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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Current Version: **24 July 2018**
Prior Version: March 2014
Original - January 2013

Approving Officials:

CTMB Chief	Date
	7/26/2018
ETCTN Program Director	Date
	07.26.2018
IDB Chief	Date
	7/26/18
CTEP Associate Director	Date
	7/26/18

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List of Acronyms

AE	Adverse Event
AO	Affiliated Organization
AP	Associate Plus
CAPA	Corrective and Preventative Action
CDUS	Clinical Data Update System
CIRB	Central Institutional Review Board
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
DO/DR	Disease Outcome/Response
DQ	Data Quality
DTL	Delegation of Tasks Log
E	Eligibility
EDDOP	Early Drug Development Opportunity Program
ETCTN	Experiemental Therapeutics Clinical Trials Network
GCP	Good Clinical Practice
IC	Informed Consent (process)
ICC	Informed Consent Content
IDB	Investigational Drug Branch
IDSC	Investigational Drug Steering Committee
IND	Investigational New Drug
FDA	Food and Drug Administration
IRB	Institutional Review Board
LAO	Lead Academic Organization
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NExT	NCI - Invesigational New Drug [IND] agents
NIH	National Institutes of Health
OHRP	Office of Human Research Protections
PMB	Pharmaceutical Management Branch
PRC	Protocol Review Committee
QA	Quality Assurance
QC	Quality Control
RCR	Registration and Credential Repository
Rx	Treatment
SOP	Standard Operating Procedure
TSDV	Target Source Data Verification

List of Definitions

Annual Site Visit is conducted by CTMS approximately one year subsequent to the Initial Site Visit and annual thereafter, as long as pertinent Phase 1, selected Phase 1/2 and Phase 2 studies are ongoing. The purpose is to review regulatory documentation; pharmacy operations, drug accountability, storage and security procedures; and review and verify source documentation of patient case data (Data Review) of the study participants enrolled onto CTMS monitored clinical studies.

Comprehensive Monitoring is conducted of Phase 1 and some early Phase 2 studies assigned for CTMS Comprehensive Monitoring. Review of source documentation and procedures are conducted via an Annual Site Visit and two Data Review/Data Audit visits within the same year depending on patient enrollment.

Data Review/Data Audit is conducted twice a year (in addition to the Annual Site Visit) to assess the availability and organization of source documentation, to verify submitted data and check for accuracy, to review the informed consent forms and to review adverse events to ensure Expedited Adverse Event Report Requirements are being met. In addition, copies of the Drug Accountability Records and patient registration lists will be retrieved and reviewed for deficiencies.

Off-cycle audit is a special audit used for circumstances such as 'for cause'. These types of audits may be warranted when there are significant irregularities found through quality control procedures or when allegations of possible scientific misconduct are made. It is the responsibility of the organization or Clinical Investigator to immediately notify CTMB upon learning of any significant irregularities or allegations related to scientific misconduct by a staff member or site participating in their research program.

Off-site review under certain circumstances there may be a limited review of data/source documentation at an affiliated site or at CTMS headquarters. This type of review can be done by having documentation either mailed or sent by email to CTMS for review.

Response Audit is a special audit that may be may be conducted when there are initial promising findings. These types of audits may include independent radiologic review for confirmation of disease response. CTEP or a sponsor may request a 'response audit' and CTEP determines if this type of audit is warranted.

Routine Monitoring is conducted for Phase 2 studies usually assigned for CTMS Routine Monitoring. A review of all components (Regulatory Documentation, Pharmacy and Patient Cases) is performed. Reviews are conducted on a 18 to 36 month basis. More frequent visits may be conducted if warranted by accrual, due to safety concerns or concerns related to data quality or timely submission.

WebReporting can be done at any time during the study to perform aggregated adverse event evaluations to assist with detecting patterns or other early signs of toxicty that may be of concern. It is a tool used by the Medical Officers in CTEP and clinical investigators participating on NCI-sponosered ETCTN clinical trials.

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 pharmaceuctial collaborators:

- NExT is the program in the NCI Developmental Therapeutics Program that selects agents for NCI-sponsored pre-clinical and clinical development.

- The ETCTN is the clinical trials network administered through the Investigational Drug Branch (IDB) that performs early phase clinical studies of the agents that are approved through NExT (NCI - Invesigational 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. It accomplishes its objectives, with oversight by the Investigational Drug Steering Committee (IDSC), by forming multi-site, multi-disciplinary project teams to define drug development for NCI Investigational New Drug (IND) agents. ETCTN investigators collborate with NCI staff to achieve ETCTN objectives. 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 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.

Limited ETCTN participation has also been extended to NCI-designated Cancer Centers not affiliated with the ETCTN that successfuly competed for Early Drug Development Opportunity Program (EDDOP) supplements to their Cancer Center Support Grants (P30). ETCTN participation can also be extended to non-member collaborator sites on a case-by-case basis.

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.

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 on-site 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 on-site visit 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. While they were never finalized, the proposed regulations, which called for an annual site visit to each investigator, had a profound effect on the sponsors of clinical trials of investigational agents in the United States. Most sponsors changed their practices to conform to these proposals.

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 DCTD to maintain a monitoring program. The Clinical Trials Monitoring Branch (CTMB) of the CTEP in the DCTD, provides direct oversight of the Quality Assurrance program which includes monitoring and auditing.

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) or in some circumstances, summary of the clinical data is submitted to CTEP via the CDUS (see http://ctep.cancer.gov/protocolDevelopment/electronic_applications/cdus.htm).
- 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 requirments, Good Clinical Practices (GCPs) and applicable Standard Operating Procedures (SOPs) generated by the CTMS and/or CTEP. These types are listed under Section 3.0.

SECTION 2 ROLES AND RESPONSIBILITIES FOR THE CONDUCT OF THE QUALITY CONTROL AND QUALITY ASSURANCE 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 patient/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 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 for reviewing and assessing the adequacy of the Corrective and Preventative Action (CAPA) plans.

Any data irregularities identified through quality control procedures or through the monitoring program that raise any suspicion of intentional misrepresentation of data must be immediately reported to CTMB, CTEP, NCI. The CTMB must be notified immediately by telephone (240) 276-6545 of any findings suspicious and/or suggestive of intentional misrepresentation of data and/or disregard for regulatory safeguards for any of the three components (regulatory documentation, pharmacy and patient cases) 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 when they learn of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their research program. It should be emphasized the irregularity/misrepresentation of data does not need to be proven. A reasonable level of suspicion suffices for CTEP notification. It is essential that involved individual(s) and/or institutions follow their own institution's misconduct procedures in these matters.

2.2 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, (eg, pathology, radiotherapy, surgery, and administration of study agents)
- Educational functions which address data collection, data management, and overall data quality

2.3 Quality Assurance

Quality assurance is the mechanism in which research clinical trials are conducted, recorded, and reported in accordance with the protocol, 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 patients/study participants on a trial.

2.3.1 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 patients/study participants and optimal conduct of the research such that the patients' participation is meaningful. Accurate and timely knowledge of the progress of each study is critical to ensure oversight and appropriate monitoring of the clinical trials. This responsibility includes the following elements:

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

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

2.3.2 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, and the dates recorded, analyzed and accurately reported according to the protocol, sponsor's SOPs, GCP, and the applicable regulatory requirements. It is a snapshot in time, commonly an on-site process, and consists of reviewing a subset of patient/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, applicable regulatory requirements, and adherence to the policies and procedures of each ETCTN LAO and, if necessary provide institution staff with resources for a more thorough understanding of the regulatory requirements, GCPs, data collection and data management practices.

2.3.3 CTMB – Audit Information System (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 providing a username and password at: https://ctepcore.nci.nih.gov/CTMBWeb/.

SECTION 3 Oversight of Early Phase Clinical Trials

3.1 Types of Monitoring Methods

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

3.1.1 Comprehensive Monitoring (CTMS-monitored Trials)

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). Information on CTMS reporting is available at http://theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11.

3.1.2 Routine Monitoring (CTMS-monitored Trials)

Protocols assigned for CTMS Routine Monitoring (Phase 2), data is to be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11.

3.2 Types of Visits and Frequency

3.2.1 Clinical Trials Designated for Comprehensive Monitoring

- Data Review - review of selected patient cases (based on enrollment)
- Annual Site Visit - review of all components (Regulatory Documentation, Pharmacy, and Patient Cases)

Generally, there are two Data Review and one Annual Site Visit per year, per institution. Additional Data Reviews may be mandated based on the protocol.

3.2.2 Clinical Trials Designated for Routine Monitoring

Review of these clinical trials usually occur less often but on a regular basis.

- Routine Visit – review of all components (Regulatory Documentation, Pharmacy and Patient Cases). Depending on the extent or circumstances of the monitoring, the review may be conducted on-site or off-site.
- Frequency – reviews are conducted on a 18 to 36 month basis. More frequent visits may be conducted to consolidate CTMS routine visits with CTMS comprehensive visits, if warranted by accrual. Additional visits may occur if there are patient safety concerns, or concerns related to data quality or timely submission.

3.3 Clinical Trials Designated for CDUS Monitoring *(Legacy Studies)*

Protocols assigned to be Clinical Data Update System (CDUS) monitored consist of cumulative protocol and patient data collections. These data are submitted by the sites electronically to CTEP on a quarterly basis. Limited data is made available for viewing via internal systems. However, for reviewing a more complete dataset, the CDUS data is uploaded into Web Reporting (see Section 3.4 for more information on Web Reporting).

Note: CDUS monitoring method does not apply to trials in Rave or using TSDV (Targeted Source Data Verification).

When a site undergoes a CTMS monitoring visit for a routine visit (as described in Sections 3.2.1 and 3.2.2), that also has CDUS-monitored trials, patient cases from these CDUS monitored trials may be selected for review during the same visit. Review of these patient cases are conducted in the same manner as the patient cases selected for review for the CTMS monitored trials.

During routine and comprehensive monitoring annual visits, the CTMS monitor meets with the lead Clinical Investigator to review their responsibilities and obtain an update on the progress of the clinical trial. The CTMS monitor determines whether the clinical trial-related activities were conducted according to the protocol, GCPs, and applicable regulatory requirements.

If an institution is withdrawn, continued collection of follow-up data of enrolled patient/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.

3.4 CTEP Web Reporting

WebReporting is a web-based tool to perform aggregated adverse event evaluations at any time during the conduct of a clinical investigation. The tool provides cummulative safety data on adverse events by grade and attribution. WebReporting provides information on accrual by site and treatment assignment as well as AEs occuring by treatment assignment. Investigational agent activity and overall study compliance by the institution are accessable. This tool is used by the Medical Officers in CTEP's Investigational Drug Branch and all clinical investigators on NCI-sponsored ETCTN clinical trials. Monthly attestation of review and monitoring is captured for review.

3.5 Special Audits

A special audit can be a response audit or an off-cycle audit.

A response audit may be conducted when there are initial promising findings. Such audits may include independent radiologic review for confirmaiton of disease response. CTEP or a sponsor may request a 'response audit' and CTEP determines if this type of audit is warranted.

An 'off-cycle' audit (for cause) may be warranted when there are significant irregularities found through quality control procedures or when allegations of possible scientific misconduct are communicated. It is the responsibility of the organization or Clinical Investigator to immediately notify CTMB upon learning of any significant irregularities or allegations related to scientific misconduct by a staff member or site participating in their research program.

CTMB may coordinate or request that the CTMS coordinate a special audit. Selection of auditors to conduct these types of audits will be made by the NCI. Other federal agencies or offices may be invited to participate in a special audit at the discretion of the NCI.

3.6 Monitioring Withdrawn Institutions

If an institution is withdrawn, continued collection of follow-up data of enrolled patient/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 4 PREPARING FOR THE MONITORING VISIT

This section discusses the timing of notifying a site of a monitoring visit, selecting the monitoring team, and selecting the protocols and patient cases for review.

4.1 Arranging the Monitoring Visit

A planned site visit is entered into the Clinical Trials Monitoring Branch-Audit Information System (CTMB-AIS) by CTMS when the previous visit for the same institution is considered complete (i.e., monitoring report and CAPA plan are reviewed and acknowledged by 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 site is provided with a list of protocols and patient cases selected for review one month in advance of the visit to allow the institution staff sufficient time to prepare, assemble and label the required materials. In the event of a 'for cause' visit, advance notice for conducting an on-site visit and the selection of protocols and/or patient cases to be reviewed may be limited due to the nature of the visit.

4.2 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.

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).

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(s) being visited.

4.3 Selection of Protocols and Patient Cases for Review

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

In the event of a patient case transfer to another site (another CTEP Code), it is the 'date of transfer' that the responsibility shifts to the new Clinical Investigator/institution where the patient case resides.

4.4 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 patient/study participant source documents or copies of the complete record. This includes radiology imaging reports, research notes, regulatory documents, NCI DARFs, informed consent documents, Delegation of Tasks Log (DTL) and other relevant information. It is recommended that staff from other institutuions that are familiar with the submitted records be present.

To facilitate the review process, it is advisable that institution staff label all documents such as hospital/clinic records, research notes, on-study labs, scans and imaging reports, consent forms, etc. If the institution utilizes electronic medical records (EMRs), the records may be printed for viewing by the monitors, or computers with EMR access must be provided. A staff member must be present to assist with navigating through the system, if necessary.

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

In preparation for the monitoring visit, certain documents such as Regulatory Documentation and DARFs may be reviewed prior to an on-site visit.

5.1 Assessing Findings from the Monitoring Visit

A visit consists of reviewing and evaluating: (1) regulatory documentation including conformance to IRB regulations and guidelines, informed consent requirements, and maintenance of a delegation log (if applicable) (2) pharmacy operations and use of NCI DARFs, or NCI approved drug accountability logs, and (3) individual patient cases. During the visit, each of the three components will be independently 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 patient/study participant and/or the quality and integrity of the data; includes serious violation of safeguards in place to ensure safety of a patient/study participant and/or manipulation and intentional misrepresentation of data (see http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500178525.pdf).

Major Deficiency

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

Lesser Deficiency

Finding does not have significant impact on the outcome or interpretation of the study and is not described above as a major deficiency. An unacceptable frequency/quantity of lesser deficiencies should be treated as a major deficiency when determining the final assessment of a component.

5.2 Review of the Regulatory Documentation

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

For each protocol selected for an 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 patient registration
- Unanticipated problems, serious non-compliance and/or continuing non-compliance problems as defined by Office of Human Research Protections (OHRP) not reported (see https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html)

5.2.2 Review of the Local IRB - IRB of Record

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

- Documentation of full-board initial IRB approval
- Documentation of full-board IRB continuing review on at least an annual basis
- Documentation of timely IRB approval (or disapproval) of protocol amendments that affect more than minimal risk
- Documentation of IRB approval or reapproval prior to patient registration
- Documentation of expedited review done appropriately
- Documentation of internal safety reports submitted timely
- Documentation of external safety reports (when required by the local IRB) submitted timely

The following descriptive terms should be used in assessing compliance:

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

Amendments (addendums or updates) must be approved (or disapproved) by the IRB of record within 90 days of posting on the CTSU website. Amendments that are editorial or administrative in nature are exempt from the 90 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 as defined by the OHRP (see OHRP guidance: https://www.hhs.gov/ohrp/sites/default/files/ohrp/policy/advevntguid.pdf) including external safety reports must be reported to the IRB within 90 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 CIRB/IRB compliance. This list does not represent an all-inclusive list of possible deficiencies that may be found during a monitoring visit.

5.2.3.1 CIRB – IRB of Record

Critical CIRB Deficiency

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

Major CIRB Deficiencies

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

Lesser CIRB Deficiencies

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

5.2.3.2 Local IRB – IRB of Record

Critical IRB Deficiency

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

Major IRB Deficiencies

- Initial approval by expedited review instead of full-board review
- Expedited reapproval for situations other than approved exceptions
- Registration and/or treatment of patient prior to full IRB approval
- Reapproval delayed greater than 30 days, but less than one year
- Registration of patient on protocol during a period of delayed reapproval or during a temporary suspension (i.e., Request for Rapid Amendment)
- Missing reapproval

- Expired reapproval
- Internal reportable adverse events reported late or not reported to the IRB
- Lack of documentation of IRB approval of a protocol amendment that affects more than minimal risk or IRB approval is greater than 90 days after Lead Academic Organization (LAO); this includes a 'Request for Rapid Amendment (RRA)' resulting from an Action Letter indicating temporary suspension of accrual with expedited review permitted
- Failure to submit or submitted after 90 days, any reportable external safety report to the IRB that is considered an unanticipated problem as defined by OHRP, unless there is a local IRB policy that does not mandate reporting of external safety reports Unanticipated problems as defined by the OHRP (see https://www.hhs.gov/ohrp/sites/default/files/ohrp/policy/advevntguid.pdf)
- Other (explain)

Lesser IRB Deficiencies

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

5.2.4 Review of the Informed Consent Content (ICC)

The content of the local informed consent documents for at least three protocols (if there are three or more protocols) must be reviewed for content regardless of patient registration/enrollment to ensure the informed consent forms contain the elements required by federal regulations.

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.

Critical ICC Deficiency

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

Major ICC deficiencies

- Missing any of the following statements or language specific to the elements required per the federal regulations, when appropriate:
  - Involves research, purposes; duration of participation; description of procedures; identification of experimental procedures
  - Description of foreseeable risks or discomforts
  - Description of any benefits to subjects or others
  - Disclosure of alternative procedures or treatments
  - Description of the extent of confidentiality of records
  - Explanation regarding compensation and/or whether treatments are available if injury occurs, including who to contact if injury occurs.
  - Explanation of whom to contact for answers to pertinent questions about the research and whom to contact for questions related to research subject's rights
  - Statement that participation is voluntary; refusal to participate involves no penalty or loss of benefits; subject may discontinue participation at any time
  - Unforeseeable risks to subject, embryo or fetus
  - Statement that circumstances in which subject's participation may be terminated by the investigator without subject consent
  - Statement of additional costs to subject that may result from participation in the study
  - Statement of consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
  - Statement that significant new findings which may be related to subject's willingness to continue participation will be provided to subject
  - Disclosure of approximate number of subjects involved in the study
  - Statement: "A description of this clinical 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 local IRB, including changes to questions that do not match the model consent form
- Multiple cumulative effect of lesser deficiencies for a given consent form

- Other (explain)

Lesser ICC Deficiencies

- Failure to have the informed consent document (after CIRB amendment approval) locally implemented within 30 days of notification (posted on the CTSU website)
- Language/text is missing or added that is administrative or editorial in nature (e.g., rephrasing a sentence/section to add clarity, reformatting the document and/or changes made related to contact information are examples of an editorial or administrative change)
- IRB approved informed consent document with incorrect version date
- Other (explain)

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

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

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

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

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

Critical DTL Deficiency

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

Major DTL Deficiencies

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

Lesser DTL Deficiencies

- Other (explain)

5.2.6 Assessment of the Regulatory Documentation Review

Each item reviewed as part of the visit can be found to be Critical, Major, Lesser, OK, or Not Reviewed. If an item that was planned to be reviewed as part of the visit was not reviewed for any reason (e.g., insufficient time for monitor to review, etc.), this must be explained in the Regulatory Documentation section of the monitoring report.

One of the following designations must be used when assigning an assessment for the review of the Regulatory Documentation component:

Acceptable

- No deficiencies identified and no follow-up being requested
- Few lesser deficiencies identified
- Any major deficiency identified during the monitoring visit 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 clinical investigator because no similar deficiency has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a deficiency is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, CTMB must receive a copy of the CAPA plan at the time the monitoring report is uploaded into the CTMB-AIS or by the date follow-up is due.

Acceptable Needs Follow-up

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

Unacceptable

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

If the Regulatory Documentation Review is rated as Acceptable Needs Follow-up or Unacceptable, the institution will be required to submit a written response and/or CAPA plan to the CTMS. A copy of the written CAPA plan/response must be uploaded into the CTMB-AIS (for CTMB review) by the CTMS. The CAPA plan/response must be available for review by CTMB within 45 calendar days from the date the monitoring report was completed and uploaded into the CTMB-AIS. A re-visit is mandatory if an institution continues to participate in the ETCTN (or other Early Phase Program) for any component rated as Unacceptable. A re-visit should be done no later than a year after an Unacceptable rating.

5.3 Review of Accountability of Investigational Agents and Pharmacy Operations

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

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

5.3.1 Control Dispensing Area/Pharmacy

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

The Control Dispensing Area is responsible for:

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

5.3.2 Satellite Dispensing Area/Pharmacy

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

The Satellite Dispensing Area is responsible for:

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

5.3.3 Imaging Studies/Cancer Control

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

5.3.4 Guidelines for Conducting the Pharmacy Review

There are challenges with categorizing a deficiency as critical, major or lesser for the pharmacy component of the 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 required pharmacy procedures to ensure they are being followed for NCI-sponsored and/or funded trials using study-supplied agents, including cancer control/ prevention and imaging 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 and imaging agents may be supplied by other vendors.

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

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

NCI DARFs COMPLETELY AND CORRECTLY FILLED OUT

Compliance

- Maintain complete, accurate and timely records of agent disposition of all study-supplied agents using NCI Investigational Agent (Drug) Accountability Record Forms (DARFs)
- Oral study-supplied agents are documented on the Oral DARF
- NCI DARFs are utilized to track cancer control/imaging study-supplied agents, or other accountability log captures the same information as NCI DARF
- Paper and/or electronic DARFs (eDARFs) contains all required information; paper printout of eDARF is identical to NCI DARF
- Corrections on DARFs are lined out, initialed and dated with no erasures and whiteouts; corrections on eDARFs are documented
- Agent was dispensed to a registered patient/study participant and documented on the appropriate DARF
- Appropriate documentation of multi-dose vial agent dispensing to multiple patients/study participants on separate lines of the DARF
- Patient/study participant returns of oral study-supplied agents are documented on the oral DARF
- Patient/study participant returns of non-oral, non-patient-specific agent supplies are *not* documented on the DARF
- Patient/study participant returns of non-oral, patient-specific agent supplies are documented on the DARF
- [For NCI-sponsored Study] An institution or centralized pharmacy service (Control) may receive NCI-supplied study agent directly from NCI and is permitted to deliver (transport, not re-ship or repackage) NCI-supplied study agent to the institution's Satellite Dispensing Areas
- [For NCI-sponsored Study] Study Agent has been transferred to an authorized investigator and/or protocol with CTEP approval

Non-Compliance

- NCI DARF not maintained or not maintained completely, accurately or on a timely basis
- Oral NCI DARF not maintained for oral study-supplied agents, not maintained completely, accurately or on a timely basis
- Lack of a DARF(s) to verify cancer control/imaging study supplied agents are administered to patients/study participants
- Paper and/or electronic DARFs (eDARFs) do not contain all information or are not completed as required; paper printout of eDARF is not identical to the NCI DARF
- Erasures or "whiteouts" on paper DARF
- Corrections are not lined out, initialed and dated on paper DARF
- Corrections are not appropriately documented on eDARF in electronic inventory system
- Study-supplied agent dispensed to a registered patient/study participant and not recorded on the appropriate DARF
- Multiple dose vials not used for more than one patient/study participant and/or doses not documented correctly on separate lines of the DARF
- Dispensing of study-supplied agent to a non-registered patient/study participant recorded on the DARF
- Patient/study participant returns of oral study-supplied study agents *not* documented on the Oral DARF
- Patient/study participant returns of non-oral, non-patient-specific agent supplies are documented on the DARF
- Patient/study participant returns of non-oral, patient-specific agent supplies are not documented on the DARF
- [For NCI-sponsored Study] NCI-supplied study agents are repackaged and/or reshipped to other investigators, patients, or locations by mail or express carrier
- [For NCI-sponsored Study] Study agent has been transferred to an unauthorized investigator or protocol without CTEP approval

DARFs PROTOCOL AND STUDY AGENT SPECIFIC

Compliance

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

Non-Compliance

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

SATELLITE RECORDS OF DISPENSING AREA

Compliance

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

Non-Compliance

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

NCI DARFs KEPT AS PRIMARY TRANSACTION RECORD

Compliance

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

Non-Compliance

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

RETURN OF STUDY AGENT [NCI-sponsored studies]

Compliance

- Return of unused/un-dispensed NCI-supplied study agent to NCI or locally destroyed with NCI authorization when notified study agent is no longer suitable for clinical use; Return Form or local destruction authorization is maintained
- Return of unused/un-dispensed NCI-supplied study agent to NCI or locally destroyed with NCI authorization or transferred to another NCI protocol (with NCI approval), when studies are complete or discontinued. Return Form or local destruction authorization is maintained
- NCI-supplied study agent is returned, transferred or locally destroyed within 90 days of study completion, when requested by the NCI, or when patients/study participants are in follow-up and NCI-supplied agent is not being administered
- [For Non-NCI sponsored Study] Study agent final disposition of inventory is documented on DARF

Non-Compliance

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

STUDY AGENT STORAGE

Compliance	Non-Compliance
• Each study-supplied agent is stored separately by protocol, strength, 'dosage form' (e.g., oral, injectable) and by ordering investigator • Study-supplied agent is stored under proper conditions (i.e., refrigeration, freezer or room temperature) with appropriate documentation and maintenance of temperature monitoring	• Study-supplied agent is not stored separately by protocol, strength, 'dosage form' (e.g., oral, injectable) and/or by ordering investigator • Study-supplied agent not stored under proper temperature conditions; temperature monitoring documentation not maintained

ADEQUATE SECURITY

Compliance	Non-Compliance
• Study-supplied agent is stored in a secure area that can be locked • Storage areas shall be accessible only to authorized individuals; unauthorized individuals are supervised by an authorized individual	• Study-supplied agent is stored in an unsecured area • Unauthorized individuals have access to a secure area without supervision

AUTHORIZED PRESCRIPTION(S)

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

5.3.5 Assessing the Accountability of Investigational Agents and Pharmacy Operations

Monitor discretion can be used for minor problem(s) identified during the review of the pharmacy. The number of active patients/study participants on NCI-sponsored and/or funded clinical trials, and the number of open protocols reviewed should be considered in the evaluation.

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

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

Note: Any finding identified before or during a monitoring visit that is suspected to be fraudulent activity should be cited as Critical-Non-Compliant (see definition for Critical under Section 5.1)

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

Acceptable

- Compliance in all categories and no follow-up being requested
- Any Non-Compliance item identified during the monitoring visit 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 clinical investigator because no similar deficiency has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a deficiency is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, CTMB must receive a copy of the CAPA plan at the time the monitoring report is uploaded into the CTMB-AIS or by the date follow-up is due.

Acceptable Needs Follow-up

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

Unacceptable

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

No Assessment Required

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

Limited Review Needs Follow-up *(applies to 'on-site' visits of the pharmacy)*

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

If the Pharmacy Review is rated as Limited Review Needs Follow-up, Acceptable Needs Follow-up or Unacceptable, the institution will be required to submit a written CAPA plan/response to the CTMS. A copy of the written CAPA plan/response must be uploaded into the CTMB-AIS (for CTMB review) by the CTMS. The CAPA plan/response must be available for review by CTMB within 45 calendar days from the date the monitoring report was completed and uploaded into the CTMB-AIS. A re-visit is mandatory if an institution continues to participate in the ETCTN (or other Early Phase Program) for any component rated as Unacceptable.

A re-visit 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 re-visit due to non-compliance related to storage and/or security, it must be conducted on-site.

5.4 Review of Patient Case Records

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

- Properly signed and dated informed consent document, including consent process
- Eligibility of a patient/study participant
- Correct treatment and treatment sequence
- Evaluation of disease outcome/tumor response
- Reporting of adverse events related to treatment
- General quality of the data collected

If records are not in English, then a qualified translator chosen by the monitor(s) or institution must be present. Source documentation of each patient case selected for review considered missing at the time of the monitoring visit must be supplied to CTMS within 10 business days of the monitoring visit.

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. The term 'intervention' is intended to include non-treatment studies such as cancer control, prevention, advanced imaging, etc.

Informed Consent – Critical Deficiencies

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

Informed Consent – Major Deficiencies

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

Eligibility – Critical Deficiency

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

Eligibility – Major Deficiencies

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

  [Exception: Patients deemed ineligible based on laboratory/pathology reports following registration and changes based on central review of material.]
- Other (explain)

Treatment – Critical Deficiencies

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

Treatment – Major Deficiencies

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

- Unjustified delays in treatment/intervention
- Other (explain)

Disease Outcome/Response – Critical Deficiency

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

Disease Outcome/Response – Major Deficiencies

- Inaccurate documentation of initial sites of involvement
- Tumor measurements/evaluation of status or disease not performed, not reported, or not documented per protocol
- Protocol-directed response criteria not followed
- Claimed response (i.e., partial response, complete response, stable) cannot be verified or monitor could not verify the reported response
- Failure to detect cancer (as in a prevention study) or failure to identify cancer progression
- Other (explain)

Adverse Events – Critical Deficiency

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

Adverse Events – Major Deficiencies

- Failure to report or delayed reporting of an adverse event that would require filing an expedited Adverse Event (AE) report
- Adverse events not assessed by the investigator in a timely manner (per protocol)
- Grades, types, or dates/duration of serious adverse events inaccurately recorded
- Adverse events cannot be substantiated
- Follow-up studies necessary to assess adverse events not performed
- Recurrent under- or over-reporting of adverse events
- Other (explain)

General Data Management Quality – Critical Deficiency

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

General Data Management Quality – Major Deficiencies

- Recurrent missing documentation in the patient/study participant records
- Protocol-specified laboratory tests not done, not reported, or not documented
- Protocol-specified diagnostic studies including baseline assessments not done, not reported, or not documented
- Protocol-specified research/advanced imaging studies not done or submitted appropriately

- Frequent data inaccuracies
- Errors in submitted data
- Delinquent data submission (greater than 6 months delinquent is considered a major deficiency; a 3-6 month delinquency is considered a lesser deficiency)
- Other (explain)

Assigning Lesser Deficiencies

As defined under Section 5.1, a lesser deficiency may be assigned under each of the above categories if it is judged to not have a significant impact on the outcome or interpretation of the study and is not described above as a major deficiency. An unacceptable frequency/quantity of lesser deficiencies should be treated as a major deficiency in determining the final assessment of a component.

5.4.2 Assessing the Findings from the Patient Case Review

Each category (IC, E, Rx, DO/DR, AE, DQ) for each patient case reviewed can be found to be Critical, Major, Lesser, OK or Not Reviewed. If one or more categories is not reviewed for any reason (e.g., subject did not receive treatment, insufficient time for monitor to review, etc.) or the patient chart was designated as the Unannounced case, this must be explained in the patient case section of the monitoring report.

One of the following designations must be used when assigning an assessment for the review of the Patient Case component.

Acceptable

- No deficiencies identified and no follow-up being requested
- Few lesser deficiencies identified and no follow-up being requested
- Any major deficiency identified during the monitoring visit 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 clinical investigator because no similar deficiency has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a deficiency is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, CTMB must receive a copy of the CAPA plan at the time the monitoring report is uploaded into the CTMB-AIS or by the date follow-up is due.

Acceptable, Needs Follow-up

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

Unacceptable

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

If the Patient Case Review is rated as Acceptable Needs Follow-up or Unacceptable, the institution will be required to submit a written CAPA plan/response to the CTMS. A copy of

the written CAPA plan/response must be uploaded into the CTMB-AIS (for CTMB review) by the CTMS. The CAPA plan/response must be available for review by CTMB within 45 calendar days from the date the monitoring report was completed and uploaded into the CTMB-AIS. A re-visit is mandatory if an institution continues to participate in the ETCTN (or other Early Phase Program) for any component rated as Unacceptable.

A re-visit should be done no later than a year after an Unacceptable rating or when sufficient new patients/study participants have accrued. If sufficient new patients/study participants have not accrued within a year from the previous visit, further discussion with CTMB is necessary prior requesting to post-pone the re-visit.

5.5 Role of the Investigator During the Monitoring Visit

The Clinical 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 Clinical Investigator and designated staff be present at the exit interview. 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

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 clincial investigator at the site by CTMS. This occurs for both Data Reviews and the Annual Site Visits. A copy of the letter is uploaded into the CTMB-AIS database. The monitoring report must be submitted to the institution within 6 weeks of the last day of the monitoring visit.

For Data Reviews, a site-specific report summarizes the findings for the review of the patient cases since only the patient cases are reivewed at a Data Review visit. Recommendations from the monitor(s) are noted in the General Comments or Exit Interview sections of the Monitoring Report.

For Annual Site Visits of studies assigned to be monitored as CTMS-comprehensive or CTMS-routine, a site specific report summarizes the findings for each of the three components reviewed (Regulatory Documentation, Pharmacy, and Patient Cases). Recommendations from the monitor(s) are noted in the General Comments or Exit Interview sections.

6.1.2 Content

The following information should be included in the Monitoring Report:

6.1.2.1 General Information

- Provide information specific to the institution such as number of patient cases reviewed, average annual accrual, and institution staff present at the visit
- Identify members of the monitoring team; indicating title and affiliation

6.1.2.2 Regulatory Documentation

- The CTMB-AIS will populate each protocol title for protocols reviewed and list the number patient 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)
- Indicate if each protocol selected for review is utilizing the NCI CIRB or a local IRB
- Designate whether critical, major, or lesser deficiencies were identified under CIRB/IRB and Informed Consent Content (ICC) and describe each critical, major or lesser deficiency; otherwise indicate OK
- Designate whether major or lesser deficiencies were identified for review of the Delegation of Tasks – Log, if so, describe; otherwise indicate OK
- Indicate if any portion of the Regulatory Documentation review was reviewed ‘off-site’
- Provide an overall assessment for this component and indicate if a re-visit is required, including timeframe

6.1.2.3 Accountability of Investigational Agents and Pharmacy Operations

- Indicate the number of DARFs reviewed (i.e., number of study agents reviewed), and the number of patients cross-checked against the DARF, if applicable
- For each item identified as Critical-Non-Compliance and/or Non-Compliance, select the appropriate Not Compliant description or descriptions; otherwise indicate OK or Not Reviewed
- Summarize in the pharmacy narrative any items that require a response, any items not reviewed and explain why they were not reviewed (see Section 5.3.5); include guidance or recommendations provided to the institution. [Other examples of information that may be included under the pharmacy narrative may include descriptions of non-compliance issues not outlined in the monitoring guidelines; review of temperature logs and excursions; rationale of why IND or study-supplied agents were not selected for review, etc.]
- For a full review of the pharmacy component, provide an overall assessment (Acceptable, Acceptable needs F/U, or Unacceptable) and indicate if a re-visit is required, including timeframe
- For a limited review of the pharmacy, indicate which items were reviewed (i.e., storage, security, and/or pharmacy procedures). If follow-up is required when conducting a limited review, describe the non-compliance finding(s). The overall assessment for a 'limited review' of the pharmacy should be: 'No Assessment Required' or 'Limited Review Needs Follow-up

6.1.2.4 Patient Cases

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

6.1.2.5 Monitoring Procedures

This section indicates monitoring procedures such as how the visit was conducted, if any items were reviewed as part of Centralized Monitoring and other pertinent information.

6.1.2.6 General Comments

This section may be used to indicate if any additional data or correspondence was submitted by the site to the CTMS 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 Possible Actions Due to Delinquent Data and/or Findings

Data are to be submitted via Medidata Rave to CTMS every two weeks (eg, 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. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS staff. Metrics for timeliness will be followed and assessed on an ongoing basis.

All major 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/or action to be taken in order to prevent future occurences.

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

6.2.2 Probation of Participating Institutions

For the purpose of Site Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due. Sites with data greater than 20% past due at the end of the quarter will be placed on probation.

If a participating site is deemed Unacceptable for the same component on two consecutive visits, the insitution 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 patient registration and timely review of data submission.

6.2.3 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 Clinical Investigator stating that the CAPA plan/response is overdue and a five business day grace period will be granted.

- If follow-up or a CAPA plan is not received within the five day grace period, the patient 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, all new patient 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 Clinical Investigator detailing the reason for the delay must be included. Suspension of patient registration 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.

6.2.4 Withdrawn Institutions

If improved performance is not documented at the time of the second re-visit, the site may be permanently 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’ visit may take place at any site, at any time, if patient safety or scientific misconduct is suspected.