ETCTN

Experimental Therapeutics Clinical Trials Network

Team Driven. Cancer Therapy Focused.

National Cancer Institute at the National Institutes of Health

NCI GUIDELINES FOR MONITORING THE EXPERIMENTAL THERAPEUTICS CLINICAL TRIALS NETWORK (ETCTN) AND OTHER EARLY PHASE CTMS-MONITORED STUDIES

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Effective: 15 August 2025

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LIST OF ACRONYMS

AO	Affiliated Organization
AP	Associate Plus
CAPA	Corrective and Preventative Action
CIRB	Central Institutional Review Board
CLASS	Compliance, Learning, and SOP Solutions
CRA	Clinical Research Associate
CRF	Case Report Form
CTEP	Cancer Therapy Evaluation Program
CTMB	Clinical Trials Monitoring Branch
CTMB-AIS	Clinical Trials Monitoring Branch - Automated Information System
CTMS	Clinical Trials Monitoring Service
CTSU	Cancer Trials Support Unit
DARF	Drug Accountability Record Form
DCTD	Division of Cancer Treatment and Diagnosis
DSMB	Data Safety Monitoring Board
DTL	Delegation of Tasks Log
EMR	Electronic Medical Record
ETCTN	Experimental Therapeutics Clinical Trials Network
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICC	Informed Consent Content
ICH	International Council for Harmonisation
IDB	Investigational Drug Branch
IDSC	Investigational Drug Steering Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IVR	Physician Investigator (as designated in RCR)
LAO	Lead Academic Organization
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NLF	No Longer Funded
NPIVR	Non-Physician Investigator (as designated in RCR)
OHRP	Office of Human Research Protections
PEP-CTN	Pediatric Early Phase - Clinical Trials Network
PII	Personally Identifiable Information
RCR	Registration and Credential Repository
TSDV	Targeted Source Data Verification

SECTION 1 BACKGROUND AND PURPOSE OF THE EXPERIMENTAL THERAPEUTICS CLINICAL TRIALS NETWORK AND OTHER EARLY PHASE CTMS-MONITORED STUDIES

1.1 Introduction

The National Cancer Institute (NCI) has formed partnerships in the pharmaceutical industry, academic institutions, and individual investigators for the early clinical evaluation of innovative cancer therapies. The Experimental Therapeutics Clinical Trials Network (ETCTN) was created to evaluate these therapies using a coordinated, collaborative, and inclusive team-based approach to early phase experimental therapeutic clinical trials.

Two programs run in sequence to manage a portfolio of partnerships between NCI and pharmaceutical collaborators:

- NExT is the program in the NCI Developmental Therapeutics Program that selects agents for NCI-sponsored pre-clinical and clinical development. NCI negotiates collaborative research agreements (CRADAs) with the pharma partners supplying the selected agents for CTEP-sponsored development.
- The ETCTN is the clinical trials network administered through the Investigational Drug Branch (IDB) that performs early phase clinical studies of these agents (NCI - Investigational New Drug [IND] agents).

The ETCTN is complementary to the National Clinical Trials Network (NCTN) which focuses on late phase development with an emphasis on Phase 3, disease-specific studies.

The ETCTN is funded through a UM1 cooperative agreement mechanism. NCI staff collaborate with pharma partners under terms set out in the CRADAs, and ETCTN investigators under the terms set out in their research awards, to achieve the ETCTN objectives of advancing the early clinical development of NCI IND agents. NCI provides centralized support, data management, trial registration and regulatory support activities for approved, early phase clinical trials. As a clinical trials network, ETCTN awardees could have the opportunity to enroll patients on to ETCTN studies, irrespective of the specific site leading the trial. ETCTN sites are responsible for monitoring and reporting safety information throughout the conduct of all ETCTN trials.

The objectives of the ETCTN are to:

- Conduct early clinical trials of NCI-IND agents in high priority areas of unmet medical needs
- Ensure efficient and timely activation and conduct of these clinical trials
- Integrate preclinical findings using clinical samples for biomarker analysis
- Promote collaboration among institutions and investigators
- Integrate molecular characterization, pharmacology, cancer biology, and imaging into clinical trials

Early phase clinical trials by nature involve agents where the toxicity profile may not be well defined. As a result, the NCI's approach to monitoring is a risk-based approach. Sites involved in the conduct of early phase clinical trials are academic medical centers with documented expertise in early therapeutics drug development. These institutions conducting

the clinical trials are referred to as Lead Academic Organizations (LAOs), integrated components (ICs) and affiliated organizations (AOs). Additionally, these sites are visited/monitored more frequently than later phase clinical trials.

1.2 Other Early Phase CTMS-Monitored Studies

NCI supports several additional clinical trial networks and programs that conduct studies involving Cancer Therapy Evaluation Program (CTEP) sponsored investigational agents. For early phase studies, the appropriate monitoring method is determined at the CTEP Protocol Review Committee (PRC) meetings. The decision is based on the known side effects, risk profile of the investigational agent, study population, and whether the investigational agent is used alone or in combination with other agents; or novel approaches. The PRC may decide to assign such studies for CTMS (Clinical Trials Monitoring Service) monitoring. This includes oversight of sites participating in the Pediatric Early Phase - Clinical Trials Network (PEP-CTN) monitored by the CTMS which also follows guidelines outlined in this document.

1.3 Overview of the Quality Assurance Program

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

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 monitoring procedures in place. Finally, a well designed and implemented quality assurance program should serve as a valuable educational vehicle. The monitoring team should use the opportunity to share with the local staff Good Clinical Practice (GCP) techniques, data management and quality control systems that have been successfully implemented at other institutions. The local staff should use the results of the monitoring visit/review to identify operational areas where improvements can be made.

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.

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 January 2025, FDA announced the adoption of "E6(R3) Guideline for Good Clinical." 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.

To assist CTEP in fulfilling its regulatory responsibilities as an IND sponsor and to assure protocol compliance and source data verification, resources for data management and monitoring will be provided under an NCI contract through the CTMS. The benefits of centralized data management includes increased efficiency by having a single entity responsible for study build using a core set of common electronic Case Report Forms (eCRFs) to be utilized via Medidata Rave, data management, quality assurance, adverse event analysis, and study report generation.

1.4 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 the Quality Assurrance (QA) program which includes monitoring and auditing. 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 monitoring program is to verify study data that could affect the interpretation of primary study endpoints. This is done through independent verification of study data with source documents. The purpose of the monitoring program is to:

- Document the accuracy of data submitted to CTMS and CTEP via the remote data capture system (Medidata Rave)
- Verify investigator compliance with protocol and regulatory requirements
- Provide an opportunity for the monitoring team to share with the institution staff, information concerning data quality, data management, and other aspects of quality assurance

For sites participating under the ETCTN program or when CTEP is supplying study drug for an early phase study, there are various methods of oversight that may be conducted depending on the phase of the study or when toxicities may be of concern. One or more types of visits may be conducted for oversight purposes to abide by the regulatory requirements, Good Clinical Practices (GCPs) and applicable Standard Operating Procedures (SOPs) generated by the CTMS and/or CTEP. The types of monitoring methods are listed under Section 3.1.

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

The Clinical Trials Monitoring Branch (CTMB) within CTEP has direct oversight responsibilities for the quality assurance and monitoring programs used by the ETCTN, as well as, the NCI NCTN. CTEP staff work closely with CTMS and the ETCTN to ensure the integrity of data and the protection of study participants participating in NCI-sponsored clinical trials.

2.1 Clinical Trials Monitoring Branch (CTMB)

The CTMB is responsible for establishing guidance for the conduct of quality assurance monitoring activities. CTMS under the direction and oversight of the CTMB is tasked with data management, study monitoring and auditing of the ETCTN and other early phase CTMS-monitored sites. These activities allow the CTMS to ensure the sites are complying with protocol and regulatory requirements.

The CTMB staff serves as an educational resource to the cancer research community on issues related to monitoring and regulatory requirements for conducting clinical trials. CTMB staff is responsible for overseeing the scheduling of all monitoring visits, for reviewing monitoring reports and findings, and for reviewing and assessing the adequacy and acceptability of Corrective and Preventative Action (CAPA) plans.

A monitoring visit consists of reviewing the below categories under the three components:

Regulatory Documenation Component:

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

Pharmacy Component:

- 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 misrepresenta-tion of data and/or disregard for regulatory safeguards for any component (Regulatory Documentation Review, Pharmacy Review and Participant Case Review) of a monitoring visit. 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 ETCTN Lead Academic Organization (LAO) or Lead Site of the study 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 institution's misconduct procedures in these matters. See 'Guidance for Allegations of Research Misconduct' under Appendix 1.

2.2 Quality Assurance

Quality assurance is the mechanism in which research clinical trials are conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), 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 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 study participant participation is meaningful. Accurate and timely knowledge of the progress of each study is critical to ensure oversight and appropriate monitoring of the clinical trials. This responsibility includes 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

Failure to comply with timely submission and query resolution may result in temporary suspension of site accrual and require submission of a CAPA plan.

2.2.2 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 is to document the accuracy of data submitted to CTMS and NCI/CTEP, to verify investigator compliance with the protocol and applicable regulatory requirements and guidelines. If necessary, provide institution staff with resources for a more thorough understanding of the regulatory requirements, good clinical practices (GCPs), data collection and data management practices.

2.3 Quality Control

Quality control is a complex topic spanning the entire range of diagnostic and therapeutic modalities. Generalization concerning optimal quality control is not possible. Cost and benefit are important factors in this assessment. The CTMS utilizes a variety of quality control procedures:

- Built-in edit checks within the Electronic Data Capture System
- Cross check of data between various electronic reporting systems
- Institution performance evaluations
- Special Response reviews to verify outcome data
- Committees for central review of major elements that impact on the outcome of clinical trials, (e.g., pathology, radiotherapy, surgery, and administration of study agents)
- Education and training which address data collection, data management, and overall data quality

2.4 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) has been established for the ETCTN for review of data for randomized Phase 2 studies activated on and after October 1, 2019.

The DSMB's role is to assist the NCI maintain the integrity of randomized phase 2 clinical trials by providing independent supervision of the efficacy and safety outcomes of the trial while blinding the study team and CTEP staff to efficacy data during the course of the trial. Specifically, trials placed under the DSMB are phase 2 trials where the comparison of clinical outcome of two or more treatment arms will be determined. The DSMB will review and evaluate the safety and efficacy data for study participants treated in the randomized phase II portion of the studies at protocol-specified time/data points, make recommendations on possible protocol modifications and other pertinent recommendations for the conduct of the studies and oversee the conduct of the trial's interim analyses to ensure the pre-specified trial algorithm (where applicable) is being implemented as designed.

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).

2.5 CTMB – Audit Information System (CTMB-AIS)

The CTMB has designed an information system which permits the on-line submission and collection of all data/findings from monitoring visit and audits. This includes scheduling and tracking monitoring visits and audits, transmission of final reports for monitoring and auditing, collection and tracking of follow-up responses to findings, and capturing

documentation for the review of preliminary reports, final 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/

2.6 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 monitoring activities include:

2.6.1 Site Monitoring/Auditing Portal

The Site Audit Portal (SAP) is an application in the monitoring and auditing area of the CTSU website that serves as the communications link between CTMB- AIS and Medidata Rave. The SAP seamlessly coordinates audit and monitoring 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/monitors 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 monitor/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

2.6.2 Monitoring/Auditing Participant Cases for Studies in Medidata Rave

TSDV is a tool in Rave utilized by monitor/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. 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: https://www.ctsu.org/master/simplepage.aspx?ckey=HELP-AUDITING-USINGVERIFICATION

2.6.3 Monitoring/Auditing Participant Cases Utilizing the Source Document Portal

The CTSU Source Document Portal (SDP) (https://sdp.ctsu.org) is an application which allows site staff to identify and upload source documents for activities such as central monitoring, remote monitoring visits/auditing, 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 monitoring visits/audits, 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 is conducted separately.

The following instructions on conducting remote monitoring visits/auditing using the SDP are available in both the SAP and the SDP (login required).
Remote/Off-site Visit Instructions for Monitors/Auditors:
https://www.ctsu.org/master/simplepage.aspx?ckey=HELP-REMOTE-AUDITING-AUDITORS#Introduction

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

All monitors including volunteer monitors 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 OVERSIGHT OF EARLY PHASE CLINICAL TRIALS

3.1 Types of Monitoring Methods

Prior to its activation, an early phase clinical trial is assigned one of following types of monitoring methods:

3.1.1 Comprehensive Monitoring Designation (CTMS-Monitored Trials)

For protocols assigned for CTMS Comprehensive Monitoring (Phase 1 and early Phase 2, or trials where toxicities may be of concern), data is to be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP).

3.1.2 Routine Monitoring Designation (CTMS-Monitored Trials)

For protocols assigned for CTMS Routine Monitoring, data is to be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP).

3.2 Frequency of CTMS Monitoring

3.2.1 Clinical Trials Designated for Comprehensive Monitoring

Generally, there are two Data Reviews and one Annual Review per year, per institution. Additional Data Reviews may be mandated based on the protocol. Due to frequency of visits, reaudits are not designated as a type of visit for the CTMS Comprehensive monitored studies (see Section 4.3).

3.2.2 Clinical Trials Designated for Routine Monitoring

Reviews are conducted on an 18 to 36 month basis. More frequent reviews may be conducted to consolidate CTMS routine with CTMS comprehensive reviews, if warranted by accrual. Additional visits may also occur if there are participant safety concerns, concerns related to data integrity or concerns with deliquent data submissions.

3.3 Oncology Automated Reporting System (previously referred to as Web Reporting)

CTEP Oncology Automated Reporting System (OARS) is a web-based tool to perform aggregated adverse event evaluations at any time. This tool assists with detecting patterns or other early signs of toxicity that may be of concern during the conduct of a clinical investigation. The tool also provides cummulative safety data on adverse events by grade and attribution. OARS provides information on accrual by site and treatment assignment as well as AEs occurring by treatment assignment. Investigational agent activity and overall study compliance by the institution are accessible. OARS is used by the Medical Officers in CTEP's Investigational Drug Branch and all Principal Investigators on NCI-sponsored ETCTN clinical trials and other early phase CTMS-monitored trials. Monthly attestation of review and monitoring is captured for review.

SECTION 4 PREPARING FOR THE MONITORING VISIT

The Clinical Trials Monitoring Service (CTMS) must carefully plan for monitoring visits months in advance.

4.1 Scheduling and Arranging the Monitoring Visit

Monitoring visits are scheduled in CTMB-AIS by CTMS. If there was a previous visit for the same institution in the CTMB-AIS, the prior visit must be considered complete (i.e., monitoring report and CAPA plan are reviewed and acknowledged by CTMB) before a new visit can be scheduled. The scheduling of a for-cause review may be scheduled at any time after consultation with CTMB.

The site to be monitored is usually contacted two months in advance of the visit to ensure sufficient notification for the site to prepare for the visit. The list of protocols and study participant cases selected for review are to be provided to the site one month in advance of the visit to allow the institution staff sufficient time to collect, prepare, assemble and label the required materials.

In the event of a for-cause visit, 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 Cancellation of a Monitoring Visit

If the CTMS needs to cancel a monitoring visit for unforeseen circumstances and it is within three business days prior to the audit date, they must notify the CTMB liaison.

4.3 Types of Monitoring Visits in CTMB-AIS

Monitoring visits may be scheduled in the CTMB-AIS as follows:

CTMS-Comprehensive Studies

- Data Reviews are scheduled for review of selected study participant cases only based on rate of enrollment
- Annual Reviews are scheduled for review of all components (Regulatory Documentation, Pharmacy, and Participant Cases) on an annual basis

CTMS-Routine Studies

- Routine Monitoring visits are conducted on an 18 to 36 months basis; more frequent reviews may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission

PEP-CTN Studies (see Section 1.2)

- PEP-CTN Audits are scheduled on an annual basis
- PEP-CTN Reaudits are scheduled when there are concerns based on the prior audit (by component) and oversight is required sooner than a regular audit

Off-cycle Reviews

Off-cycle reviews are scheduled for the below circumstances:

- More frequent reviewing 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 when there are allegations of possible scientific misconduct.

4.4 Location of the Monitoring Visit

For continued oversight of study participant safety, there may be circumstances when remote monitoring/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 monitoring, it may require extending the duration of the review (i.e., # of days).

When scheduling the monitoring visit, below are location options to select in the CTMB-AIS. The location of the visit is at the discretion of the CTMS in consultation with CTMB.

- On-Site Review: conducted at the institution being monitored
- Off-Site/Remote Review:
  - Review conducted at parent/affiliated site
  - Review conducted remotely at CTMS location

For on-site visits, institutions may require all entrants (including monitors) to display a government issued ID. For off-site/remote visits, institutions may require the monitor to display a government issued ID. However, Personally Identifiable Information (PII) should not be requested of the monitor. Examples of what should not be provided are birthdate, copy of monitor's driver's license, social security number, etc. Their IAM account number may be used in lieu of these identifiers. Furthermore, monitors 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 Monitoring

The CTMS selects the protocols and participant cases for review. While most cases will be selected from study participants accrued since the previous visit, any participant case can be reviewed, at any time.

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 monitoring visit/review 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 subject's information after the transfer takes place.

4.6 Selection of the Monitor or Monitoring Team

The monitor or monitoring team is composed of staff from the CTMS which may include Clinical Research Associates (CRAs), nurses, pharmacists and physicians. On occasion, the monitoring team may be augmented with staff from the NCI or extramural physicians who serve as volunteer monitors.

If there are particular concerns at an institution, selection of monitors to conduct for-cause (off-cycle review) may include input from the NCI. Representatives from other federal agencies or offices may also be invited to participate in the visit at the discretion of the NCI.

Monitors are selected based on monitoring experience, knowledge of the federal regulations, GCPs, NCI guidelines and other procedural documents. All monitors must be registered minimally as an Associate Plus (AP) level in the Registration and Credential Repository (RCR). All reviewers 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 CTMS staff when scheduling a monitoring visit to ensure there is no 'Conflict of Interest (COI)', or potential COI, between the monitor(s) and the institution being visited.

4.7 Institution Responsibilities

The Lead Academic Organization (LAO) or Lead Institution is responsible for ensuring that all relevant materials are available for review at the time of the visit. In most cases, monitoring visits will be conducted on-site. However, in some circumstances (low accrual, geographical proximity) institutions may be requested to send records to the LAO or Lead Institution for review. In this case, the LAO or Lead Site of the study must ensure institutions provide either the original study participant source documents or copies of the complete record. Alternatively, if reviews take place entirely off-site/remotely, records will need to be provided via an agreed upon mechanism(s).

The following records must be available the day of the visit 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 review
- 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 number. The CTMS should provide guidance on how preparation of documents for the visit should be done. If multiple institutions with the same parent are being reviewed 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 monitors, or computers with EMR access must be provided. A site staff member must be available to assist with navigating through the EMR system.

For reviews 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 Monitoring Withdrawn Institutions

If an institution is withdrawn, continued collection of follow-up data of enrolled study participants according to the study schedule is required. Therefore, these sites remain eligible for a monitoring visit. The selection of a withdrawn site for monitoring is at the discretion of the CTMB.

SECTION 5 CONDUCTING THE VISIT

During the visit, the monitors 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

In preparation for the monitoring visit, certain documents such as regulatory documents, informed consent documents, delegation of tasks logs (DTLs) and DARFs may be reviewed prior to the visit.

5.1 Assessing Findings from the Monitoring Visit

An annual visit 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 visit, each of the 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 visit. An inclusive and precise definition of what constitutes an 'unacceptable' finding is difficult to construct. Rather than developing an inclusive quantitative definition, the CTMS 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 the visit, resulting in a standard format for monitoring 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, Lead Academic Organization (LAO), and/or CTMS outside of a monitoring visit (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 Delegtion of Tasks Logs (DTLs) with no study participant enrollment are not required to be selected for review.

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

For each protocol selected for an review, 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 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 review, 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 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 posting on the CTSU website. 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.

Amendments that are editorial or administrative in nature are exempt from the 90 calendar day requirement, 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: 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 posting on the CTSU website.

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 a monitoring visit 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 IRB
- 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 Lead Academic Organization's (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 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 LAO specific document not submitted or not submitted timely to the LIRB
- Other (explain)

5.2.4 Review of the Informed Consent Content (ICC)

If the CIRB is utilized, a minimum of five (5) informed consent forms must be reviewed for content from the protocols selected for review. If there are more than ten (10) informed consent forms to review, then a random sample of at least 50% must be selected for review. Priority for selection must be given to registration trials. If deficiencies are noted, additional protocols may be reviewed for ICC at the monitor's discretion.

If the local IRB is utilized, an informed consent form must be reviewed for all protocols selected for review. The review of informed consent content is to ensure all elements are included per the federal regulations.

The following items must be reviewed for each CIRB and local IRB approved informed consent document selected:

- 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 forms, the only change allowed is the incorporation of the CIRB-approved boilerplate (local context)
- Multiple cumulative effects of lesser deficiencies 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 a monitoring visit 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 trials will be available on the 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
- 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 monitor will review a minimum of five (5) DTLs. If there are more than ten (10) DTLs, then a random sample of at least 50% must be selected for review. Priority for selection must be given to registration trials. The monitor will review the log to evaluate appropriate implementation and maintenance. If deficiencies are noted, additional DTLs may be reviewed at the monitor'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 a monitoring visit as defined under Section 5.1.

<u>Critical DTL Deficiency</u>

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

<u>Major DTL Deficiencies</u>

- 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)

<u>Lesser DTL Deficiencies</u>

- 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 monitoring visit for which a written and dated Corrective and Preventative Action (CAPA) plan exists and no further action is required by the CTMS, 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 monitoring report and CTMB must receive a copy of the CAPA plan at the time the monitoring 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 visit
- 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 CTMS. A copy of the CAPA plan/response, along with an assessment of adequacy by CTMS must be uploaded into the CTMB-AIS (for CTMB review) within 45 calendar days from the date the monitoring report is finalized, acknowledeged by CTMB and submitted to the site/recipient.

For PEP-CTN studies, a reaudit is mandatory for any component rated as Unacceptable. The reaudit should be done no later than a year after an Unacceptable rating.

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

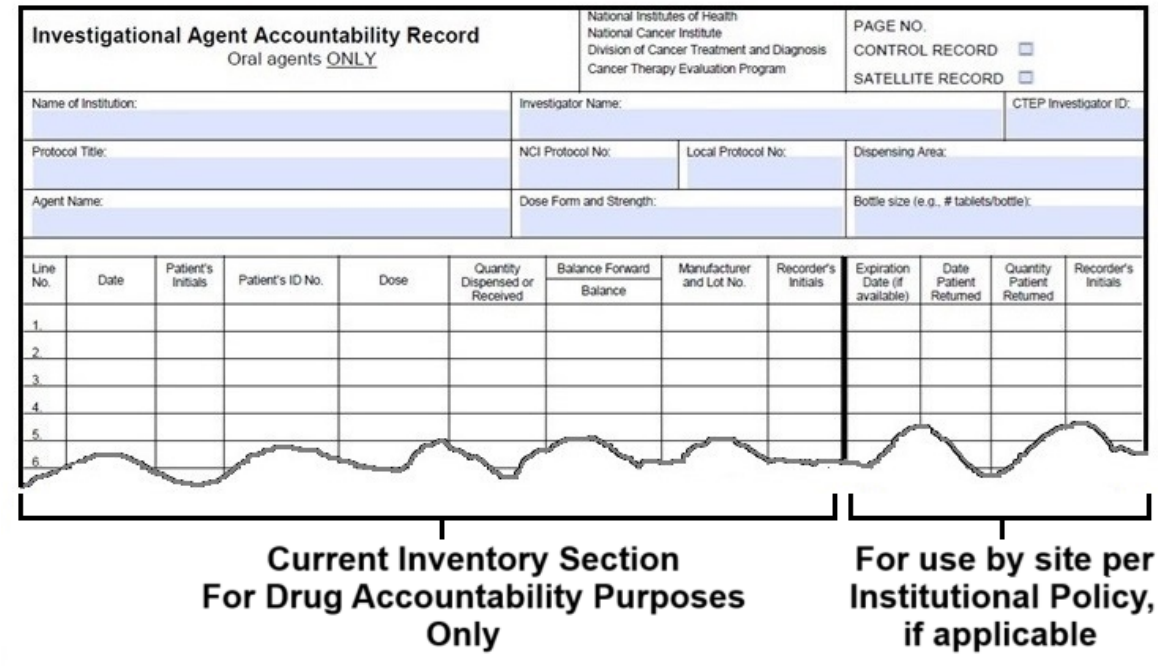
Agent accountability and storage procedures described in this section are required under federal regulations and NCI policy for NCI IND studies where agents are provided by CTEP. See CTEP policies under: https://dctd.cancer.gov/research/ctep-trials/for-sites/agent-management. Investigational agent accountability 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 monitoring purposes (see Figure 1).

Figure 1 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 agent 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 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/Radiopharmaceutical Therapy Agents/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 and radiopharmaceutical therapy agents are usually manufactured on-site or purchased from and distributed by commercial vendors. Even though these study agents are not usually distributed by the NCI, cancer control/imaging 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 visit. As a result, the CTMS monitors determine the rating based on identified non-compliance items. The monitor will review: drug accountability, proper use of NCI DARFs, adherance to appropriate storage and security measures and ensure required pharmacy procedures are being followed for NCI-sponsored and/or funded trials using study-supplied agents, including cancer control/prevention, imaging and radio-pharmaceutical therapy agents. DARFs are reviewed by protocol and study agent. When capturing the number of DARFs reviewed on the monitoring 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; including 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

Monitor 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 reviewed under the pharmacy component are 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 monitoring visit for which a written and dated CAPA plan exists and no further action is required by the CTMS, 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 non-compliance item(s) must still be cited and described in the monitoring report and CTMB must receive a copy of the CAPA plan at the time the monitoring 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
- 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'

If the Pharmacy 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 CTMS. A copy of the CAPA plan/response, along with an assessment of adequacy by CTMS must be uploaded into the CTMB-AIS (for CTMB review) by the CTMS within 45 calendar days from the date the monitoring report is finalized, acknowledged by CTMB and submitted to the site/recipient.

For PEP-CTN studies, a reaudit is mandatory for any component rated as Unacceptable. The reaudit should be done 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, it must be conducted on-site.

5.4 Review of Study Participant Cases

If records are not in English, then a qualified translator chosen by the monitor(s) or institution must be present.

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 a monitoring visit 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

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

- 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 of 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)

[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 – 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)

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 report
- 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)

[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.
[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.

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
- 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:

[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.

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 monitoring visit for which a written and dated CAPA plan exists and no further action is required by the CTMS, 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 monitoring report and CTMB must receive a copy of the CAPA plan at the time the monitoring 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 visit
- Multiple lesser deficiencies identified

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 CTMS. A copy of the CAPA plan/response must be uploaded into the CTMB-AIS (for CTMB review) by the CTMS within 45 calendar days from the date the monitoring report is finalized, acknowledged by CTMB and submitted to the site/recipient.

For PEP-CTN studies, a reaudit is mandatory for any component rated as Unacceptable. The reaudit should be done no later than a year after an Unacceptable rating or when sufficient new study participants have enrolled since the previous monitoring visit. If sufficient new study participants have not enrolled within a year from the previous visit, further discussion with CTMB is necessary prior requesting to postpone the reaudit.

5.5 Role of the Investigator During the Monitoring Visit

The Principal Investigator or designee and his/her research staff must be available throughout the monitoring visit to answer any questions and help the monitors 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 monitoring visit is conducted on-site or off-site. During the exit interview the monitor(s) will review with the institution, the preliminary findings, items reviewed just prior to the visit (if applicable), and discuss any recommendations from the monitor(s). If applicable, the monitors should mention the expectation of providing a CAPA plan/response to any findings and clarify the approximate timeframe of when the institution will need to submit their CAPA plan or follow-up response(s). The exit interview should be an opportunity for education, immediate dialogue, feedback, and clarification for both the institution staff and the monitors.

SECTION 6 REPORT OF FINDINGS AND POSSIBLE ACTIONS

6.1 Monitoring Report

6.1.1 Submission

Clinical Trials Monitoring Service (CTMS) generates and uploads the monitoring report into CTMB-AIS database for CTMB review. The report and a letter summarizing the findings is sent to the responsible Principal Investigator at the site by CTMS. The monitoring report must be submitted to the institution within 6 weeks of the last day of the monitoring visit.

6.1.2 Content

The following information should be included in the Monitoring Report:

6.1.2.1 General Information

- On the front page of the report, provide information specific to the institution such as number of cases reviewed, and average annual accrual
- List the names and titles of site staff involved or present during the monitoring visit
- List the names, titles and affiliation of each member of the monitoring team

6.1.2.2 Review of the Regulatory Documentation

- The CTMB-AIS will populate each protocol title for protocols reviewed 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)

6.1.2.3 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 monitoring 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.

- Provide an overall assessment for this component (Acceptable, Acceptable needs F/U, or Unacceptable)

6.1.2.4 Review of the Study Participant Cases

- For each category in the monitoring report, indicate if critical, major or lesser deficiency is being cited, and describe; otherwise indicate OK or Not Reviewed
- If category is designated as 'Not Reviewed' for a participant case selected for review (i.e., announced case), an explanation (rather than a deficiency description) must be summarized by participant ID and category in the monitoring 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 identifies 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)

6.1.2.5 Monitoring Procedures

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

6.1.2.6 General Comments

This section may be used to indicate if any additional data or correspondence was submitted to the CTMS by the institution following the visit.

6.1.2.7 Exit Interview

Indicate who was present and summarize discussion of the findings, clarifications requested by the institution staff, and any recommendations made by the monitor(s). If any portion of the visit was conducted off-site (in addition to Centralized Monitoring), the findings of that review should be discussed at the exit interview.

6.2 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 responses are uploaded into the CTMB-AIS within 45 calendar days from the date the final audit report is uploaded in the CTMB-AIS by the CTMS. Other pertinent correspondence or documentation related to the monitoring visit may also be uploaded. The CAPA plan must include a cover letter from the CTMS stating that the CTMS 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 monitoring visit date.

Other pertinent correspondence or documentation related to the audit may also be uploaded. It must be uploaded to the Document Management tab in the CTMB-AIS by corresponding CTEP Site Code and audit date.

6.3 Timeline for Uploading Monitoring Reports and CAPA Plans into CTMB-AIS

Submission Type	Due Date to Upload into CTMB-AIS
Monitoring Report	Within 15 business days from the last day of the monitoring visit
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 CTMS, therefore the site should provide their CAPA plan to the CTMS sooner, per requirements set by the CTMS.

6.4 Possible Actions Due to Findings and/or Delinquent Data

Data are to be submitted via Medidata Rave to CTMS every two weeks (e.g., Treatment, Adverse Event, Follow-up). The data will undergo a centralized clinical Quality Assurance review at the CTMS and queries will be issued by CTMS staff directly within Rave. The queries will appear on a Task Summary Tab within Medidata Rave for the CRA/site staff at the site to resolve.

All deficiencies identified during a monitoring visit need to be addressed in writing by the institution. It must consist of actions to be taken that address each concern and action to be taken in order to prevent future occurrences.

6.4.1 Probation of Principal Investigator

If the concerns appear to be investigator specific, mentoring and retraining will be the primary focus, if appropriate. After further evaluation by CTMB in collaboration with the NCI ETCTN Program Director or the Investigational Drug Branch (IDB) Branch Chief, the investigator may be taken off probation if documentation exists that support the specific actions were taken.

Repeated and deliberate failure to comply with these monitoring guidelines will result in one or more of the following actions:

- Replace Principal Investigator
- Re-analyze or retract published results
- Request a formal investigation by the Office of Research Integrity
- Revoke the Investigator's Form FDA 1572
- Privileges in participating on any NCI sponsored clinical study will be terminated

6.4.2 Probation of Participating Institutions

If a participating site is deemed Unacceptable for the same component on two consecutive visits, the institution will be placed on probation. During the probationary period, accrual will be closely monitored with increased utilization of quality control procedures at the time of study participant registration and timely review of data submission.

6.4.3 Suspension of Participating Institutions

If delinquent data issues persist and are not resolved, registration privileges will be suspended until all delinquent data are submitted.

If an institution fails to provide a CAPA plan for one or more components rated as Acceptable needs Follow-up or Unacceptable within the required 45 calendar days, the following actions will be imposed:

- A written notice will be provided by CTMB/CTMS to the Lead Principal Investigator stating that the CAPA plan/response is overdue and a five business day grace period will be granted.
- Follow-up or a CAPA plan is not received within the five business day grace period, new study participant registration privileges at the site will be immediately suspended.
- If the institution is under the responsibility of a LAO or Lead Site of the study, new study participant registrations will be suspended from both the institution and the LAO or Lead Site of the study.
- If follow-up or a CAPA plan is not submitted during the five business day grace period, a written explanation from the Principal Investigator detailing the reason for the delay must be included. Suspension of new study participant

registrations will not be lifted until the site submits the CAPA plan to the CTMB/CTMS, and is reviewed and approved by CTMB. Failure to submit a timely CAPA plan may result in permanent termination from participation in the ETCTN and/or other NCI programs.

6.4.4 Withdrawal of a Participating Institution

If improved performance is not documented after subsequent visits, the site may be withdrawn. Any such action will be done in consultation with CTMB and the NCI ETCTN Program Director or the IDB Branch Chief. A for-cause (i.e., off-cycle review) 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)."

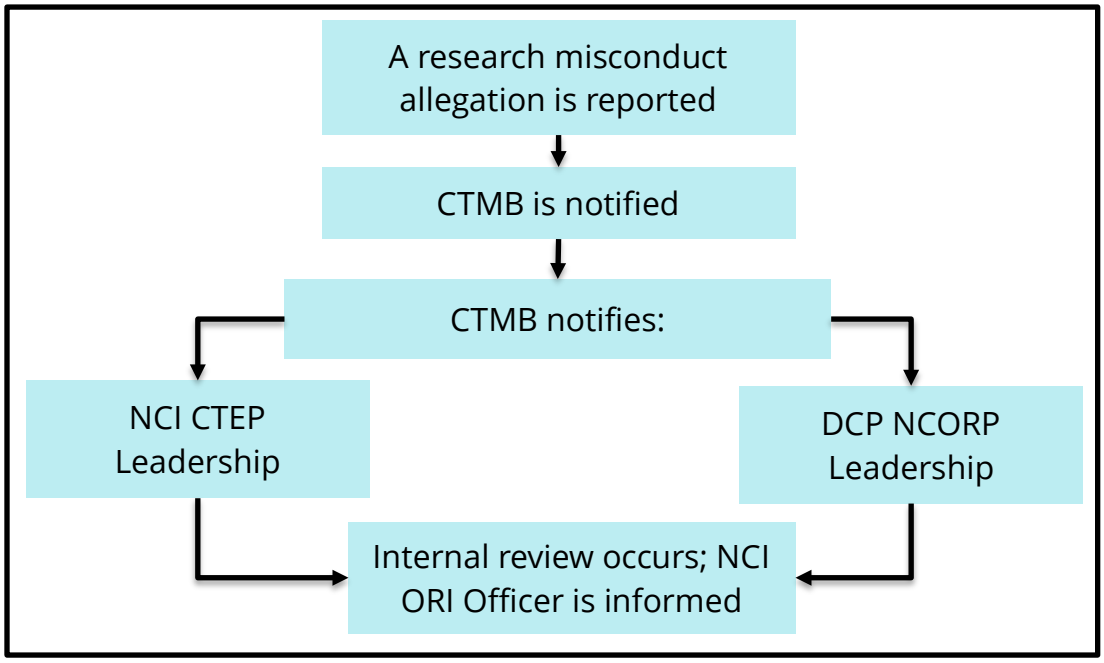
D. **Plagiarism** means the "appropriation of another person's ideas, processes, results, or words without giving credit (42 CFR 93.103)."

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	☐	☐	
CIRB 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)	☐	☐	
CIRB 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	☐	☐	
LIRB 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	☐	☐	

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)	☐	☐	
LIRB 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	☐	☐	
ICC 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	☐	☐	

ICC 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	☐	☐	

ICC Major Deficiencies (cont…)	Yes	No	Comments
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)	☐	☐	
ICC 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	☐	☐	
DTL 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)	☐	☐	
DTL 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 sdverse 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.