NCI GUIDELINES FOR AUDITING AND MONITORING CANCER SCREENING RESEARCH NETWORK (CSRN) TRIALS

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LIST OF ACRONYMS

ACCESS	Accrual, Enrollment, and Screening Site
AP	Associate Plus (as designated in RCR)
CAPA	Corrective and Preventative Action
CCC	Coordinating and Communication Center
CIP	Cancer Imaging Program
CIRB	Central Institutional Review Board
CLASS	Compliance, Learning, and SOP Solutions
COI	Conflict of Interest
CSRN	Cancer Screening Research Network
CTEP	Cancer Therapy Evaluation Program
CTMB	Clinical Trials Monitoring Branch
CTMB-AIS	Clinical Trials Monitoring Branch-Audit Information System
CTMS	Clinical Trial Monitoring Service
CTSU	Cancer Trials Support Unit
EMR	Electronic Medical Record
DCP	Division of Cancer Prevention
DCTD	Division of Cancer Treatment and Diagnosis
DSMB	Data Safety Monitoring Board
DTL	Delegation of Tasks Log
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IAM	Identity and Access Management
ICC	Informed Consent Content
ICH	International Council for Harmonisation
IDE	Investigational Device Exemption
IVR	Physician Investigator (as designated in RCR)
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NPIVR	Non-Physician Investigator (as designated in RCR)
PII	Personally Identifiable Information
RCR	Registration and Credential Repository
SDMC	Statistics and Data Management Center
SDP	Source Document Portal
SDV	Source Data Verification

CTMB-AIS DEFINITIONS

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

Audit Category: A type of protocol being audited, for CSRN studies the Audit Category is Prevention.

Audit Type: Routine, Reaudit or Off-cycle

Membership Start Date: Date institution first joined ACCESS Hub, this date does not change. The roster history indicates changes over time regarding participation in the ACCESS Hub.

Membership Status: Active, Withdrawn or No Longer Funded

- Active is when an institution is an actively participating member of the CSRN.
- Withdrawn is when an institution is no longer an active member of an ACCESS Hub, this action may either be initiated by the CSRN Coordinating and Communication Center (CCC) or DCP.
- No Longer Funded (NLF) indicates that an ACCESS HUB or single institution under ACCESS HUB is no longer being funded. The institution is in a transition phase with their study participants on-study or in follow-up until data submission is no longer required. Once the transition phase is completed, the CCC will request to change the site(s) status to withdrawn. The NLF status allows the CCC to request a new membership type/role for an individual institution in the ACCESS HUB. This term NLF is only used in CTMB-AIS. In the RSS, the corresponding term is ‘Follow-up”.

Membership Status Date: Status date is when the CCC makes changes to an institution’s record such as status change (e.g., active, withdrawn) or other changes to the membership type/role, name, or auditable flag. The CCC determines when the change is effective.

Membership Type: ACCESS Hub, Hub Affiliate, Hub Sub Affiliate

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

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

Record Status: Active or Inactive

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

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

SECTION 1 BACKGROUND AND PURPOSE OF THE AUDITING PROGRAM FOR THE CANCER SCREENING RESEARCH NETWORK

1.1 Introduction and Purpose

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, includes direct oversight of the CSRN's quality assurance and auditing program.

The National Cancer Institute (NCI)/Division of Cancer Prevention (DCP) requires Quality Assurance (QA) audits of clinical trials data and processes at each ACCESS Hub and Hub Affiliates. Audits are conducted by the CSRN Coordinating and Communication Center (CCC) and overseen by the CTMB.

Auditing is an independent quality assurance function for systematic evaluation of trial processes and documents to determine whether trial-related activities are conducted, and data are recorded, analyzed, and accurately reported according to the protocol, the sponsor's Standard Operating Procedures (SOPs), relevant Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, federal regulations, and National Institutes of Health (NIH)/NCI/DCP policies. Audits are performed by CCC on a routine and non-routine basis and are a snapshot in time of the ACCESS Hub's compliance with program requirements.
The specific purpose of the auditing program is as follows:

- Document the accuracy of data submitted to Medidata Rave, and DCP
- Verify investigator compliance with protocol and regulatory requirements
- Verify adherence to CSRN policies and procedures
- Ensure participant safety
- Provide site staff with resources for a more thorough understanding of regulatory requirements, GCP, data collection and data management practices, as necessary
- Provide the opportunity for CSRN entities to work together to identify areas for systemic and policy-level improvements in order to increase both efficiency and compliance, to better ensure the protection of human subjects, and to enhance the quality and integrity of CSRN clinical trials

1.2 CSRN Background

As one of the world's largest publicly funded sponsors of 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.

The NCI's Cancer Trials Support Unit (CTSU) was implemented in 1999. Several of the key functions of the CTSU are designed to streamline clinical trials through the development

and operation of a comprehensive system for clinical trials management. The functions include regulatory support, assistance with audit activities, participant enrollment, development of a clinical trials informatics support system, and the development and conduct of education and training in the CTSU website.

The CSRN is an NCI network whose purpose is to conduct cancer screening trials and studies. This Network is designed to take advantage of large and diverse populations receiving routine care in a variety of healthcare settings. The CSRN will engage these populations in rigorous studies focused on cancer screening to improve early cancer detection and evaluate emerging cancer screening modalities with the ultimate goal of reducing cancer incidence, and cancer-related morbidity and mortality. ACCESS Hubs which recruit participants to CSRN studies, will be subject to audit by the CCC. The CTSU will assist with and review audit activities for the Network.

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

The Clinical Trials Monitoring Branch (CTMB) within the Cancer Therapy Evaluation Program (CTEP) has direct oversight responsibilities for the quality assurance and auditing programs including the Cancer Screening Research Network (CSRN). CTEP staff with representatives from other NCI programs, have worked closely to design, implement, and evaluate the quality assurance program. Working together we have implemented policies and procedures to standardize processes. For example: the establishment of the CIRB for studies in all phases, creation and updating of the informed consent form template for all NCI-sponsored clinical trials, setting standards for criteria when evaluating data timeliness and query for data resolution, implementation of RAVE (a common data capture system) and RAVE audit templates, and the ongoing modifications of the CTMB audit guidelines.

It is recognized that there may be inherent differences in the methodologies and processes when auditing. The Coordinating and Communication Center (CCC) and ACCESS Hubs may establish additional policies and procedures specific to their recruitment sites.

2.1 Clinical Trials Monitoring Branch (CTMB)

The CTMB is responsible for establishing guidance for the conduct of quality assurance audits. CTMB provides oversight and monitors compliance of the Cancer Screening Research Network (CSRN) with the NCI/CTMB auditing guidelines. Compliance with applicable federal regulations and GCP is also monitored by CTMB.

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

An audit or monitoring visit consists of reviewing various categories under the two components as follows:

<u>Regulatory Documentation Component</u>:

- IRB of record documentation
- Informed consent content (ICC)
- Delegation of Tasks Log (DTL)

<u>Participant Case Component</u>:

- Informed Consent
- Eligibility
- Screening Modality
- Screening Outcome
- Endpoint Assessment
- Adverse Event
- Correlative Studies, Tests, and Procedures
- General Data Management Quality

The CTMB must be notified immediately by telephone (240) 276-6545 and by email (ReportingResearchMisconductConcerns@nih.gov) of any findings suspicious and/or suggestive of intentional misrepresentation of data and/or disregard for regulatory safeguards for either component (Regulatory Documentation Review or Participant Case Review) of an audit or 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 Coordinating and Communication Center (CCC) auditors/monitors to immediately notify CTMB when they learn of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their research program. It should be emphasized that the irregularity/misrepresentation of data does not need to be proven. A reasonable level of suspicion suffices for CTMB notification. It is essential that involved individual(s) and/or institution(s) follow their own institutional misconduct procedures regarding these matters. See 'Guidance for Allegations of Research Misconduct' under Appendix 1.

2.2 CSRN ACCESS Hubs

The multi-center nature of CSRN clinical trials presents a variety of challenging procedural problems relating to assurance of quality and consistency in study conduct. The need for formal mechanisms of medical review and quality assurance is essential.

2.2.1 Quality Assurance

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

2.2.1.1 Auditing Program

Auditing is a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, dates recorded, analyzed and accurately reported according to the protocol, sponsor's SOPs, GCP, and the applicable regulatory requirements. It is a snapshot in time and consists of reviewing a subset of study participants on a trial.

The purpose of the auditing program is to document the accuracy of data submitted from the participating institution to the Statistics and Data Management Center (SDMC). Specifically, the CCC auditors/monitors will verify investigator compliance with the protocol, applicable regulatory requirements, and adherence to ACCESS Hub policies and procedures. If necessary, the ACCESS Hub may provide institution staff with resources for a more thorough understanding of the regulatory requirements, good clinical practices (GCPs), data collection and data management practices.

2.2.1.2 Monitoring Program

Monitoring is the act of overseeing the progress of a clinical trial. All clinical research carries with it the obligation to ensure optimal conduct of research procedures such that participant participation is meaningful. Accurate and timely knowledge of the progress of each study is a critical ACCESS Hub responsibility that includes many of the following elements:

- Precise tracking of study participant accrual
- Ongoing assessment of study participant eligibility and evaluability
- Adequate measures to ensure timely submission of study data
- Adequate measures to ensure timely medical review and assessment of data for each study participant
- Rapid reporting of adverse events and intervention-related morbidity information
- Periodic evaluation of outcome measures and study participant safety information including oversight by a DSMB for randomized studies

2.2.2 Quality Control

Quality control is a complex topic spanning the entire range of cancer screening and diagnostic modalities employed by the CSRN. In addition to centralized quality control procedures, it is expected that the ACCESS Hubs will establish internal quality control procedures as well.

Some of the central quality control procedures are:

- Institutional performance evaluations
- Committees for central review of major elements that impact on the outcome of clinical trials, e.g., screening mechanism, pathology, radiotherapy, surgery, and imaging
- Educational and training which addresses data collection, data management, and overall data quality
- Credentialing of investigators or other staff when specialized training and/or expertise is required for a research study

2.3 CTMB – Audit Information System (AIS)

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

2.4 CSRN Coordinating and Communication Center (CCC)

The CSRN utilizes the same quality assurance programs as those used by the Network Groups and NCORPs. The overall purpose is to ensure that clinical trials conducted by the CSRN ACCESS Hubs and Hub Affiliates adhere to the federal regulations, GCP and the CTMB audit guidelines.

The CCC must develop its own auditing programs that meet the minimum requirements established by the NCI. The CCC must perform audits per the CTMB audit guidelines including scheduling audits, auditing, generating and uploading final audit reports and obtaining and uploading Corrective and Preventative Action (CAPA) plans into the CTMB-AIS.

2.5 Cancer Trials Support Unit (CTSU)

The CTSU provides an array of support including roster management, regulatory support, participant enrollment, data collection, and the use of the CTSU website for posting appropriate material. Services specifically tailored to auditing or monitoring activities are:

2.5.1 Site Audit Portal (SAP)

The Site Audit Portal (SAP) is an application in the auditing and monitoring 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 participants, visit-associated queries in Rave and 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 auditor/monitor access to the SAP to view visit details and access 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

2.5.2 Auditing/Monitoring Participant Cases for Studies in Medidata Rave

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

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

2.5.3 Source Document Portal (SDP)

The CTSU Source Document Portal (https://sdp.ctsu.org) is an application which allows site staff to identify and upload source documents for activities such as remote auditing/monitoring visits, central monitoring, and the support of safety reporting in CTEP-AERS. The Coordinating and Communication Center (CCC) and other stakeholder staff with appropriate privileges are then able to access the documents within the application. In the case of remote auditing/monitoring visits, the SDP provides an alternative for reviewing 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 auditing/monitoring visits using the SDP are available in both the SAP and the SDP (login required).

Remote/Off-site Visit Instructions for Auditors/Monitors: 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 auditors/monitors including volunteer auditors, must complete the Source Document Portal (SDP) module under Auditor and Monitor Training Course in the Compliance, Learning, and SOP Solutions (CLASS) system before they will be able to access documents in the SDP.

SECTION 3 MEMBERSHIP TYPES UNDER THE CSRN PROGRAM

All institutions must be listed on a CSRN roster in the CTMB-AIS for a monitoring visit or an audit to be scheduled. The CCC is responsible for timely and accurate maintenance of the roster for all ACCESS Hubs.

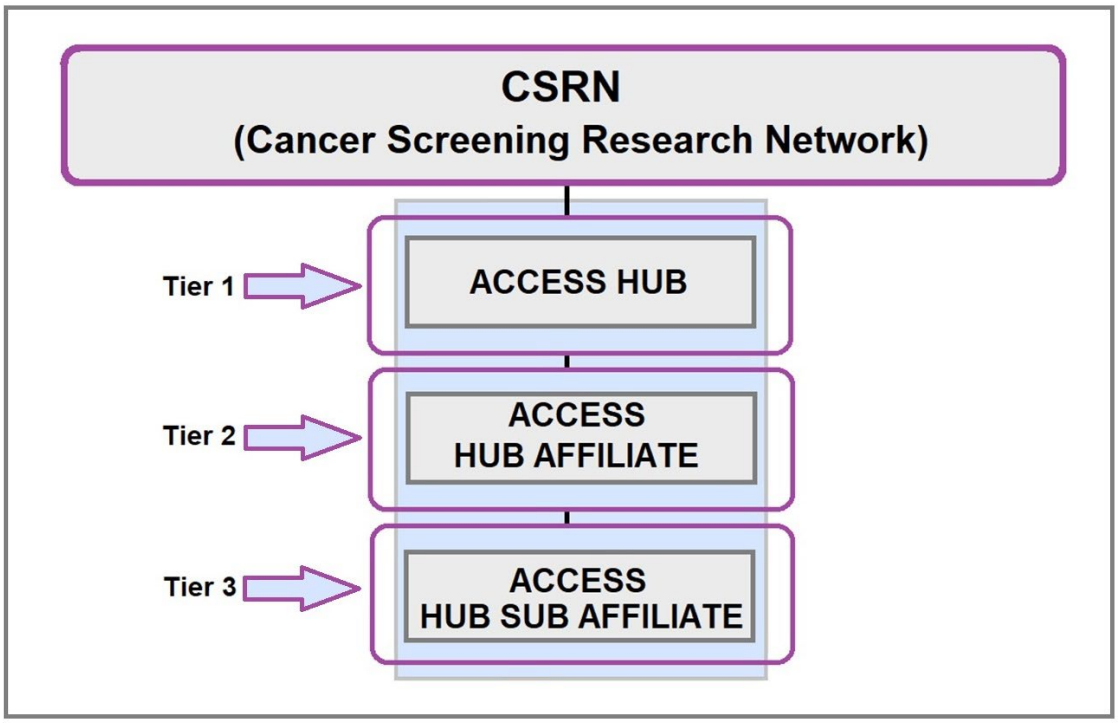
Storefronts are administrative sites that do not accrue or treat participants. All CSRN ACCESS Hubs must contain an administrative component which acts as a storefront. The CSRN storefronts handle the regulatory, registration, data management and financial aspects for their Hub Affiliate institutions. The CSRN storefronts designate the grant institution responsible for grant related activities, including distribution of funding to the enrolling institution(s) within a ACCESS Hub grant.

Hub Affiliates and Hub Sub Affiliates are expected to enroll participants and provide significant accrual to the CSRN program.

3.1 CSRN Membership Types in CTMB-AIS Roster

Principal Investigators participating in CSRN research come from a wide variety of academic and/or community practice settings. All institutions must be a member of at least one ACCESS Hub to participate in CSRN-sponsored clinical trials. Categorization of membership type is based on the CSRN Program Guidelines and the policies determined by the CCC. All institutions must be recognized across the CSRN as one of the following mutually exclusive Membership Types for funding and accrual purposes (see Figure 1).

Figure 1 Organizational Chart for the Cancer Screening Research Network (CSRN) by Membership Type



3.1.1 ACCESS Hubs (Administrative Entities)

ACCESS Hubs are funded through the Division of Cancer Prevention (DCP). ACCESS Hubs are comprised of any of the following: hospitals, clinics, Health Maintenance Organizations (HMOs), groups of practicing physicians, consortiums, or other healthcare organizations which agree to work with a Principal Investigator through a single administrative unit.

Administrative sites oversee the financial, regulatory, registration and data management for the ACCESS Hubs and Affiliate Organizations within the ACCESS Hub. An ACCESS Hub administrative entity is an administrative site, known as a 'storefront' which is a site that does not actively accrue or treat study participants.

3.1.2 CSRN Institution Types

A Hub Affiliate is defined as a hospital, academic center or clinic, physician practice, or other institution where participants are enrolled on a regular and ongoing basis to the menu of NCI-approved clinical trials available to the CSRN Network.

A Hub Sub Affiliate is defined as a practice or organization where study participants are enrolled but is under the oversight of the Hub Affiliate site. It may be located in a separate geographical location, is part of the Hub Affiliate's business entity, and is managed by the Hub Affiliate.

Hub Affiliates and Hub Sub Affiliates must be on the ACCESS Hub roster if:

- Consenting and/or registering (enrolling) participants, or
- Receiving investigational device used alone or in combination with the intervention under Investigational Device Exemption (IDE)

Requirements of the Hub Affiliates and Hub Sub Affiliates:

- Can only be listed once on an ACCESS Hub roster
- Must be affiliated with the central IRB
- Must be linked to a single ACCESS Hub

3.1.3 Principal Investigator Responsibilities at the Linked ACCESS Hub

- Overseeing protocol-related activities
  - Ensuring that they have IRB oversight
  - Ensuring the study interventions are administered in accordance with the IRB-approved protocol
  - Ensuring appropriate arrangements are made for reporting protocol-related data and any unexpected adverse events
- Monitoring the conduct of research
  - Ongoing assessment of regulatory and study participant data
  - Compliance with NCI policies and federal regulations (as applicable)

- The review of the appropriateness of the Hub Sub Affiliate's corrective and preventative action (CAPA) plan and its implementation that addresses:
  - Any concern related to the conduct of the research
  - Any findings as a result of an audit

3.2 Auditable and Non-Auditable Institutions

An 'auditable' institution (auditable flag set to 'yes' in the CTMB-AIS) is an institution that is designated to be audited as stand-alone audit with its own preliminary report and final audit report. This 'auditable' designation is required for all enrolling ACCESS Hubs and Hub Affiliates categorized as Tier 1 and Tier 2 (see Figure 1).

A 'non-auditable' institution (auditable flag set to 'no' in the CTMB-AIS) is an institution that is audited but in combination with other site(s). These types of audits are referred to auditing 'as a whole'. It is an audit comprised of more than one institution being reviewed and all information and audit findings incorporated into one preliminary report and one final audit report under the parent institution, or Tier 1 site, (consisting of multiple CTEP site codes).

For ACCESS Hubs, the designation of the auditable flag may vary and is at the discretion of the CCC. For instance, the auditable flag can be set to 'no' for Hub Affiliates (Tier 2) but the ACCESS Hub (Tier 1) must then be set to yes. Note that the auditable flag for a Tier 1 and Tier 2 institutions within the same ACCESS Hub cannot be both set to 'No' for an audit to be scheduled correctly. See Section 3.4 for alternative methods for setting the auditable flag.

Tier 3 sites (Hub Sub Affiliates) are routinely 'non-auditable' (auditable flag set to 'no' in the CTMB-AIS). The audits for these sites are scheduled to be in combination with the parent site. CTMB in consultation with the ACCESS Hub may request to schedule a stand-alone audit of a Tier 3 site if there are reasons for concern. In this scenario, the auditable flag would need to temporarily change from 'No' to 'Yes' for the audit to be scheduled appropriately in CTMB-AIS.

For audits that include non-auditable institutions, protocols and participant cases must be selected for review from the parent and each non-auditable institution being audited.

3.3 Hub Affiliate and Hub Sub Affiliate Auditing Intervals

The initial audit of a Hub Affiliate must take place within 18 months after entry of the first study participant. If an institution accrues rapidly, the initial audit should be conducted sooner than 18 months. Following the initial audit, Hub Affiliates and Hub Sub Affiliates institutions must be audited at least once every 36 months. For high accruing institutions, it may be appropriate for the CCC to audit these institutions on a more frequent interval given the high number of cases for review.

The CCC may select one of three audit methods to conduct an audit of the Hub Affiliate and its Hub Sub Affiliates:

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

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

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

SECTION 4 PREPARATIONS FOR CONDUCTING THE AUDIT

The CCC must carefully plan for an audit months in advance. This document will further outline how audits are scheduled, conducted and reported. If the review type is designated as a Monitoring visit (see Sections 4.3.2 and 4.5.2), it will follow the same process as audits but may differ in frequency of visits.

4.1 Scheduling and Arranging the Audit

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

The audit date should be entered into the CTMB-AIS four or more weeks in advance. This will ensure sufficient notification to the institution and will allow CTMB staff to decide which audits they or their designee will attend. However, the scheduling of a 'for-cause' audit may be scheduled at any time after consultation with CTMB.

The institution is to be provided with a list of protocols and participant cases selected for review at least four but no more than six weeks prior to the audit. This will allow the institution staff sufficient time to collect, prepare, assemble and label the required materials. In the event of a 'for-cause' audit, advance notice for selection of protocols and/or participant cases to be reviewed may be limited due to the nature of the review.

4.2 Cancellation of an Audit

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

4.3 Types of Audits/Visits

Audits/visits may be scheduled in the CTMB-AIS on or off-site as listed below:

4.3.1 Audits

Routine audits can occur within 12 to 36 month intervals. The frequency of audits may depend on whether a particular site(s) is considered a high enrolling site or the rate of accrual is unusually high.

Reaudits are scheduled when there are concerns based on the prior audit (by component) and therefore oversight of the site should occur sooner, usually within 12 to 18 months from the prior audit.

Off-cycle audits may be scheduled depending on the circumstances below:

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

4.3.2 Monitoring

Monitoring can be scheduled in the CTMB-AIS database as an Initial or Routine visit. The Initial Visit is an on-site observation of study activities and discussions with site staff. The visit will include a tour of the physical space of the site which may include clinics and laboratories, and observation of processes related to recruitment, consent, study visits, handling and shipment of specimens and internal monitoring procedures. These visits will also serve as an opportunity for feedback from the CCC monitors to staff as well as feedback from site staff on study operations to the CCC and SDMC.

Ongoing monitoring of a site's performance will be primarily report-driven. Reports will be focused on recruitment progress, timeliness and completeness of baseline as well as post-baseline data, specimen shipment accuracy and timeliness, specimen quality and condition upon receipt, and timeliness of other study-specific procedures. Reports will be reviewed by the Performance Monitoring Committee (PMC) and if there is any area in which a site appears to be struggling, additional training or monitoring (either remote or in-person) could be warranted. These would be Routine visits and the frequency of such visits would be based on the severity of the problem.

Along with the site monitoring, incoming data will be monitored for completeness and consistency across forms. Depending on the trial, study procedures and study forms, this data monitoring may be in real time (if it will impact the management of a participant) or at defined study timepoints.

4.4 Location of the Audit or Monitoring Visit

For continued oversight of participant safety, there may be circumstances when off-site/remote auditing or monitoring is necessary. To the extent possible, this approach should include remote access to the site's Electronic Medical Records (EMRs) system. Due to logistical issues and unfamiliarity with the site's EMR system related to conducting remote audits, it may require extending the audit duration (i.e., of days). Use of the Source Document Portal (SDP) as described under Section 2.5.3 is an alternative and may also be used in combination with other approaches. When scheduling the audit, below are location options to select from in the CTMB-AIS:

- On-Site Review: conducted at the institution being audited
- Off-Site/Remote Review:
  - Review conducted at parent/affiliated site
  - Review conducted remotely at CCC

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

4.5.1 Auditing

An institution may be designated to have an audit of protocols and participant cases from one or more protocols. All institutions that accrue participants to CSRN clinical trials are eligible for a routine audit every 12 months. However, an institution may be audited at any time as directed by the PMC or CTMB.

When auditing an ACCESS Hub Affiliate, a minimum of 10% of the participant cases accrued since the last audit will need to be selected for review by the CCC. For the ACCESS Hub Sub Affiliates, the CCC is expected to select a representative sampling from each Sub Affiliate to audit under the parent institution. Selecting 10% of participant cases from each Sub Affiliate is not required. Under certain circumstances, CTMB may mandate an independent audit of any Sub Affiliate site.

For selection purposes, 10% of the chosen cases must be rounded up (e.g., if 12 participant cases are eligible for audit selection, at least two cases must be audited). While most cases will be selected from participants accrued since the previous audit or monitoring visit, any participant case may be reviewed at any time.

4.5.2 Monitoring

Data is submitted to the SDMC (accessible to the CCC) per protocol via Medidata Rave. Each ACCESS Hub will have an initial monitoring visit after accrual of a pre-determined percentage or number of the total anticipated participants. Monitoring may also be performed for a pre-specified percentage or number of screen-positive study participants. The frequency will be determined on a protocol-by-protocol basis. More frequent reviews may be conducted if warranted by accrual, due to concerns regarding data quality, timely submission, or change in key personnel.

4.6 Selection of Unannounced Participant Cases

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

4.7 Review of Transferred Participant Cases

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

4.8 Selection of the Audit or Monitoring Team

Selection of the review team should receive special consideration. Reviewers should be selected based on auditing and/or monitoring experience, knowledge of the federal

regulations, GCPs, NCI guidelines and other procedural documents. It is expected that each reviewer will also be cognizant of the NCI guidelines and procedures of the CCC. All reviewers 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 CCC to ensure there is no 'Conflict of Interest (COI)', or potential COI, between the reviewer and the institution(s) being reviewed. Documentation such as an "Auditor/Monitor Confidentiality Agreement' must be maintained by the CCC and readily accessible, if requested.

4.8.1 CCC Auditors/Monitors

The review team should include CCC staff such as clinical research associates, data managers or statistical center personnel. The team must include qualified individuals capable of providing medical assessments, evaluating protocol compliance, and conducting an effective exit interview with the responsible Principal Investigator and institution staff. The auditors/monitors must be knowledgeable about clinical trial methodology, NCI policies, and federal regulations.

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

As determined by the NCI, representatives from the CTMB, DCP and/or representatives from other federal regulatory agencies may attend audits as observers. The CTMB or their representative will notify the CCC of the audits the observers will attend. If CTMB staff or NCI designees are present during an audit they must have full access to all documents and materials present for the audit. The exit interview is an integral part of the audit and NCI staff or designees must be included in all exit interview discussions.

4.9 Institution Responsibilities

The institution is responsible for ensuring that all relevant materials are available for review at the time of the audit. The location of the audit may be at the institution being audited, the linked-parent (per the CTMB-AIS or at the CCC (off-site/remotely). Regardless, the following records must be available the day of the audit or sooner, if requested:

- IRB documents, copies of the locally utilized informed consent documents, Delegation of Tasks Logs (DTLs) and other regulatory documentation, if applicable
- Complete medical records (or copies) of participant cases selected for audit, including but not limited to operative/procedure reports, pathology reports
- Dictated reports 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 the documents such as hospital/clinic records, research notes, on-study labs, scans, imaging reports, informed consent documents, etc. by participant case number. The CCC should provide guidance on how preparation of documents for the audit 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 auditors/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 the visits/audits conducted off-site/remotely, the circumstances vary depending on the approach used to review the documentation. A site staff member must also be available to contact and assist with questions.

4.10 Auditing/Monitoring of Withdrawn Institutions

If an institution's membership or participation in an ACCESS Hub is withdrawn, continued long-term follow-up of registered/enrolled participants and the collection of good quality data according to the study schedule are required. Therefore, these institutions remain eligible for an audit or monitoring visit. If a Hub Affiliate or Hub Sub Affiliate institution is withdrawn, the CCC remains responsible for auditing/monitoring.

In the case of a withdrawn organization, a close-out audit should be considered by the CCC. The decision whether to conduct an audit is based on the following:

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

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

SECTION 5 CONDUCTING THE AUDIT OR MONITORING VISIT

During the auditing or monitoring visit, the auditors or 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 to access 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)
- In-patient and out-patient medical records
- Progress notes
- Procedures/Operative Reports
- Pathology Reports
- Dictated reports of all imaging studies (X-rays, scans, MRIs, PET, etc.)
- Laboratory data
- Admission and discharge summaries
- Research records that are signed and dated on 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
- Adverse event logs

At the discretion of the CCC, certain documents such as regulatory documents, informed consent documents, and delegation of tasks logs (DTLs) may be reviewed prior to the audit/monitor visit date. These documents must be made available to the CCC auditors/monitors, if requested. Findings from the off-site/remote review must be included in the Preliminary Report, discussed at the Exit Interview, and described in the Audit/Monitoring Report.

5.1 Assessing Auditing and Monitoring Findings

An auditing or monitoring visit consists of reviewing and evaluating two components: (1) Regulatory Documentation which includes conformance with IRB regulations and guidelines, informed consent form requirements, and maintenance of DTLs, and (2) individual Participant Cases. A Review Worksheet for each of these components can be found under Appendices 2 and 3, respectively.

During the audit/monitor visit, each component 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 CCC will use a common set of terms or examples of Critical, Major and Lesser deficiencies. A common system is utilized for assessing each component of an audit, resulting in a standard format for final audit reports generated in the CTMB-AIS. See definitions below:

Critical Deficiency

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

NOTE: See 'Guidance for Allegations of Research Misconduct' (Appendix 1) for reporting any allegation of research misconduct that is detected by site staff and/or review by the CCC outside of an audit (i.e., through internal Quality Assurance review procedures).

Major Deficiency

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

Lesser Deficiency

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

5.2 Review of the Regulatory Documentation

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

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

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

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

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

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

- Documentation of full-board initial LIRB approval
- Documentation of full-board LIRB annual reapproval
- Documentation of timely LIRB approval (or disapproval) of protocol amendments that affect more than minimal risk
- Documentation of LIRB approval or reapproval prior to participant registration
- Documentation of expedited review done appropriately
- Documentation of internal safety reports submitted timely
- Documentation of external safety reports (when required by the local LIRB) submitted timely

The following descriptive terms should be used in assessing compliance:

- Delayed reapproval: Protocol reapproval by the LIRB delayed up to one year
- Expired reapproval: Protocol reapproval by the LIRB delayed for greater than one year
- Missing reapproval: Missing documentation of protocol reapproval (e.g., no letter from LIRB stating reapproval granted, LIRB 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.htmlhttps://www.hhs.gov/ohrp/regulations-andpolicy/guidance/guidance-on-expedited-review-procedures/index.html)
- Other: Any regulatory concern not described above

Amendments (addendums or updates) must be approved by the LIRB of record within 90 calendar days of the CSRN's notification. Each ACCESS Hub has its own methods for notifying its institutions. Notification of temporary suspension of new participant registration will be disseminated by the ACCESS Hub as soon as possible with further instructions, as necessary.

Amendments that are editorial or administrative in nature are exempt from the 90 calendar day requirement and may be deemed a lesser deficiency. Typographical corrections, rephrasing a sentence/section to add clarity, reformatting the document and/or changes made related to contact information are examples of an editorial or administrative change.

Unanticipated problems, serious non-compliance and/or continuing non-compliance problems as defined by OHRP (see https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html) including external safety reports must be reported to the LIRB within 90 calendar days of the ACCESS Hub's notification. A random sample of at least 10% of external safety reports that were reported to the IRB (reportable per OHRP policy) must be reviewed for each protocol selected for an audit.

5.2.3 Listing of IRB Deficiency Types

The following are examples of critical, major and lesser deficiencies to be considered when assessing IRB compliance. This list does not represent an all-inclusive list of possible deficiencies that may be found during an audit as defined under Section 5.1.

5.2.3.1 CIRB – IRB of Record

Critical CIRB Deficiency

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

Major CIRB Deficiencies

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

Lesser CIRB Deficiencies

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

5.2.3.2 LIRB – 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 screening of participant prior to full LIRB approval
- Annual reapproval delayed greater than 30 calendar days, but less than one year
- Registration of participant on protocol during a period of delayed reapproval or during a temporary suspension (i.e., Request for Rapid Amendment)
- Missing annual reapproval
- Expired annual reapproval

- Internal reportable adverse events reported late or not reported to the LIRB
- Lack of documentation of LIRB approval of a protocol amendment that affects more than minimal risk or LIRB approval is greater than 90 calendar days (or 120 calendar days for sites outside of the U.S.) after ACCESS Hub/CCC notification; this includes a 'Request for Rapid Amendment (RRA)' resulting from an Action Letter indicating temporary suspension of accrual with expedited review permitted
- Failure to submit or submitted after 90 calendar days, any reportable external safety report to the LIRB that is considered an unanticipated problem as defined by OHRP, unless there is a LIRB policy that does not mandate reporting of external safety reports
- Other (explain)

Lesser 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 an intervention
- Amendment editorial revision or administrative in nature or other Network specific document not submitted or not submitted timely to the LIRB
- Other (explain)

5.2.4 Review of Informed Consent Content (ICC)

The content of the local informed consent documents for at least four protocols (if there are four or more protocols) must be reviewed to ensure the informed consent documents contain the elements required by federal regulations.

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

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

The following are examples of critical, major and lesser deficiencies to be considered when assessing ICC deficiencies. This list does not represent an all-inclusive list of possible deficiencies that may be found during an auditing or 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 trial will be available on www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time"
- Statement that a copy of the informed consent form will be given to the subject
- Failure to revise the informed consent document in response to an NCI Action Letter regarding risks

- Significant or substantial changes to the consent form document deviating from the CIRB-approved boilerplate (other than local context) not approved by the CIRB
- Consent form document contains changes not approved by the IRB of record, including changes to questions that do not match the model consent form
- Cumulative effect of multiple lesser deficiencies
- Other (explain)

Lesser ICC Deficiencies

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

5.2.5 Review of the Delegation of Tasks Log (DTL)

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

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

The auditor/monitor will review the DTL for each protocol selected for audit (by institution). The auditor/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 an audit.

Critical DTL Deficiency

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

Major DTL Deficiencies

- Performing tasks not assigned to individual
- Individual performing study-related activities not listed on DTL

- Individual performing study-related activities with no PI signature/initials on DTL unapproved greater than 30 calendar days
- Other (explain)

Lesser DTL Deficiencies

- Individual performing study-related activities with no PI signature/initials on DTL unapproved less than or equal to 30 calendar days
- Other (explain)

5.2.6 Assessment of the Regulatory Documentation Review

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

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

Acceptable Rating

- No deficiencies identified, and no follow-up required
- Few lesser deficiencies identified, and no follow-up required
- Any major deficiency identified during the review that was addressed and/or corrected prior to being notified of the audit for which a written and dated Corrective and Preventative Action (CAPA) plan exists and no further action is required by the ACCESS Hub, the institution, or the Principal Investigator because no similar deficiency has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a deficiency is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, the major deficiency(s) must still be cited and described in the audit report and CTMB must receive a copy of the CAPA plan at the time the final audit report is uploaded into the CTMB-AIS or by the date follow-up is due.

Acceptable Needs Follow-up Rating

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

Unacceptable Rating

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

If the Regulatory Documentation Review is rated as Acceptable Needs Follow-up or Unacceptable, the institution will be required to submit a written Corrective and Preventative Action (CAPA) plan and/or written response to the CCC. A copy of the CAPA plan/response, along with an assessment of adequacy by the ACCESS Hub must be uploaded into the CTMB-AIS (for CTMB review) by the CCC within 45 calendar days from the date the final audit report was uploaded into the CTMB-AIS. CCC policies and procedures may recommend and/or require additional actions or sanctions.

A reaudit is mandatory if an institution continues to participate in the CSRN for any audit component rated as Unacceptable. A reaudit should be conducted no later than a year after an Unacceptable audit.

5.3 Review of Participant Case Records

If records are not in English, then a qualified translator chosen by the review team or institution must be present. Source documentation of each participant case selected for review considered missing at the time of the auditing or monitoring visit must be supplied to the CCC within 10 business days of the audit date/monitoring visit.

5.3.1 Deficiency Type by Category

The following examples of deficiencies do not represent an all-inclusive list of possible deficiencies that may be found during the audit/monitoring visit as defined under Section 5.1. The term ‘intervention’ is intended to include non-treatment studies such as cancer screening, 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 missing
- Translated consent form document, short form or other form of translation not available or signed/dated by a non-English speaking study participant
- Consent form document not signed/dated by study participant prior to study registration/enrollment

- Consent form document does not contain all required signatures
- Consent form document signed was not the most current IRB-approved version at the time of participant registration
- Consent form document signed does not include updates or information required by IRB of record
- Study participant not re-consented or notified as required
- Consent form document for ancillary/advanced imaging studies not executed properly
- Other (explain)

Eligibility – Critical Deficiency

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

Eligibility – Major Deficiencies

- Review of documentation available confirms 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: Participant deemed ineligible based on laboratory/pathology reports following registration and changes based on central review of material.)
- Other (explain)

Screening Modality– Critical Deficiencies

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

Screening Modality– Major Deficiencies

- Incorrect screening modality
- Screening tests not reported or documented
- Screening tests not done per protocol
- Screening tests done but not reported
- Unjustified delays in screening
- Imaging agent not given per protocol
- Screening specimen not obtained or not appropriately obtained per protocol
- Other (explain)

Screening Outcome – Critical Deficiency

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

Screening Outcome – Major Deficiencies

- Screening result(s) not communicated to study participant

- Screening result(s) communicated incorrectly to study participant
- Screening result(s) incorrectly documented
- Diagnostic procedure(s) not performed
- Diagnostic procedure(s) not documented
- Standard of care not documented per protocol
- Other (explain)

Endpoint Assessment – Critical Deficiencies

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

Endpoint Assessment – Major Deficiencies

- Failure to report or document diagnosis of cancer
- Failure to report or document participant vital status (e.g., death)
- 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 or reporting to the ACCESS Hub and CCC
- 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
- Recurring under- or over-reporting of adverse events
- Other (explain)

Correlative Studies, Tests, and Procedures – Critical Deficiency

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

Correlative Studies, Tests, and Procedures – Major Deficiencies

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

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
- Additional screening tests not documented per protocol or documented incorrectly
- Standard of care screening not documented per protocol or documented incorrectly
- Frequent data inaccuracies in primary source documentation[a]; un-redacted data[b]
- Significant number of errors in submitted data[a]; data cannot be verified
- Delinquent data submission[c]
- Other (explain)

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

[b] 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.).

[c] 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, screening, follow-up, etc), and phase of the trial. ACCESS Hub and SDMC policies should be taken into consideration.

Assigning Lesser Deficiencies

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

5.3.2 Assessment of the Participant Case Review

Each category (Informed Consent, Eligibility, Screening Modality, Screening Outcome, Endpoint Assessment, Adverse Event, General Data Management Quality) for each participant case audited can be found to be Critical (as defined under Section 5.1), Major, Lesser, OK or Not Reviewed. If one or more categories is not reviewed for any reason (e.g., insufficient time for auditor/monitor to review, etc.) it must be explained in the participant case review section of final audit report.

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

Acceptable Rating

- No deficiencies identified, and no follow-up required
- Few lesser deficiencies identified, and no follow-up required

- Any major deficiency identified during the review that was addressed and/or corrected prior to being notified of the audit for which a written and dated Corrective and Preventative Action (CAPA) plan exists and no further action is required by the ACCESS Hub, the institution, or the Principal Investigator because no similar deficiency has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a deficiency is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, the major deficiency(s) must still be cited and described in the audit report and CTMB must receive a copy of the CAPA plan at the time the final audit report is uploaded into the CTMB-AIS or by the date follow-up is due.

Acceptable, Needs Follow-up Rating

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

Unacceptable Rating

- A single critical deficiency
- Multiple major deficiencies identified
- Multiple lesser deficiencies of a recurring nature found in most 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 CCC. A copy of the CAPA plan/response, along with an assessment of adequacy by the ACCESS Hub must be uploaded into the CTMB-AIS (for CTMB review) by the CCC within 45 calendar days from the date the final audit report was uploaded into the CTMB-AIS. CCC policies and procedures may recommend and/or require additional actions or sanctions.

A reaudit is mandatory, if an institution continues to participate in the CSRN for any audit component rated as Unacceptable. A reaudit should be conducted no later than a year after an Unacceptable audit or when sufficient new study participants have enrolled since the previous audit. If sufficient new study participants have not enrolled within a year from the previous audit, further discussion with CTMB is necessary prior to requesting an extension of the reaudit timeline in the CTMB-AIS.

5.4 Role of the Investigator During the Audit

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

5.5 Exit Interview

It is expected that the responsible Principal Investigator and designated staff be present at the exit interview whether the audit is conducted on-site or off-site. During the exit interview the audit team will review with the institution the preliminary findings, including items

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

SECTION 6 REPORTING OF AUDIT FINDINGS AND FOLLOW-UP

6.1 Preliminary Report of Audit Findings

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

6.1.1 Submission

The Preliminary Report of Audit Findings Form must be uploaded into the CTMB-AIS within one business day of completing the audit. The CTMB must be notified immediately by telephone (240) 276-6545 and by email (ReportingResearchMisconductConcerns@nih.gov) of any findings suspicious and/or suggestive of intentional misrepresentation of data and/or disregard for regulatory safeguards for either component (Regulatory Documentation and Participant Case Review) of an audit.

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

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

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

Participant Case Section - Briefly describe all deficiencies identified and appropriately label each deficiency as critical or major. If a participant case was reviewed that was not designated as an unannounced case, explain why it was not reviewed in full.

A revised Preliminary Report may be uploaded into the CTMB-AIS if it is within ten business days of Day 1 of the audit. The revisions must be identified and briefly described on page 2 of the Preliminary Report. Deficiencies identified or revised after 10 business days after Day 1 of the audit must be briefly described in the Final Audit Report.

6.1.2 Content

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

- Regulatory Documentation Review
- Participant Case Review*

* The total number of cases reviewed with any critical and major deficiencies identified must be listed by category in the Preliminary Report of Audit Findings.

6.2 Final Audit Report

6.2.1 Submission

The Final Audit Report must be uploaded into the CTMB-AIS within 70 calendar days of day one of the audit. Monitoring Reports are to be submitted within x days. This institution-specific report should summarize the findings at the time of the audit for each of the components of the audit. Recommendations by the auditors from the CCC should be noted in the General Comments or Exit Interview sections of the final audit report.

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

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

Final Audit Reports that are returned to the CCC for a correction or clarification must be returned (uploaded in the CTMB-AIS) within 10 business days. Also, all corrections or clarifications made should be explained in the General Comments section of the report.

6.2.2 Content of Final Audit Report

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

6.2.2.1 General Information

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

6.2.2.2 Review of the Regulatory Documentation

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

6.2.2.3 Review of the Participant 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)

- For findings related to documentation or reporting, ensure the deficiency is captured by category (i.e., informed consent; eligibility; screening modality; screening outcome; endpoint assessment; adverse event; test, correlative studies, tests, and procedures) where appropriate, rather than under General Data Management Quality
- The CTMB-AIS pre-populates and summarizes the deficiencies for each study participant and category in a table embedded in the report; this table calculates the total number of critical, major and lesser deficiencies for the total participant cases reviewed; if a participant case was selected for review but no categories were reviewed, it must not be listed in the table of the final report
- If a participant case was not reviewed in full that is not designated as an unannounced case, explain why it was not reviewed in full
- Under the Participant Case Review Assessment section of the final report, 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 response
- Provide an overall assessment for this component (Acceptable, Acceptable needs F/U, or Unacceptable), and indicate if a reaudit is required, including timeframe

6.2.2.4 Audit Procedures

In this section, summarize what was reviewed onsite versus off-site. Include mention of any pertinent information as it relates to the audit. Also provide an explanation if any component or category did not have a complete review, as planned.

6.2.2.5 General Comments

This section may be used to indicate if any data or correspondence was submitted by the institution following the audit which affects the information reported on the Preliminary Report of Audit Findings. Indicate which categories were affected and how.

6.2.2.6 Exit Interview

Indicate who was present and summarize the discussion of the audit findings, clarifications by the staff, and any recommendations by the audit team. If any portion of the audit was conducted off-site (in advance of the audit), the findings of that review should be discussed at the exit interview.

6.3 Monitoring Report

Feedback from the visit will be given to the ACCESS Hub Principal Investigator at the close of the visit and a written report will be uploaded to CTMB-AIS within 15 days of the visit. The PI will be given 2 weeks to respond in writing to any concerns identified. Both the site visit report and response will be provided to the PMC for their review and any further recommendations.

6.4 Corrective and Preventative Action (CAPA) Plan/Follow-up Response

As outlined under Sections 5.2.6 and 5.3.2, CAPA plan/follow-up responses are uploaded into the CTMB-AIS within 45 calendar days from the date the final report is uploaded in the CTMB-AIS by the CCC for CTMB review. The CAPA plan must include a cover letter from the CCC stating that the CCC has reviewed the CAPA plan/response(s) and find the response(s) adequate. Other pertinent correspondence or documentation related to the audit or visit 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.

Feedback from the visit will be given to the ACCESS Hub Principal Investigator at the close of the visit and a written report will be uploaded to CTMB-AIS within 15 days of the visit. The PI will be given 2 weeks to respond in writing to any concerns identified. Both the site visit report and response will be provided to the PMC for their review and any further recommendations.

6.5 Timeline for Uploading Preliminary Reports, Audit/Monitoring Reports, and CAPA Plans into CTMB-AIS

Submission Type	Due Date to Upload into CTMB-AIS
Preliminary Report for Audit Findings (Audits Only)	Within 1 business day of completing the audit
Monitoring Report	Within 15 business days from the last day of the monitoring visit
Audit Report	Within 70 calendar days of Day 1 of the audit date
CAPA Plan*	Within 45 calendar days from the date the final audit report is uploaded in the CTMB-AIS

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

6.6 Reaudits

When a reaudit is designated to take place as described under Sections 5.2.6 and 5.3.2, the reaudit requirement remains linked to the institution in the CTMB-AIS regardless of its status (i.e., active or withdrawn). If the institution is being withdrawn, the reaudit timeline on the final audit report for the applicable audit components are to be designated ‘No Reaudit’. If the institution rejoins the same ACCESS Hub at a later date, the reaudit must be conducted within 12 months from the first new accrual. The ‘No Reaudit’ timeline allows the CCC, ACCESS Hub, and CTMB to track these institutions that require a reaudit, if reactivated. For tracking purposes, any off-site/remote audit or reaudit must also be scheduled and reported in the CTMB-AIS.

6.7 For-cause Audits

A for-cause audit may be warranted when there are concerns or irregularities found through quality control procedures or when there are allegations of possible scientific misconduct. It is the responsibility of the CCC to immediately notify CTMB upon learning of any significant irregularities or allegations related to scientific misconduct by a staff member or institution participating in their research program. CTMB may coordinate or request that the CCC coordinate the for-cause audit. Selection of auditors to conduct For- Cause audit will be made jointly by the NCI, CCC and a joint course of action will be planned. Other federal agencies or offices may be invited to participate in an audit at the discretion of the NCI.

6.8 Probation of a Principal Investigator

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

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

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

6.9 Probation of a Participating Institution

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

The institution may also be assigned a mentor by the ACCESS Hub. The CCC may be involved in the development of the Site Improvement Plan in conjunction with the institution and ACCESS Hub. The institution Site Improvement Plan must address key infrastructural issues contributing to poor performance. A copy of the Site Improvement Plan is to be submitted to CTMB within 45 calendar days of the second unacceptable audit.

6.10 Suspension of a Principal Investigator and/or Participating Institution

If a critical deficiency is cited it will result in suspension of the Principal Investigator and/or participating institution. Additionally, if an audited institution fails to provide a CAPA plan for one or more audit components rated as acceptable needs follow-up or unacceptable within the required 45 calendar day timeline, the following actions will be imposed by the CCC.

- The CCC will provide written notice to the Principal Investigator at the institution that the response/CAPA plan is overdue and a 5 business day grace period will be granted for the submission of the response/CAPA plan.

- If follow-up or a CAPA plan is not received by the CCC during the 5 business day grace period, the ACCESS Hub will immediately suspend new participant registrations from that institution.
- If the audited institution is a Hub Affiliate of an ACCESS Hub, all new participant registrations will be suspended from both the Hub Affiliate and any associated Hub Sub Affiliates
- No new registrations will be accepted by the ACCESS Hub
- If follow-up or a CAPA plan is not submitted during the 5 business day grace period, a written explanation from the Principal Investigator detailing the reason for the delay must be included. Suspension of participant registrations will not be lifted until the institution submits the response/CAPA plan to the CCC and ACCESS Hub and the response/CAPA plan is reviewed and approved by CTMB. CTMB must receive written notification of the suspension and of the reinstatement (if applicable) of the institution.
- On subsequent audits, the failure to submit a timely response/CAPA plan may result with the institution being prohibited to participate in NCI-sponsored clinical trials through the CSRN.

6.11 Withdrawal of a Participating Institution

If improved performance is not documented after reaudits have taken place, the institution may be withdrawn by the CCC. Any such action will be done in consultation with CTMB. A for-cause (i.e., off-cycle audit) may take place at any site, at any time, if study participant safety or scientific misconduct is suspected.

Appendix 1 Guidance for Allegations of Research Misconduct

Guidance for Allegations of Research Misconduct

Reason for Guidance:

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

Who is affected by this Guidance:

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

Responsible Office:

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

Email: ReportingResearchMisconductConcerns@mail.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)."

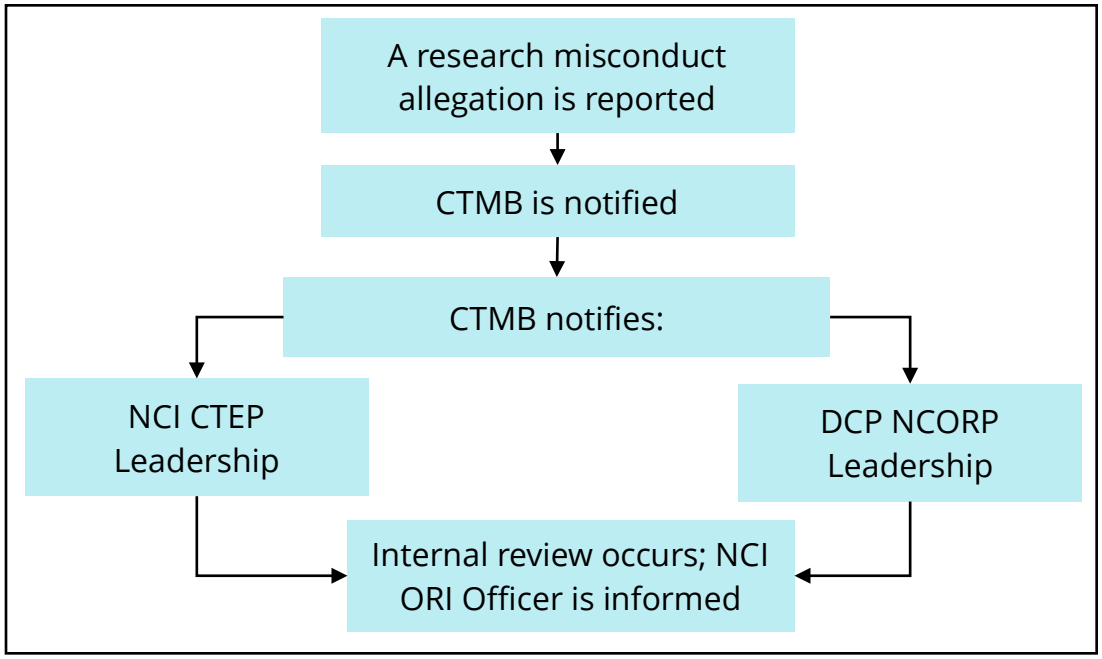
E. **Allegation** means the "disclosure of possible research misconduct through any means of communication (42 CFR 93.201)." The allegation can be communicated via written, oral, or other communication means to the institution.

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 have 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@mail.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)

Code of Federal Regulations. (2022). 42 CFR 93 (https://www.ecfr.gov/current/title-42/chapter-I/subchapter-H/part-93)

Appendix 2 Regulatory Documentation Review Worksheet

NATIONAL CANCER INSTITUTE
Division of Cancer Treatment & Diagnosis

Clinical Trials Monitoring Branch (CTMB)
Cancer Therapy Evaluation Program (CTEP)
and the Division of Cancer Prevention (DCP)

CSRN Regulatory Documentation Review Worksheet

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

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

Overall Comments:

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

Central Institutional Review Board (CIRB): Types of Deficiencies

Critical Deficiency	**Yes**	**No**	**Comments**
Any finding, identified before or during the review, that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines.	☐	☐	
Major Deficiencies	**Yes**	**No**	**Comments**
Unanticipated problems, Serious Non-Compliance and/or Continuing Non-Compliance (per OHRP) problems not reported	☐	☐	
Institution enrolls under an incorrect CTEP site code and the institution or institution CTEP site code is not covered by the CIRB	☐	☐	
Other (explain)	☐	☐	

Lesser Deficiencies	**Yes**	**No**	**Comments**
Copy of CIRB approval letter/study worksheet is not available or accessible at the time of the review	☐	☐	
Other (explain)	☐	☐	

Local Institutional Review Board (LIRB): Types of Deficiencies

Critical Deficiency	**Yes**	**No**	**Comments**
Any finding, identified before or during the review, that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines.	☐	☐	
Major Deficiencies	**Yes**	**No**	**Comments**
Initial approval by expedited review instead of full-board review	☐	☐	
Expedited reapproval for situations other than approved exceptions	☐	☐	
Registration and/or screening 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	☐	☐	

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 ACCESS Hub/CCC notification; this includes a 'Request for Rapid Amendment (RRA)' resulting from an Action Letter indicating temporary suspension of accrual with expedited review permitted	☐	☐	
Failure to submit or submitted after 90 calendar days, any reportable external safety report to the LIRB that is considered an unanticipated problem as defined by OHRP, unless there is a LIRB policy that does not mandate reporting of external safety reports	☐	☐	
Other (explain)	☐	☐	

Lesser Deficiencies	**Yes**	**No**	**Comments**
Protocol annual reapproval delayed 30 calendar days or less	☐	☐	
Delayed annual reapproval for protocol closed to accrual for which all study participants have completed an intervention	☐	☐	
Amendment editorial revision or administrative in nature or other Network specific document not submitted or not submitted timely to the LIRB	☐	☐	
Other (explain)	☐	☐	

Informed Consent Content (ICC): Types of Deficiencies

Critical Deficiency	**Yes**	**No**	**Comments**
Any finding, identified before or during the review, that meets the definition of a critical finding as defined in the CTMB auditing and monitoring guidelines.	☐	☐	
Major Deficiencies	**Yes**	**No**	**Comments**
Missing any of the following statements or language specific to the elements required per the federal regulations, when appropriate:	☐	☐	
a. Involves research, purposes; duration of participation; description of procedures; identification of experimental procedures	☐	☐	
b. Description of foreseeable risks or discomforts	☐	☐	
c. Description of any benefits to subjects or others	☐	☐	
d. Disclosure of alternative procedures or treatments	☐	☐	
e. Description of the extent of confidentiality of records	☐	☐	
f. Explanation regarding compensation and/or whether treatments are available if injury occurs, including who to contact if injury occurs	☐	☐	
g. Explanation of whom to contact for answers to pertinent questions about the research and whom to contact for questions related to research subject's rights	☐	☐	

h. Statement that participation is voluntary; refusal to participate involves no penalty or loss of benefits; subject may discontinue participation at any time	☐	☐	
i. Unforeseeable risks to subject, embryo or fetus	☐	☐	
j. Statement that circumstances in which subject's participation may be terminated by the investigator without subject's consent	☐	☐	
k. Statement of additional costs to subject that may result from participation in the study	☐	☐	
l. Statement of consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	☐	☐	
m. Statement that significant new findings which may be related to subject's willingness to continue participation will be provided to subject	☐	☐	
n. Disclosure of approximate number of subjects involved in the study	☐	☐	
o. Statement: "A description of this clinical trial will be available on www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time"	☐	☐	
Statement that a copy of the consent form will be given to the subject	☐	☐	
Failure to revise the informed consent document in response to an NCI Action Letter regarding risks	☐	☐	
Significant or substantial changes to the consent form document deviating from the CIRB-approved boilerplate (other than local context) not approved by the CIRB	☐	☐	

Consent form document contains changes not approved by the IRB of record, including changes to questions that do not match the model consent form	☐	☐	
Cumulative effect of multiple lesser deficiencies	☐	☐	
Other (explain)	☐	☐	
Lesser Deficiencies	**Yes**	**No**	**Comments**
Failure to have the informed consent document (after CIRB amendment approval) locally implemented within 30 calendar days of notification (posted on the CTSU website)	☐	☐	
Language/text is missing or added that is administrative or editorial in nature (e.g., rephrasing a sentence/section to add clarity, reformatting the document and/or changes made related to contact information are examples of an editorial or administrative change)	☐	☐	
IRB approved informed consent document with incorrect version date	☐	☐	
Other (explain)	☐	☐	

Delegation of Tasks Log (DTL): Types of Deficiencies

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

Appendix 3 Participant Case Review Worksheet

NATIONAL CANCER INSTITUTE
Division of Cancer Treatment & Diagnosis

Clinical Trials Monitoring Branch (CTMB)
Cancer Therapy Evaluation Program (CTEP)
and the Division of Cancer Prevention (DCP)

CSRN 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	☐	☐	☐	☐	☐	
Screening Modality	☐	☐	☐	☐	☐	
Screening Outcome	☐	☐	☐	☐	☐	
Endpoint Assessment	☐	☐	☐	☐	☐	
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	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)	☐	☐	

Screening Modality: 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**
Incorrect screening modality	☐	☐	
Screening tests not reported or documented	☐	☐	
Screening tests not done per protocol	☐	☐	
Screening tests done but not reported	☐	☐	
Unjustified delays in screening	☐	☐	
Imaging agent not given per protocol	☐	☐	
Screening specimen not obtained or not appropriately obtained per protocol	☐	☐	
Other (explain)	☐	☐	

Screening Outcome: 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
Screening result(s) not communicated to study participant	☐	☐	
Screening result(s) communicated incorrectly to study participant	☐	☐	
Screening result(s) incorrectly documented	☐	☐	
Diagnostic procedure(s) not performed	☐	☐	
Diagnostic procedure(s) not documented	☐	☐	
Standard of care not documented per protocol	☐	☐	
Other (explain)	☐	☐	

Endpoint Assessment: 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 document diagnosis of cancer	☐	☐	
Failure to report or document participant vital status (e.g., death)	☐	☐	
Other (explain)	☐	☐	

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 ACCESS Hub and CCC	☐	☐	
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	☐	☐	
Recurring under- or over-reporting of adverse events	☐	☐	
Other (explain)	☐	☐	

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	☐	☐	
Additional screening tests not documented per protocol or documented incorrectly	☐	☐	
Standard of care screening not documented by protocol or documented incorrectly	☐	☐	
Frequent data inaccuracies in primary source documentation[a]; unredacted data[b]	☐	☐	
Significant number of errors in submitted data[1]; data cannot be verified	☐	☐	
Delinquent data submission[c]	☐	☐	
Other (explain)	☐	☐	

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

[b] 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.).

[c] 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, screening, follow-up, etc.), and phase of the trial. ACCESS Hub and SDMC policies should be taken into consideration.