery information
- Timely final disposition of undispensed inventory (e.g., returns, authorized transfers, authorized local destructions, eDARF local destruction)
- Destruction of study participant returns of 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 study participants as prescribed and verifying that authorized, study-eligible physician investigator (IVR) or non-physician investigator (NPIVR) writing orders is an authorized, study-eligible person with an active registration status in the CTEP Registration and Credential Repository (RCR), and is qualified to write orders per institutional policy, and their local, state laws and regulations, or follow applicable international requirements
- Timely return of undispensed inventory to the Control Pharmacy Dispensing Area for final disposition or destruction
- Destruction of study participant returns of study-supplied agents per applicable regulations and institutional policies and procedures

5.3.3 Imaging Studies/Cancer Control

Imaging and radiopharmaceutical therapy agents may or may not be managed by the pharmacy depending on the protocol. Imaging and radiopharmaceutical therapy agents are usually delivered directly to the imaging, radiation oncology, nuclear medicine or nuclear pharmacy department or center that is performing the imaging study or radiopharmaceutical therapy. Cancer control/prevention and imaging study and radiopharmaceutical therapy 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 and radiopharmaceutical therapy studies must abide by the same NCI/CTEP policies. NCI DARFs must be utilized to track these study agents as described in the protocol.

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, imaging and radiopharmaceutical therapy 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 imaging and radiopharmaceutical therapy 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 study participant and/or the quality and integrity of the data; includes serious violation of safeguards in place to ensure safety of a 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

Compliant	Non-Compliant
NCI DARF/Oral DARF/eDARF maintained and maintained completely, accurately and in real-time basis	NCI DARF/Oral DARF/eDARF not maintained or not maintained completely, accurately or in real-time basis
Paper and/or eDARF contains all required information; paper printout of eDARF is identical to NCI DARF	Paper and/or eDARF are not completed as required; paper printout of eDARF is not identical to NCI DARF
No erasures or whiteout used on paper DARF	Erasures or whiteout used on paper DARF
Corrections are lined out, initialed and dated on paper DARF	Corrections are not lined out, initialed, and dated on paper DARF
Corrections are appropriately documented on eDARF in electronic inventory system	Corrections are not appropriately documented on eDARF in electronic inventory system
Study-supplied agent dispensed to a registered study participant is recorded on the appropriate DARF	Study-supplied agent dispensed to a registered study participant is not recorded on the appropriate DARF
Multiple dose vials appropriately used for more than one study participant with doses documented correctly on separate lines of the DARF	Multiple dose vials not used for more than one study participant and/or doses not documented correctly on separate lines of the DARF
Study-supplied agent is appropriately dispensed to a registered study participant	Study-supplied agent dispensed to a non-registered study participant recorded on the DARF
Handling of study participant returns of oral study-supplied agents are documented in the study participant return section of the oral DARF if applicable per institutional policy	Study participant return of oral agents are documented as part of ‘current inventory’ section on DARF
Study participant returns of non-oral study agent are not documented on the NCI DARF	Study participant returns of non-oral study agent are documented on NCI DARF
Study agent final disposition of undispensed inventory is documented on DARF	Study agent final disposition of undispensed inventory is not documented on DARF
NCI DARF maintained to verify cancer control/imaging study-supplied agent is administered to study participant	NCI DARF not maintained to verify cancer control/imaging study-supplied agents is administered to study participant

DARFS ARE PROTOCOL AND STUDY AGENT SPECIFIC

Compliant	Non-Compliant
Study agent is appropriately dispensed and administered to study participant when study agent is supplied per protocol	Non-study drug is dispensed and/or administered to study participant when NCI study agent is supplied by protocol
DARF maintained with multiple Lot #s, if multiple lots have been recieved	DARF maintained by Lot #, when multiple lots have been received
Separate DARF is maintained by protocol, study agent, strength, formulation and ordering investigator	Separate DARF not maintained by protocol, study agent, strength, formulation and ordering investigator when agent is supplied by protocol
Maintain separate DARF for each study participant on participant-specific supply studies as dictated by protocol	Separate DARF not maintained for each study participant on participant-specific supply studies as dictated by protocol
Study-supplied agent is only used for pre-clinical or laboratory studies with written approval from NCI	Study-supplied agent used for pre-clinical or laboratory studies without written approval from NCI

SATELLITE RECORDS OF DISPENSING AREA

Compliant	Non-Compliant
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	No Satellite DARFs in use when required (i.e., stored more than a day)
Satellite Dispensing Area records are available at the time of review	Satellite DARFs not available at the time of review
Satellite Dispensing Area and Control records match and are accurately maintained	Satellite and Control records do not match or are not accurately maintained
Undispensed study-supplied agent is documented as returned and transported to Control Dispensing Area; Satellite Dispensing Area appropriately returns study agent to Control pharmacy for final disposition/destruction	Undispensed 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

AGENT INVENTORY AND ACCOUNTABILITY DOCUMENTATION

Compliant	Non-Compliant
Study-supplied agent order receipts/ documentation (paper or electronic) are retained and available for review	Study-supplied agent order receipts/ documentation (paper or electronic) are not retained or not available for review
Documentation on Control DARF for study-supplied agent transactions including local destruction of undispensed inventory	No documentation on Control DARF of study-supplied agent transactions including local destruction of undispensed inventory
Quantities accounted for in physical inventory, and quantities match with DARF	Quantities not accounted for in inventory; quantities do not match DARF
[For NCI sponsored study] NCI oral study agent shipped to study participant per NCI oral agent shipment policy	[For NCI-sponsored study] NCI oral study agent shipment policy is not followed when shipping directly to study participant

RETURN OF UNDISPENSED STUDY AGENT
[NCI sponsored study]

Compliant	Non-Compliant
Study agent is transferred to another site, authorized investigator, or protocol with NCI written approval	Study agent is transferred to another site, investigator or protocol without NCI written approval
Undispensed study-provided agent not returned to NCI when supplied by another source	Undispensed study-provided agent returned to NCI when supplied by another source
Return Form or documentation of local destruction authorization for undispensed inventory is maintained	Return Form or documentation of local destruction for undispensed inventory is not maintained
Undispensed NCI-supplied study agent is returned, transferred or locally destroyed within 90 calendar days when requested by the NCI	Undispensed NCI-supplied study agent not returned, transferred or locally destroyed within 90 calendar days when requested by the NCI
Undispensed NCI-supplied study agent is returned to NCI within 90 days of when all study participants transition to follow-up or study is closed to enrollment and no NCI-supplied study agent is being administered	Undispensed NCI-supplied study agent remains on inventory greater than 90 days after all study participants are in follow-up, or study is closed to enrollment and no NCI-supplied study agent is being administered

STUDY AGENT STORAGE

Compliant	Non-Compliant
Study-supplied agent is stored separately by protocol, agent, strength, formulation and by ordering investigator	Study-supplied agent is not stored separately by protocol, agent, strength, formulation and/or by ordering investigator
Study-supplied agent is stored under proper temperature conditions; temperature monitoring documentation is maintained	Study-supplied agent is not stored under proper temperature conditions; temperature monitoring documentation not maintained

ADEQUATE SECURITY

Compliant	Non-Compliant
Study-supplied agent is stored in a secure area	Study-supplied agent is not stored in a secure area
Only authorized individuals have access to the secure areas	Unauthorized individuals have access to a secure area without supervision

AUTHORIZED PRESCRIPTION(S)

Compliant	Non-Compliant
[For NCI sponsored study] Prescribing investigator (IVR) or non-physician investigator (NPIVR) writing orders for study-supplied agent has an active registration status in the CTEP Registration and Credential Repository (RCR)	[For NCI sponsored study] Prescribing investigator (IVR) or non-physician investigator (NPIVR) writing orders for study-supplied agent does not have an active registration status in the CTEP Registration and Credential Repository (RCR)
[For NCI sponsored study] Prescribing investigator (IVR) or non-physician investigator (NPIVR) is an authorized, study-eligible person, and is qualified to write orders per institutional policy, their local, state laws and regulations, and follow applicable international requirements	[For NCI sponsored study] Prescribing investigator (IVR) or non-physician investigator (NPIVR) writing orders is not an authorized, study-eligible person, or is not qualified to write orders per institutional policy, their local, state laws and regulations, or follow applicable international requirements
Pharmacy has procedures in place to ensure the person prescribing and writing orders for study-supplied agent is an authorized person	Pharmacy does not have procedures in place to ensure person prescribing and writing orders for study-supplied agent is an authorized person

5.3.5 Assessment of the Pharmacy Review

Auditor discretion can be used for minor problem(s) identified during the review of the pharmacy. The number of active 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 the review that meets the definition of a critical finding

The assessment of this component is based on the number and types of non-compliance (deficiencies). One of the following designations is assigned as the assessment for the review of the Pharmacy component:

Acceptable Rating

- Compliance in all categories and no follow-up required
- Any Non-Compliance item identified during the review 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 Principal 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, the non-compliance item(s) must still be cited and described in the audit report and 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 Rating

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

Unacceptable Rating

- 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 person is authorized to prescribe or write orders and has an active status in the CTEP Registration and Credential Repository (RCR)
  - Review of security, storage and pharmacy procedures (described above) were found to be 'compliant'

Limited Review Needs Follow-up

- 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 Corrective and Preventative Action (CAPA) plan and/or written response to the Network Group or NCORP Research Base. A copy of the 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 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 reaudit is mandatory if an institution continues to participate in the Network Group or NCORP Research Base for any audit component rated as Unacceptable. A reaudit should be conducted no later than a year after an Unacceptable rating or when there is sufficient activity to assess the effectiveness of the CAPA plan.

If the pharmacy requires a reaudit due to non-compliance related to storage and/or security, the reaudit 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 Study Participant Cases

If records are not in English, then a qualified translator chosen by the audit team or institution must be present. Source documentation of each participant case selected for review considered missing at the time of the audit must be supplied to 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 as defined under Section 5.1. The term 'intervention' is intended to include non-treatment studies such as cancer control, prevention, advanced imaging, etc.

<u>Informed Consent – Critical Deficiencies</u>

- Any finding identified before or during the review that meets the definition of a critical finding

- Consent form document not signed and dated by the study participant (or parent/legally authorized representative, if applicable)
- Study participant signature cannot be corroborated
- Consent form document is not protocol specific

Informed Consent – Major Deficiencies

- Failure to document the informed consent process with the study participant; electronic/remote consent process not followed
- Study participant signs consent form document containing changes not approved by the IRB of record
- Consent form document is missing
- Translated consent form document, short form or other form of translation not available or signed/dated by a non-English speaking study participant
- Consent form document not signed/dated by study participant prior to study registration/enrollment
- Consent form document does not contain all required signatures
- Consent form document signed was not the most current IRB-approved version at the time of participant registration
- Consent form document signed does not include updates or information required by IRB of record
- Study participant not re-consented or notified as required
- Consent form document for ancillary/advanced imaging studies not executed properly
- Other (explain)

Eligibility – Critical Deficiency

- Any finding identified before or during the review that meets the definition of a critical finding

Eligibility – Major Deficiencies

- Review of documentation available 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: Patient/study participant 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 the review that meets the definition of a critical finding
- 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; or not administered correctly
- Timing and sequencing of treatment/intervention not per protocol
- Unjustified delays in treatment/intervention
- Treatment/intervention not documented in source documentation; or not documented correctly[1]
- Treatment/intervention not reported; or not reported correctly on Case Report Forms[2]
- Other (explain)

Note regarding Treatment category: Review of documentation for how and when treatment is administered should focus on the study/IND agents under investigation (i.e., start/stop times), unless otherwise specified in the protocol. Documentation of standard of care drug(s) should include total dose and start/stop dates for prolonged IV infusions ≥ 24 hours.

Disease Outcome/Response – Critical Deficiency

- Any finding identified before or during the review that meets the definition of a critical finding

Disease Outcome/Response – Major Deficiencies

- Inaccurate documentation of initial sites of involvement
- Tumor measurements/evaluation of 'status of disease' not performed
- Tumor measurements/evaluation of 'status of disease' not documented in source documentation; or not documented correctly[3]
- Tumor measurements/evaluation of 'status of disease' not reported; or not reported correctly on Case Report Forms[4]
- Protocol-directed response criteria not followed
- Claimed response (i.e., partial response, complete response, stable) cannot be verified
- Failure to identify cancer progression or failure to detect cancer in adjuvant or prevention study
- Other (explain)

[1] Assigning a major or lesser is based on the extent of treatment data not documented; or not documented correctly.
[2] Assigning a major or lesser is based on the extent of not reporting treatment data; or not reporting correctly.
[3] Assigning a major or lesser is based on the extent of disease outcome/response data not documented; or not documented correctly.
[4] Assigning a major or lesser is based on the extent of not reporting disease outcome/response data; or not reporting correctly.

Adverse Event – Critical Deficiency

- Any finding identified before or during the review that meets the definition of a critical finding

Adverse Event – 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
- Grades, types, or dates/duration of serious adverse events inaccurately recorded
- Adverse events not assessed by the investigator in a timely manner per protocol
- Serious adverse events reported on Case Report Forms but cannot be substantiated in source documentation
- Routine adverse events not documented in source documentation; or not documented correctly[5]
- Adverse events not reported; or not reported correctly on Case Report Forms[6]
- Follow-up studies necessary to assess adverse events not performed
- Recurring under- or over-reporting of adverse events
- Other (explain)

Correlative Studies, Tests, and Procedures – Critical Deficiency

- Any finding identified before or during the review that meets the definition of a critical finding

Correlative Studies, Tests, and Procedures – Major Deficiencies

- Protocol-specified diagnostic studies including baseline assessments not done, not reported or not documented
- Protocol-specified laboratory tests or other parameters not done, not reported, or not documented
- Protocol-specified research (Quality of Life forms, collection of research samples, etc.)/advanced imaging studies not done, not submitted or submitted inappropriately
- Other (explain)

General Data Management Quality – Critical Deficiency

- Any finding identified before or during the review that meets the definition of a critical finding

General Data Management Quality – Major Deficiencies

- Recurring missing documentation in the study participant records

[5] Assigning a major or lesser is based on the extent of adverse event data not documented; or not documented correctly.
[6] Assigning a major or lesser is based on the extent of adverse event data not reported; or not reporting correctly.

- Frequent data inaccuracies in primary source documentation[7]; unredacted data[8]
- Significant number of errors in submitted data[7]; data cannot be verified
- Delinquent data submission[9]
- Other (explain)

Assigning Lesser Deficiencies

As defined under Section 5.1, a lesser deficiency may be assigned under each of the above sub-categories if it is judged as not having a significant impact on the outcome or interpretation of the study.

5.4.2 Assessment of the Study Participant Case Review

The assessment of this component is based on the number and types of deficiencies (i.e., critical, major, lesser) across all cases reviewed. One of the following designations is assigned as the assessment for the review of the Participant Case Review component:

Acceptable Rating

- No deficiencies identified, and no follow-up required
- Few lesser deficiencies identified, and no follow-up required
- Any major deficiency identified during the review 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 Principal Investigator because no similar deficiency has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a deficiency is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, the major deficiency(s) must still be cited and described in the audit report, and 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 Rating

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

[7] Assigning a major or lesser deficiency is dependent on the number of instances or extent of inaccurate data or errors in submitted data.

[8] Assigning a major or lesser deficiency is dependent on the number of instances and type of unredacted data (e.g., security number, study participant name, etc.).

[9] Assigning a major or lesser deficiency is based on the following: extent of the delay, percentage or number of delinquent forms, type of form (baseline, treatment, follow-up, etc.), phase of the trial, and study participant on active treatment versus follow-up. Network Group/NCORP policies and decisions from the Data Quality Working Group should be taken into consideration.

Unacceptable Rating

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

If the Participant Case Review is rated as Acceptable Needs Follow-up or Unacceptable, the institution will be required to submit a written Corrective and Preventative Action (CAPA) plan and/or written response to the Network Group or NCORP Research Base. A copy of the 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 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 reaudit is mandatory, if an institution continues to participate in the Network Group or NCORP Research Base for any audit component rated as Unacceptable. A reaudit should be conducted no later than a year after an Unacceptable rating or when sufficient new study participants have enrolled since the previous audit. If sufficient new study participants have not enrolled within a year from the previous audit, further discussion with CTMB is necessary prior to requesting an extension of the reaudit timeline in the CTMB-AIS.

5.5 Role of the Investigator During the Audit

The Principal 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 Principal Investigator and designated staff be present at the exit interview whether the audit is conducted on-site or off-site. 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 CAPA plan/response 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 via the Email Notification Response Management module in the CTMB-AIS.

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. The CTMB must be notified immediately by telephone (240) 276-6545 and by email (ReportingResearchMisconductConcerns@nih.gov) 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 Participant Case Review) of an audit.

A separate Preliminary Report of Audit Findings is required for each audited institution. However, if the audit was conducted as a combined audit ‘as a whole’ (parent and their non-auditable institutions), a single Preliminary Report is 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 person is authorized to prescribe or write orders, and has an active status in the CTEP in RCR), 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.

Participant Case Review Section - Briefly describe all deficiencies identified, and appropriately label each deficiency as critical or major. If a participant case was reviewed that was not designated as an unannounced case, explain why it 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. The revisions must be identified and briefly described on page 2 of the Preliminary Report. Deficiencies identified or revised after 10 business days after Day 1 of the audit must be briefly described in the Final Audit Report.

6.2.2 Content

All critical and major deficiencies, including any non-compliance (for the pharmacy review) must be identified and described under the appropriate audit component in the Preliminary Report of Audit Findings.

- Regulatory Documentation Review
- Pharmacy Review
- Participant Case Review*

* The total number of cases reviewed with any critical and major deficiencies identified must be listed by category 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 date. 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 10 business days. 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

- On the front page of the report, provide information specific to the institution such as number of cases audited, and average annual accrual
- List the site staff names and titles involved or present at the audit
- List the names, titles and affiliations each member of the audit team
- List Co-site visitor(s) and affiliation, if applicable

6.3.2.2 Review of the Regulatory Documentation

- The CTMB-AIS will populate each protocol title for protocols audited and list the number participant cases selected for review, the IND drugs, treatment modalities used, and the disease(s) studied in each protocol (if drug is NCI-supplied study agent)
- Designate whether critical, major, or lesser deficiencies were identified under IRB, ICC, or DTL and describe each critical, major or lesser deficiency; otherwise indicate OK
- Provide an overall assessment for this component (Acceptable, Acceptable needs F/U, or Unacceptable), and indicate if a reaudit is required, including timeframe

6.3.2.3 Review of the Pharmacy

- Indicate the number of DARFs reviewed (i.e., number of study agents reviewed), and the number of participants cross-checked against the DARF, if applicable
- For each item identified as Critical-Non-Compliance or Non-Compliance, select the appropriate Not Compliant description(s); otherwise indicate Compliant or Not Reviewed
- Summarize in the pharmacy narrative any items that require a CAPA plan/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 if study-supplied agents were not selected for review, if pharmacy review was performed remotely, the method(s) by which the inspection of study storage, drug inventory, temperature monitoring, security should be described, etc.
- For a <u>full review</u> of the pharmacy component, provide an overall assessment (Acceptable, Acceptable needs F/U, or Unacceptable), and indicate if a reaudit is required, including timeframe
- For a <u>limited review</u> of the pharmacy, indicate which items were reviewed (i.e., storage, security, and/or pharmacy procedures) and why it was a limited review. The overall assessment for a ‘limited

review' of the pharmacy must be: 'No Assessment Required' or 'Limited Review Needs Follow-up' (more details Under Section 5.3.5)

- Provide an overall assessment for this component (Acceptable, Acceptable needs F/U, Unacceptable, Limited Review Needs F/U or No Assessment Required), and indicate if a reaudit is required, including timeframe

6.3.2.4 Review of the Study Participant Cases

- For each category in the audit report, indicate if critical, major or lesser deficiency is being cited, and describe; otherwise indicate OK or Not Reviewed
- If a category is designated as 'Not Reviewed' for a participant case selected for audit (i.e., announced case), an explanation (rather than a deficiency description) must be summarized by participant ID and category in the audit report
- For findings related to documentation or reporting, ensure the deficiency is captured by category (i.e., Informed Consent; Eligibility; Treatment; Disease Response/Outcome; Adverse Event; Correlative Studies, Tests, and Procedures) where appropriate, rather than under General Data Management Quality
- The CTMB-AIS pre-populates and summarizes the deficiencies for each study participant and category in a table embedded in the report; this table calculates the total number of critical, major and lesser deficiencies for the total participant cases reviewed; if a participant case was selected for review but no categories were reviewed, it must not be listed in the table of the final report
- Under the Participant Case Review Assessment section of the final report in the CTMB-AIS, provide a brief summary for each category if a CAPA plan is being requested. The brief summary should include a description of items that need to be addressed in the CAPA plan/response
- Provide an overall assessment for this component (Acceptable, Acceptable needs F/U, or Unacceptable), and indicate if a reaudit is required, including timeframe

6.3.2.5 Audit Procedures

In this section summarize is any component(s) were reviewed on-site versus off-site (e.g., consent forms, DARFs, etc). Include mention of any pertinent information as it relates to the audit. Also provide an explanation if any component or category did not have a complete review, as planned.

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 / Follow-up Response

As outlined under Sections 5.2.6, 5.3.5 and 5.4.2, CAPA plan/follow-up response must be uploaded into the CTMB-AIS within 45 calendar days from the date the final audit report is uploaded in the CTMB-AIS by the Group/NCORP Research Base. Other pertinent correspondence or documentation related to the audit may also be uploaded. The CAPA plan must include a cover letter from the auditing Group stating that the auditing Group has reviewed the CAPA plan/response(s) and find response(s) adequate. It must be uploaded to the Document Management tab in the CTMB-AIS by corresponding CTEP Site Code and audit date.

6.5 Timeline for Uploading Preliminary Forms, Final Reports and CAPA Plans into the CTMB-AIS

Submission Type	Due Date to Upload into CTMB-AIS
Preliminary Report for Audit Findings	Within 1 business day of completing the audit
Final Audit Report	Within 70 calendar days of Day 1 of the audit date
CAPA Plan*	Within 45 calendar days from the date the final audit report is uploaded in the CTMB-AIS

* CAPA plan must be uploaded into the CTMB-AIS within 45 days by the Group/ Research Base, therefore the site should provide their CAPA plan to the Group/ Research Base sooner, per the requirements set by the Group/Research Base.

6.6 Reaudits

When a reaudit is designated to take place as described under Sections 5.2.6, 5.3.5 and 5.4.2, the reaudit requirement remains linked to the institution in the CTMB-AIS regardless of its status (i.e., active or withdrawn). If the institution is being withdrawn, the reaudit timeline on the final audit report for the applicable audit components are to be designated 'No Reaudit'. If the institution rejoins the same Group/NCORP Research Base at a later date, the reaudit must be conducted within 12 months from the first new accrual. The 'No Reaudit' timeline allows the Group/NCORP Research Base and CTMB to track these institutions that require a reaudit, if reactivated. For tracking purposes, any off-site/remote audit or reaudit must also be scheduled and reported in the CTMB-AIS.

6.7 For-cause 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 a for-cause 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.

6.8 Probation of a Principal 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 Principal Investigator
- Re-analyzing or retract published results
- Requesting a formal investigation by the Office of Research Integrity
- Revoking the Investigator's Form FDA 1572
- Terminating privileges for participating on any NCI sponsored clinical trial

6.9 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 participant 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.

6.10 Suspension of a Principal Investigator and/or Participating Institution

If a critical deficiency is cited it will result in suspension of the Principal 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 Principal 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 new participant 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 participant 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 new 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 Principal Investigator detailing the reason for the delay must be included. Suspension of participant registrations 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.

6.11 Withdrawal of a Participating Institution

If improved performance is not documented after reaudits have taken place, 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 (i.e., off-cycle audit) may take place at any site, at any time, if study participant safety or scientific misconduct is suspected

Appendix 1 Guidance for Allegations of Research Misconduct

Guidance for Allegations of Research Misconduct

Reason for Guidance:

To describe the process for reporting research misconduct allegations for research conducted by National Cancer Institute (NCI) extramural program. To identify the policies and procedures to be followed when reporting research misconduct allegations.

Who is affected by this Guidance:

Extramural NCI members (grantees, contractors, faculty, and staff) conducting research under HHS funded research.

Responsible Office:

For questions about this guidance, please contact the Clinical Trials Monitoring Branch (CTMB) within the Cancer Therapy Evaluation Program (CTEP).

Email: ReportingResearchMisconductConcerns@nih.gov
Phone: (240) 276-6545

Definitions:

A. **Research misconduct** means the "fabrication, falsification, or plagiarism in proposing, performing, or reviewing research or in reporting results (42 CFR 93)."

B. **Fabrication** means "making up data or results and recording or reporting them (42 CFR 93.103)."

C. **Falsification** means "manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record (42 CFR 93.103)."

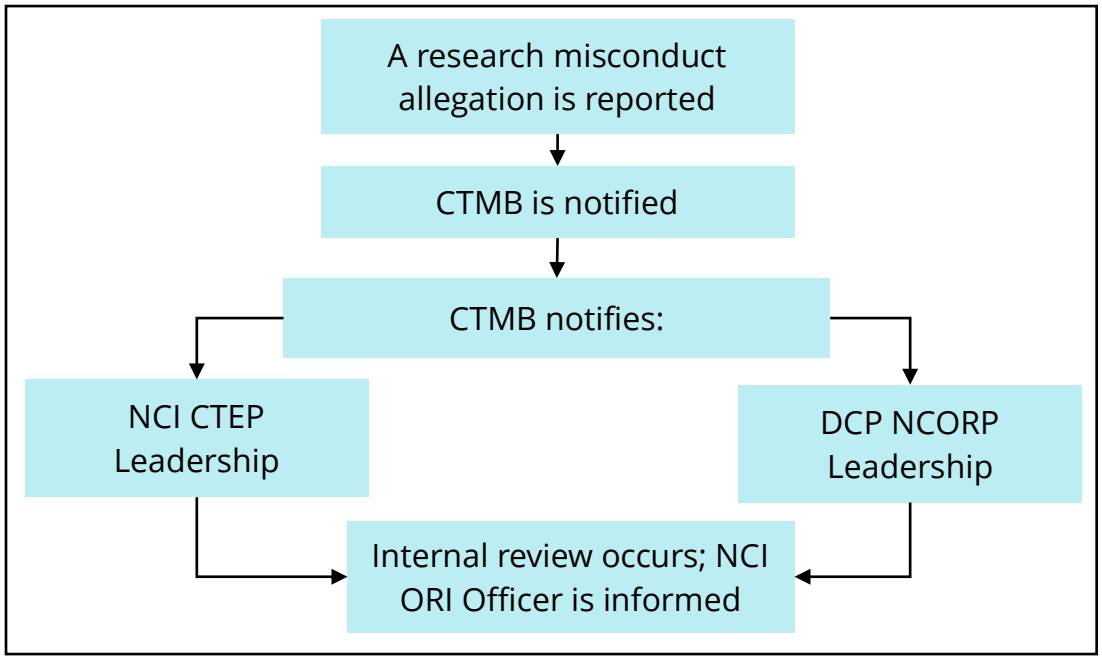
D. **Plagiarism** means the "appropriation of another person's ideas, processes, results, or words without giving credit (42 CFR 93.103)."

E. **Allegation** means the "disclosure of possible research misconduct through any means of communication (42 CFR 93.201)." The allegation can be communicated via written, oral, or other communication means to the institution.

What should be done if there is a research misconduct concern?

Per 42 CFR 93.103, research misconduct "does not include honest error or differences of opinion." The aim of this guidance is to define research misconduct allegations and delineate the reporting process. The National Institutes of Health (NIH) Grants policy statement (11.2.3.5) states that the grantee is responsible for the conduct of research and compliance with policies and procedures such as but not limited to human subjects' protection and research misconduct. The NIH awards condition and grant policy advises grantees to disclose any research misconduct investigations. This guidance document delineates the NCI CTEP and NCI Community Oncology Research Program (NCORP) expectation that research misconduct concerns will be reported to CTMB immediately.

When research misconduct concern is identified by an individual or during internal grantee/ institutional reviews, CTMB should be notified immediately. Research misconduct identified during a routine audit, central monitoring, or for-cause audit will follow CTMB guideline procedures. When reporting a research misconduct concern, provide CTMB with details and the extent of the research misconduct allegation via email or by telephone. The description of the research misconduct concern should include but not be limited to: how many protocols are involved in the allegation, which site/ institutions are involved in the concern, which NCI National Clinical Trials Network (NCTN) or Division of Cancer Prevention (DCP) NCORP group is credited the cases, and when the program director was notified of the allegation. The research misconduct allegations should be provided to CTMB to start the NCI internal review process. CTMB will notify NCI CTEP leadership, NCI NCORP leadership, and NCI Officer of Research Integrity (ORI) Official.



What are some examples of research misconduct allegations?

Category of Research Misconduct	Definition	Examples
Fabrication	Making up data or results and recording or reporting them	• Making up participants • Making up research results
Falsification	Manipulating research materials, equipment, or processes, or changing *OR* Omitting data or results such that the research is not accurately represented in the research record	• Forging consent documents • Falsifying research results • Manipulating research equipment to falsify research results
Plagiarism	Appropriation of another person's ideas, processes, results, or words without giving credit.	• Plagiarizing components of publication • Plagiarizing contents from published research

What are the procedures for reporting a research misconduct allegation?

A. If you suspect or have identified a research misconduct concern, notify CTMB immediately.

B. Provide information about the research misconduct allegation including but not limited to:

   1. Description of what has been falsified, fabricated, or plagiarized
   2. Nature of research records and research processes affected
   3. Description of manipulation of research records
   4. Site/ individual involved in the research misconduct concern
   5. Protocol involved in the research misconduct allegation
   6. Contact information

C. The information should be provided to CTMB via email or by telephone.

D. The information provided regarding the allegations of research misconduct will be confidential. The information will be reported to NCI CTEP and/or NCORP leadership.

E. CTMB will provide oversight to ensure the research misconduct allegations are reported in accordance with NIH, NCI, and HHS reporting requirements.

Who can I contact with a research misconduct allegation?

The contact person for research misconduct concerns at the NCI/CTEP is the Chief of the Clinical Trials Monitoring Branch (CTMB), Gary Smith. He can be reached at (240) 276-6545 or you may send an email to: ReportingResearchMisconductConcerns@nih.gov

What educational resources are available?

For additional information on research misconduct, the HHS Office of Research Integrity has an interactive training on research misconduct (https://ori.hhs.gov/the-lab).

References:

ORI. (2022). Handling Misconduct (https://ori.hhs.gov/handling-misconduct)

NIH Grants. (2018). Research Misconduct – Definitions (https://grants.nih.gov/policy/research_integrity/definitions.htm)

Appendix 2 Regulatory Documentation Review Worksheet

NATIONAL CANCER INSTITUTE
Division of Cancer Treatment & Diagnosis

Clinical Trials Monitoring Branch (CTMB)
Cancer Therapy Evaluation Program (CTEP)

Regulatory Documentation Review Worksheet

IRB of Record: NCI Central IRB or Local IRB **Review Date:**

CTEP Site Code: **# of NCI Protocols Reviewed:**

Overall Comments:

Category	Overall Comments
IRB of Record Review	
Informed Consent Content (ICC) Review	
Delegation of Tasks Log (DTL) Review	

Central Institutional Review Board (CIRB): Types of Deficiencies

Critical Deficiency	**Yes**	**No**	**Comments**
Any finding, identified before or during the review, that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines	☐	☐	
Major Deficiencies	**Yes**	**No**	**Comments**
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 Deficiencies	**Yes**	**No**	**Comments**
Copy of CIRB approval letter/study worksheet is not available or accessible at the time of the review	☐	☐	
Other (explain)	☐	☐	

Local Institutional Review Board (LIRB): Types of Deficiencies

Critical Deficiency	**Yes**	**No**	**Comments**
Any finding, identified before or during the review, that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines	☐	☐	
Major Deficiencies	**Yes**	**No**	**Comments**
Initial approval by expedited review instead of full-board review	☐	☐	
Expedited reapproval for situations other than approved exceptions	☐	☐	
Registration and/or treatment of study participant prior to full LIRB approval	☐	☐	
Annual reapproval delayed greater than 30 calendar days, but less than one year	☐	☐	
Registration of study participant on protocol during a period of delayed reapproval or during a temporary suspension (i.e., Request for Rapid Amendment)	☐	☐	
Missing annual reapproval	☐	☐	
Expired annual reapproval	☐	☐	
Internal reportable adverse events reported late or not reported to the LIRB	☐	☐	

Major Deficiencies (cont…)	Yes	No	Comments
Lack of documentation of LIRB approval of a protocol amendment that affects more than minimal risk or LIRB approval is greater than 90 calendar days (or 120 calendar days for sites outside of the U.S.) after Network Group/NCORP Research Base/LAO 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 LIRB that is considered an unanticipated problem as defined by OHRP, unless there is a LIRB policy that does not mandate reporting of external safety reports	☐	☐	
Other (explain)	☐	☐	
Lesser Deficiencies	**Yes**	**No**	**Comments**
Protocol annual reapproval delayed 30 calendar days or less	☐	☐	
Delayed annual reapproval for protocol closed to accrual for which all study participants have completed therapy	☐	☐	
Amendment editorial revision or administrative in nature or other Network Group/NCORP Research Base/LAO specific document not submitted or not submitted timely to the LIRB	☐	☐	
Other (explain)	☐	☐	

Informed Consent Content (ICC): Types of Deficiencies

Critical Deficiency	**Yes**	**No**	**Comments**
Any finding, identified before or during the review, that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines	☐	☐	
Major Deficiencies	**Yes**	**No**	**Comments**
Missing any of the following statements or language specific to the elements required per the federal regulations, when appropriate:	☐	☐	
a. Involves research, purposes; duration of participation; description of procedures; identification of experimental procedures	☐	☐	
b. Description of foreseeable risks or discomforts	☐	☐	
c. Description of any benefits to subjects or others	☐	☐	
d. Disclosure of alternative procedures or treatments	☐	☐	
e. Description of the extent of confidentiality of records	☐	☐	
f. Explanation regarding compensation and/or whether treatments are available if injury occurs, including who to contact if injury occurs	☐	☐	
g. 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	☐	☐	
h. Statement that participation is voluntary; refusal to participate involves no penalty or loss of benefits; subject may discontinue participation at any time	☐	☐	

Major Deficiencies (cont…)	Yes	No	Comments
i. Unforeseeable risks to subject, embryo or fetus	☐	☐	
j. Statement that circumstances in which subject's participation may be terminated by the investigator without subject's consent	☐	☐	
k. Statement of additional costs to subject that may result from participation in the study	☐	☐	
l. Statement of consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	☐	☐	
m. Statement that significant new findings which may be related to subject's willingness to continue participation will be provided to subject	☐	☐	
n. Disclosure of approximate number of subjects involved in the study	☐	☐	
o. 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 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 IRB of record, including changes to questions that do not match the model consent form	☐	☐	

Major Deficiencies (cont...)	Yes	No	Comments
Cumulative effect of multiple lesser deficiencies	☐	☐	
Other (explain)	☐	☐	
Lesser Deficiencies	**Yes**	**No**	**Comments**
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)	☐	☐	

Delegation of Tasks Log (DTL): Types of Deficiencies

Critical Deficiency	**Yes**	**No**	**Comments**
Any finding, identified before or during the review, that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines	☐	☐	
Major Deficiencies	**Yes**	**No**	**Comments**
Performing tasks not assigned to individual	☐	☐	
Failure to sign DTL annually	☐	☐	
Individual performing study-related activities not listed on DTL	☐	☐	
Individual performing study-related activities with DTL unapproved greater than 30 calendar days	☐	☐	
Other (explain)	☐	☐	
Lesser Deficiencies	**Yes**	**No**	**Comments**
Individual performing study-related activities with DTL unapproved 30 calendar days or less	☐	☐	
Other (explain)	☐	☐	

Appendix 3 Pharmacy Review Worksheet

NATIONAL CANCER INSTITUTE
Division of Cancer Treatment & Diagnosis

Clinical Trials Monitoring Branch (CTMB)
Cancer Therapy Evaluation Program (CTEP)

Pharmacy Review Worksheet

☐ On-Site
☐ Off-Site

Review Date: **CTEP Site Code:**

Were study-supplied agents in use at this site during the time period covered by the review? Yes or No

Number of NCI DARFs compared to shelf inventory:
Number of participants cross-checked with NCI DARF:
List protocols (DARFs) reviewed:

Pharmacy Review Summary:

Compliance Category	[1]Critical non-Compliant	Non-compliant	Compliant	Not Reviewed	Overall Comments
NCI DARFs Completely and Correctly Filled Out	☐	☐	☐	☐	
DARFs are Protocol and Study Agent Specific	☐	☐	☐	☐	
Satellite Records of Dispensing Area	☐	☐	☐	☐	
Agent Inventory and Accountability Documentation	☐	☐	☐	☐	
Return of Undispensed Study Agent [NCI sponsored study]	☐	☐	☐	☐	
Study Agent Storage	☐	☐	☐	☐	
Adequate Security	☐	☐	☐	☐	
Authorized Prescription(s)	☐	☐	☐	☐	

[1] Any finding identified before or during the review that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines.

Pharmacy: Types of Non-Compliance Issues

NCI DARFs Completely and Correctly Filled Out	[1]Critical	[2]NC	OK
NCI DARF/Oral DARF/eDARF not maintained or not maintained completely, accurately or in real-time basis	☐	☐	☐
Paper and/or eDARF are not completed as required; paper printout of eDARF is not identical to NCI DARF	☐	☐	☐
Erasures or whiteout used 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 study participant is not recorded on the appropriate DARF	☐	☐	☐
Multiple dose vials not used for more than one study participant and/or doses not documented correctly on separate lines of the DARF	☐	☐	☐
Study-supplied agent dispensed to a non-registered study participant recorded on the DARF	☐	☐	☐
Study participant return of oral agents are documented as part of 'current inventory' section on DARF	☐	☐	☐
Study participant returns of non-oral study agent are documented on NCI DARF	☐	☐	☐
Study agent final disposition of undispensed inventory is not documented on DARF	☐	☐	☐
NCI DARF not maintained to verify cancer control/imaging study-supplied agents is administered to study participant	☐	☐	☐
DARFs are Protocol and Study Agent Specific	**Critical**	**NC**	**OK**
Non-study drug is dispensed and/or administered to study participant when NCI study agent is supplied by protocol	☐	☐	☐
DARF maintained by Lot #, when multiple lots have been received	☐	☐	☐

[1] Critical non-compliant
[2] Non-Compliant

DARFs are Protocol and Study Agent Specific (cont…)	**Critical**	**NC**	**OK**
Separate DARF not maintained by protocol, study agent, strength, formulation and ordering investigator when agent is supplied by protocol	☐	☐	☐
Separate DARF not maintained for each study participant on participant-specific supply studies as dictated by protocol	☐	☐	☐
Study-supplied agent used for pre-clinical or laboratory studies without written approval from NCI	☐	☐	☐
Satellite Records of Dispensing Area	**Critical**	**NC**	**OK**
No Satellite DARFs in use when required (i.e., stored more than a day)	☐	☐	☐
Satellite DARFs not available at the time of review	☐	☐	☐
Satellite and Control records do not match or are not accurately maintained	☐	☐	☐
Undispensed 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	☐	☐	☐
Agent Inventory and Accountability Documentation	**Critical**	**NC**	**OK**
Study-supplied agent order receipts/documentation (paper or electronic) are not retained or not available for review	☐	☐	☐
No documentation on Control DARF of study-supplied agent transactions including local destruction of undispensed inventory	☐	☐	☐
Quantities not accounted for in inventory; quantities do not match DARF	☐	☐	☐
[For NCI-sponsored study] NCI oral study agent shipment policy is not followed when shipping directly to study participant	☐	☐	☐
Return of Undispensed Study Agent (NCI-Sponsored Studies)	**Critical**	**NC**	**OK**
Study agent is transferred to another site, investigator or protocol without NCI written approval	☐	☐	☐
Undispensed study-provided agent returned to NCI when supplied by another source	☐	☐	☐
Return Form or documentation of local destruction for undispensed inventory is not maintained	☐	☐	☐

Return of Undispensed Study Agent (cont...)	**Critical**	**NC**	**OK**
Undispensed NCI-supplied study agent not returned, transferred or locally destroyed within 90 calendar days when requested by the NCI	☐	☐	☐
Undispensed NCI-supplied study agent remains on inventory greater than 90 days after all study participants are in follow-up, or study is closed to enrollment and no NCI-supplied study agent is being administered	☐	☐	☐
Study Agent Storage	**Critical**	**NC**	**OK**
Study-supplied agent is not stored separately by protocol, agent, strength, formulation and/or by ordering investigator	☐	☐	☐
Study-supplied agent is not stored under proper temperature conditions; temperature monitoring documentation not maintained	☐	☐	☐
Adequate Security	**Critical**	**NC**	**OK**
Study-supplied agent is not stored in a secure area	☐	☐	☐
Unauthorized individuals have access to a secure area without supervision	☐	☐	☐
Authorized Prescription(s)	**Critical**	**NC**	**OK**
[For NCI sponsored study] Prescribing investigator (IVR) or non-physician investigator (NPIVR) writing orders for study-supplied agent does not have an active registration status in the CTEP Registration and Credential Repository (RCR)	☐	☐	☐
[For NCI sponsored study] Prescribing investigator (IVR) or non-physician investigator (NPIVR) writing orders is not an authorized, study-eligible person, or is not qualified to write orders per institutional policy, their local, state laws and regulations, or follow applicable international requirements	☐	☐	☐
Pharmacy does not have procedures in place to ensure person prescribing and writing orders for study-supplied agent is an authorized person	☐	☐	☐

Appendix 4 Participant Case Review Worksheet

NATIONAL CANCER INSTITUTE
Division of Cancer Treatment & Diagnosis

Clinical Trials Monitoring Branch (CTMB)
Cancer Therapy Evaluation Program (CTEP)

Participant Case Review Worksheet

Review Date: **CTEP Site Code:**

NCI Protocol #: **Study Participant Case #:**

Participant Case Summary:

Category	Critical	Major	Lesser	*NR	OK	Overall Comments
Informed Consent	☐	☐	☐	☐	☐	
Eligibility	☐	☐	☐	☐	☐	
Treatment	☐	☐	☐	☐	☐	
Disease Outcome/ Response	☐	☐	☐	☐	☐	
Adverse Event	☐	☐	☐	☐	☐	
Correlative Studies, Tests, and Procedures	☐	☐	☐	☐	☐	
General Data Management Quality	☐	☐	☐	☐	☐	

*Not Reviewed

Informed Consent: Types of Deficiencies

Critical Deficiencies	Yes	No	Comments
Any finding, identified before or during the review, that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines	☐	☐	
Consent form document not signed and dated by the study participant (or parent/legally authorized representative, if applicable)	☐	☐	
Study participant signature cannot be corroborated	☐	☐	
Consent form document is not protocol specific	☐	☐	
Major Deficiencies	**Yes**	**No**	**Comments**
Failure to document the informed consent process with the study participant; electronic/remote consent process not followed	☐	☐	
Study participant signs consent form document containing changes not approved by the IRB of record	☐	☐	
Consent form document is missing	☐	☐	
Translated consent form document, short form or other form of translation not available or signed/dated by a non-English speaking study participant	☐	☐	
Consent form not signed/dated by study participant prior to study registration/enrollment	☐	☐	
Consent form document does not contain all required signatures	☐	☐	

Major Deficiencies (cont...)	Yes	No	Comments
Consent form document signed was not the most current IRB-approved version at the time of participant registration	☐	☐	
Consent form document signed does not include updates or information required by IRB of record	☐	☐	
Study participant not re-consented or notified as required	☐	☐	
Consent form document for ancillary/ advanced imaging studies not executed properly	☐	☐	
Other (explain)	☐	☐	

Eligibility: Types of Deficiencies

Critical Deficiency	Yes	No	Comments
Any finding, identified before or during the review, that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines	☐	☐	
Major Deficiencies	**Yes**	**No**	**Comments**
Review of documentation available confirms 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: Study participant deemed ineligible based on laboratory/pathology reports following registration and changes based on central review of material.]	☐	☐	
Other (explain)	☐	☐	

Treatment: Types of Deficiencies

Critical Deficiencies	Yes	No	Comments
Any finding, identified before or during the review, that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines	☐	☐	
Incorrect agent/treatment/intervention used	☐	☐	
Major Deficiencies*	**Yes**	**No**	**Comments**
Additional agent/ treatment/ intervention used which is not permitted by protocol	☐	☐	
Dose deviations or incorrect calculations (error greater than +/- 10%)	☐	☐	
Dose modification/treatment interventions not per protocol; incorrectly calculated	☐	☐	
Treatment/intervention incorrect; or not administered correctly	☐	☐	
Timing and sequencing of treatment/ intervention not per protocol	☐	☐	
Unjustified delays in treatment/intervention	☐	☐	
Treatment/intervention not documented in source documentation; or not documented correctly[1]	☐	☐	
Treatment/intervention not reported; or not reported correctly on Case Report Forms[2]	☐	☐	
Other (explain)	☐	☐	

Note: Review of documentation for how and when treatment is administered should focus on the study/IND agents under investigation (i.e., start/stop times), unless otherwise specified in the protocol. Documentation of standard of care drug(s) should include total dose and start/stop dates for prolonged IV infusions ≥ 24 hours.

[1] Assigning a major or lesser is based on the extent of treatment data not documented; or not documented correctly.

[2] Assigning a major or lesser is based on the extent of not reporting treatment data; or not reporting correctly.

Disease Outcome/Response: Types of Deficiencies

Critical Deficiency	Yes	No	Comments
Any finding, identified before or during the review, that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines	☐	☐	
Major Deficiencies	**Yes**	**No**	**Comments**
Inaccurate documentation of initial sites of involvement	☐	☐	
Tumor measurements/evaluation of 'status of disease' not performed	☐	☐	
Tumor measurements/evaluation of 'status of disease' not documented in source documentation; or not documented correctly[3]	☐	☐	
Tumor measurements/evaluation of 'status of disease' not reported; or not reported correctly on Case Report Forms[4]	☐	☐	
Protocol-directed response criteria not followed	☐	☐	
Claimed response (i.e., partial response, complete response, stable) cannot be verified	☐	☐	
Failure to identify cancer progression or failure to detect cancer in adjuvant or prevention study	☐	☐	
Other (explain)	☐	☐	

[3] Assigning a major or lesser is based on the extent of disease outcome/response data not documented; or not documented correctly.

[4] Assigning a major or lesser is based on the extent of not reporting disease outcome/response data; or not reporting correctly.

Adverse Event: Types of Deficiencies

Critical Deficiency	Yes	No	Comments
Any finding, identified before or during the review, that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines	☐	☐	
Major Deficiencies	**Yes**	**No**	**Comments**
Failure to report or delayed reporting of an adverse event that would require filing an expedited Adverse Event report or reporting to the Group	☐	☐	
Grades, types, or dates/duration of serious adverse events inaccurately recorded			
Adverse events not assessed by the investigator in a timely manner per protocol	☐	☐	
Serious adverse events reported on Case Report Forms but cannot be substantiated in source documentation	☐	☐	
Routine adverse events not documented in source documentation; or not documented correctly[5]	☐	☐	
Adverse events not reported; or not reported correctly on Case Report Forms[6]	☐	☐	
Follow-up studies necessary to assess adverse events not performed	☐	☐	
Recurring under- or over-reporting of adverse events	☐	☐	
Other (explain)	☐	☐	

[5] Assigning a major or lesser is based on the extent of adverse event data not documented; or not documented correctly.

[6] Assigning a major or lesser is based on the extent of not reporting adverse event data; or not reporting correctly.

Correlative Studies, Tests, and Procedures: Types of Deficiencies

Critical Deficiency	**Yes**	**No**	**Comments**
Any finding, identified before or during the review, that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines	☐	☐	
Major Deficiencies	**Yes**	**No**	**Comments**
Protocol-specified diagnostic studies including baseline assessments not done, not reported or not documented	☐	☐	
Protocol-specified laboratory tests or other parameters not done, not reported or not documented	☐	☐	
Protocol-specified research (Quality of Life forms, collection of research samples, etc.)/ advanced imaging studies not done, not submitted or submitted inappropriately	☐	☐	
Other (explain)	☐	☐	

General Data Management Quality: Types of Deficiencies

Critical Deficiency	Yes	No	Comments
Any finding, identified before or during the review, that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines	☐	☐	
Major Deficiencies	**Yes**	**No**	**Comments**
Recurring missing documentation in the study participant records	☐	☐	
Frequent data inaccuracies in primary source documentation[7]; unredacted data[8]	☐	☐	
Significant number of errors in submitted data[7]; data cannot be verified	☐	☐	
Delinquent data submission[9]	☐	☐	
Other (explain)	☐	☐	

[7] Assigning a major or lesser deficiency is dependent on the number of instances or extent of inaccurate data or errors in submitted data.

[8] Assigning a major or lesser deficiency is dependent on the number of instances and type of unredacted data (e.g., security number, study participant name, etc.).

[9] Assigning a major or lesser deficiency is based on the following: extent of the delay, percentage or number of delinquent forms, type of form (baseline, treatment, follow-up, etc.), phase of the trial, and study participant on active treatment versus follow-up. Network Group/NCORP guidelines policies and decisions from the Data Quality Working Group should be taken into consideration.