Policy Name: Quality Management and Assurance Department	**Policy Number:** 17.1
Section: Quality Management – 17	**Date Revised:** December 16, 2024

17 Quality Management

The Alliance has implemented a multi-faceted quality management approach to ensure protection of human subjects, integrity of clinical research data and adherence to the principles of Good Clinical Practice. Alliance strives to continuously improve processes and systems throughout the spectrum of quality control and quality assurance activities. Quality management is conducted as a partnership between clinical and protocol operations, statistics and data management, regulatory compliance, research administration and all units supporting the conduct of Alliance clinical research. Recent developments in quality management builds on Alliance's quality assurance capabilities, including the Alliance Audit Program, Institutional Performance Evaluation Committee and Quality Monitoring and Management Committee.

17.1 Quality Management and Assurance Department

Alliance Quality Management and Assurance Department (QMA) is responsible developing and overseeing clinical trial quality management and quality assurance functions. Quality Management (QM) staff monitor new drug application (NDA) registration trial activities essential to protecting the rights, welfare, and safety of human subjects and the quality of the clinical trial data utilizing a risk-based approach. QM staff manage the Quality Monitoring and Management Committee (QMMC) process. Quality Assurance (QA) staff are responsible for implementing the Alliance audit program and other quality assurance mechanisms, according to the Clinical Trial Monitoring Branch (CTMB) Guidelines. QMA staff develop controlled documents, including standard operating procedures (SOPs) and related training to ensure inspection readiness.

QMA may be consulted on issues escalated from regulatory and trial management staff. They may also be a reference for other members of the Alliance team for recommendations on potential quality related issues and CAPA requirements.

17.2 Alliance Quality Monitoring and Management Committee (QMMC)

The QMMC provides oversight of the conduct of the trial to ensure compliance with the protocol, GCP and other applicable regulatory requirements.

17.2.1 Studies requiring QMMC oversight

All Alliance-led prospective registration trials are monitored by the QMMC.

17.2.2 Function of the QMMC

The responsibilities of the QMMC are as follows:

- Monitor trial specific site performance, utilizing key performance indicators (KPI) to identify and address trends both at the study and site level
- Review data delinquency and protocol deviation reports with a focus on data quality, safety, and trial conduct
- Assess trial-level central monitoring, remote monitoring, and on-site monitoring activities
- Implement and manage escalation and corrective and preventive action plans for identified areas of noncompliance with protocol requirements and procedures

17.2.3 Overview of the QMMC procedure

Each study monitored requires monthly review of KPI metrics and discussion by the committee members on escalation of identified safety trends. Metrics reviewed include, but are not limited to, data delinquency, protocol deviations, early terminations, and adverse event data.

17.2.4 Membership

The QMMC consists of representatives from Quality Management, Audit, Regulatory, Study Management and SDMC.

17.2.5 Review Process

QMMC reviews sites with concerns for quality of clinical trial performance and subject safety.

Input is received from Clinical Study Managers and SDMC for a full spectrum review.

17.2.6 Recommendations/escalation process

QMMC may reach out to sites to request additional information about findings.

Recommendations are made on a case-by-case basis.

Recommendations may include, but are not limited to:

- Training of clinical investigator and site staff
- Additional monitoring at the site level
- Corrective and Preventive Action Plan (CAPA)
- Clarification of protocol requirements

Policy Name: Regulatory Authority Inspection Readiness Activities	**Policy Number:** 17.3
Section: Quality Management– 17	**Date Revised:** December 16, 2024

17.3 Regulatory Authority Inspection Readiness Activities

The Quality Department is primarily responsible for regulatory authority inspection readiness and preparation for the organization. In addition, they interact with participating sites to ensure they are ready for an inspection.

- Internal activities:
  - Develop, maintain, and train personnel on controlled documents related to inspection readiness
  - Coordinate activities and primary point of contact during regulatory authority inspections of Alliance
- Participating site activities:
  - Identify sites that are at high risk for inspection with metrics such as:
    - High participant accrual
    - Serious Adverse Event rates
    - Protocol deviations rates
  - Provide ongoing support before, during, and after an inspection
    - Before: Inspection readiness checklist, pre-inspection visits, training materials
    - During: Assigned point of contact, Alliance information provided upon request
    - After: Assistance with response and CAPA plans, if needed

Upon notification of a regulatory authority related to Alliance trials, sites must inform Alliance via email at compliance@alliancenctn.org.

17.4 Monitoring

Monitoring is performed for select Alliance trials and will be specified in the protocol. It is a quality control tool for determining whether study activities are being carried out as planned, so that deficiencies can be identified and corrected. Monitoring activities include communication with the Clinical Investigator (CI) and study site staff; review of the study site's processes, procedures, and records; and verification of the accuracy of data submitted to the sponsor.

17.4.1 Central Data Monitoring

Centralized monitoring is carried out by Alliance Statistics and Data Management personnel. Verification of data entry for study-specific fields within Rave are compared to source documents uploaded by participating site staff. Key data points reviewed include eligibility, treatment, and adverse events. Further information is included in chapters 8.3-8.4

17.4.2 On-site/remote Monitoring

On-site monitoring is managed and may be performed by Alliance clinical trials staff or by staff from a Contracted Research Organization (CRO). On-site monitoring focuses on identifying data entry errors (e.g., discrepancies between source records and case report forms (CRFs)) and missing data in source records or CRFs; providing assurance that study documentation exists; identifying and reviewing protocol deviations, assessing the familiarity of the site's study staff with the protocol and required procedures; and assessing compliance with the protocol and investigational product accountability.

Remote monitoring visits may be conducted per the monitoring plan. In certain circumstances, a remote visit may be conducted in place of an on-site visit with approval from Alliance.

17.5 Institutional audits

17.5.1 History

As the world's largest sponsor of clinical trials of investigational antineoplastic agents and cancer clinical trials, the National Cancer Institute (NCI) must ensure that research data generated under its sponsorship are of high quality, reliable, and verifiable. The NCI quality assurance and monitoring policies for clinical trials have been in evolution since the start of the National Clinical Trials Network (formerly the Clinical Trials Cooperative Group) Program in 1955. One important aspect of the quality assurance program is that investigators in the NCTN undergo peer review as part of the funding process. As the NCI clinical research program has increased in size and complexity, the systems for quality control became more formal and systematic.

In 1982, the NCI made on-site monitoring a requirement for the Clinical Trials Cooperative Group Program, cancer centers, and any other investigators conducting clinical trials under its IND sponsorship. Because quality control and assurance programs were in place in many cooperative groups, the NCI delegated much of its responsibility for on-site monitoring of investigational agent studies and clinical trials to the cooperative groups. The guidelines were later expanded to include monitoring of Community Clinical Oncology Programs (CCOPs) components by cancer centers that serve as their research bases.

In 2014, the Cooperative Group Program was replaced by the NCI National Clinical Trials Network (NCTN) program. In addition, the Community Clinical Oncology Program (CCOP) combined with the NCI Community Cancer Center Program (NCCCP) to create the NCI Community Oncology Research Program (NCORP).

17.5.2 Quality assurance

Since the multicenter nature of group trials presents obvious questions about variability, the groups long ago recognized the need for formal quality control and monitoring. Procedures were developed to monitor the overall progress of studies and for ensuring adherence to protocol and procedural requirements.

The groups perform two distinct kinds of monitoring. The first is periodic review of the overall progress of each study to assure that the projected accrual goals are met on a timely basis, that over accrual is avoided, that eligibility and evaluability rates do not fall below minimum acceptable

standards, and that risks are not excessive. The groups perform this function at least semiannually prior to their group meetings.

The second type of monitoring is a systematic and independent audit of trial related activities and documents to assure the quality of trial execution at the level of the investigator. The audit process enhances the delivery of accurate and reliable clinical trials data and results according to the protocol, sponsor's standard operating procedures, applicable regulatory requirements, and good clinical practices (GCP). This is commonly an on-site process and consists of reviewing a subset of patients on a trial. The audit program assures that the data used to analyze the trials are an accurate reflection of the primary data. The program requires an on-site comparison of the submitted data with the primary medical record for a sample of patient cases. At the same time, compliance with regulatory requirements for the protection of human subjects and investigational drug accountability are checked. The audit also provides educational support to the clinical trials sites regarding issues related to data quality, data management, and other aspects of clinical research quality assurance.

Also included in these central quality assurance measures is the assessment of protocol compliance. This is done in an increasingly systematic way and on an ongoing basis. For example, most groups conduct central pathology review for selected studies to reduce variability in diagnosis. To ensure adherence to protocol-specified treatment, radiotherapy films and surgery reports are also monitored centrally. Checks of submitted data sheets for protocol compliance ensure that treatment is delivered according to protocol stipulations and that appropriate study tests have been obtained. The study chair and/or the statistical center are responsible for confirming each case's eligibility and evaluability, based on the information gathered through these quality control mechanisms.

17.5.3 NCI audit participation

The Clinical Trials Monitoring Branch (CTMB) of the NCI maintains oversight responsibility for the network group auditing programs. The most recent CTMB Audit Guidelines for the establishment of auditing programs have been incorporated into the Alliance policies. The complete federal document can be found on the NCI/CTEP website (NCI Guidelines for Auditing Clinical Trials). The CTMB Guidelines may be referenced for any policies and procedures that are not specified within the Institutional Audits Policy.

CTMB staff reviews all audit schedules and all reports of audit findings. To assure consistency of auditing across the group/cancer center research bases,

a CTMB representative may attend on-site audits. Staff from the CTMB may make specific recommendations for action if they do not believe the action taken by the network group or site has been adequate.

The CTMB, as part of their clinical trials auditing service, contracts review of some audits. The role of the NCI representative is to monitor the audit process and to ensure that the requirements of the CTMB for auditing are being met. They review the audit case reports prepared by the auditors, assess the audit exit interview, participate in the pharmacy audit, etc. and provide the CTMB with a detailed report on the conduct and outcome of the audit.

17.5.4 Overview of Alliance auditing policies and procedures

The Alliance Audit Committee was developed to provide assurance that the data reported on Alliance research records, of all types, accurately reflect the data as reported in the primary patient record.

To ensure that data management practices in each Alliance institution adhere to protocol guidelines, submitted information is accurate and complete, and all Federal Human Subjects regulations and NCI guidelines for investigational drugs have been followed, the audits conducted of member institutions examine a meaningful and random sample of the following:

- Clinical records and abstracts
- Imaging reports and techniques
- Pathology, cytochemistry and RT submission compliance, if applicable
- Operative reports
- Laboratory data
- IRB reviews and consents
- Investigational drug compliance documents

17.5.5 Scheduling of audits

17.5.5.1 Selection of main member and affiliate member institutions for audit

All institutions are audited at least once every 36 months, but all are at risk for audit during any one year. New main member institutions are audited no longer than 18 months after entry of the first patient to assure performance standards are being met and as an educational experience for the new investigators and their staff. The initial audit may be sooner based on accrual. Initial audits are conducted on-site. Routine audits will be scheduled within 36

months after the previous audit. For high accruing main member institutions, it may be appropriate to audit these institutions on a more frequent interval given the high number of cases for review.

The Alliance Audit Program may request main members to conduct on-site pharmacy audits of their affiliates, utilizing the same on-site audit procedures used by the Alliance. If requested, each main member must appoint a pharmacy audit liaison to manage the affiliate pharmacy audits. The audit liaison should be a member of Alliance who is versed in the Alliance's audit policies. All pharmacy audit liaisons should have previous auditing experience and/or are required to participate in training sessions and/or modules. Physicians and staff from affiliates may not audit another affiliate.

Alternatively, these affiliates may be audited when the Alliance conducts the on-site audit of the main member institution.

Affiliate institutions must provide all required documents to conduct the audit at the main member institution the day of the audit or earlier if determined by the Alliance. It is strongly recommended that a representative from the affiliate be present at the main member institution during the audit. A separate Preliminary Report of Audit Findings and Final Audit Report are required for the main member institution and each affiliate institution audited.

An effort will be made to audit a pharmacy on-site at least every other audit, including a re-audit, if the deficiencies are related to drug inventory and the institution has registered patients on one or more studies with IND agents since the previous audit.

17.5.5.2 Scheduling audits for NCORPs and NCORP components

One audit will usually be conducted for the NCORP as a whole. Protocols and patient cases must be selected for review from each component where accrual has occurred. If the NCORP is audited as one entry, only one preliminary report and final audit report is required. This is the preferred method for auditing NCORPs and their components. Alternatively, the NCORP components may be audited as a separate entity.

If the component audit is conducted at the main NCORP, component institutions must provide all required documents to conduct the audit.

17.5.5.3 Scheduling of audits for inactive sites

Institutions remain at risk for audit even if their membership in the Group is no longer Active, since they have made a commitment to long-term follow-up of patients with provision of good quality data according to the study schedule.

17.5.5.4 Single-Site Audit Initiative (Multi-Group Audits [MGA])

Certain sites/organizations may be subject to audit by more than one Network Group at the same time. This CTMB and CTSU initiative is intended to promote more efficient auditing practices and are conducted according to these audit guidelines. These audits are coordinated by the CTSU.

17.5.5.5 Case/protocol selection

A minimum of four protocols representing studies conducted at the site should be selected when applicable. Emphasis should be given to registration trials, IND, multi-modality, advanced imaging studies, and prevention/cancer control trials, as well as those with high accrual.

A **minimum** number of cases equivalent to 10% of patients accrued since the last audit will be reviewed. The 10% of cases reviewed apply to each participating site being audited. For selection purposes, the 10% of chosen cases will always be rounded up. For selection of patient cases the following apply where appropriate:

(1) 10% Group/NCORP cases

(2) 10% from protocols with advanced imaging studies/imaging studies embedded in treatment protocols

(3) 10% of DCP cancer control/prevention cases

(4) A patient case from every registration trial must be selected for audit. This includes every NCI site Code being audited.

While most cases will be selected from patients accrued since the previous audit, any patient case may be at risk for selection for

audit. In addition, at least one or more **unannounced** cases will be reviewed if the total accruals warrant selection of unannounced cases. These cases may have a limited or full audit review. A limited review may include reviewing the patient informed consent document, patient eligibility and general data quality. However, if the unannounced cases only receive a limited review, these cases do not count towards the minimum of 10%.

Random selection of patient cases is used as often as possible balanced with the need to consider other factors such as date of enrollment, case complexity, treatment arm, etc.

17.5.5.6 Notification of audit

Institutions are notified of the date of the audit at least three months prior to the audit, although in some special circumstances the interval may be shorter. A list of the cases selected is sent to the institution 14-28 days prior to the audit to allow adequate time to prepare.

17.5.5.7 Audit team

Audit team members include Alliance audit staff and members of the Audit Committee. Principal investigators and clinical research professionals from any Alliance institution may also be asked to serve as ad hoc auditors. The auditors must be knowledgeable about the protocols to be reviewed, Alliance audit procedures, clinical trials methodology, NCI policies, and Federal regulations. All auditors must complete Alliance auditor training prior to their first audit and must maintain a signed confidentiality agreement on file at the Chicago office of the Alliance.

Alliance auditors will not complete site-specific training, such as EMR, HIPAA, etc, but will maintain a current human subjects training certification.

Each main member or NCORP principal investigator is responsible for recommending physicians who are able to serve as physician auditors.

17.5.6 Audit preparation by the institution

Principal investigators and institutional clinical research professionals are responsible for preparing for an audit.

The institution is responsible for ensuring that all relevant materials are available for review. If an institution is audited off-site at the Network Main Member, NCORP, or LAPs main member, the following records must be available:

17.5.6.1 IRB approvals, continuing reviews, amendment approvals, and safety reports.

17.5.6.2 Current versions of requested protocols.

1. Current locally utilized informed consent forms along with applicable model consent forms.

Note: The regulatory items above may be requested prior to the audit. At least three local consent forms will be audited.

2. NCI Drug Accountability Record Forms (DARFs) for control and satellite pharmacies, agent receipts, returns/destruction logs, transfer records, and/or logs for imaging/radiopharmaceutical agents.

   Note: The pharmacy should be alerted that the auditors may conduct an on-site inspection of storage, security, and temperature monitoring logs. The pharmacy items above may be requested prior to the audit.

3. Complete medical records.

   Note: De-identified source documentation is not acceptable. When imaging is used for disease response, physician auditors may request to review images.

4. Other relevant source documents or information, e.g. reports from the Imaging Core Laboratories, Central Laboratory/Pathology reports, etc.

5. For imaging studies: source documents/worksheets used for imaging acquisition, processing, quality assurance documentation, reader's interpretation, record of imaging

administration, patient/study participant monitoring (vital signs, monitoring of contrast reactions, etc.) and log of staff signatures and imaging responsibilities.

For comprehensive instructions on preparing for an audit, please see the information posted on the Alliance website.

17.5.7 Conduct of an Alliance audit

The auditors review specific data relating to regulatory requirements and research.

17.5.7.1 Regulatory requirements

An audit consists of reviewing and evaluating (1) conformance to IRB, informed consent content requirements, and maintenance of delegation of tasks log (if applicable) (2) drug accountability and pharmacy compliance including the use of NCI DARFs, or NCI approved drug accountability forms, and (3) individual patient cases. During the audit, **each** of these three components are independently assigned an assessment of either **Acceptable, Acceptable Needs Follow-up, or Unacceptable**, based on findings at the time of the audit. Assessment is based on evaluation of critical, major and lesser deficiencies.

For each component rated as **Acceptable Needs Follow-up** or **Unacceptable**, the institution is required to electronically submit a written response and/or Corrective and Preventive Action (CAPA) plan to Audit@AllianceNCTN.org. Once approved by the Alliance, the CAPA plan will be forwarded to the CTMB. The approval of CAPA plans does not constitute approval of site-specific policies and procedures. Each audit report indicates the date the Alliance must receive the response/CAPA plan. If the plan is not received and approved by the date indicated in the audit report, patient registration may be suspended at that institution.

A re-audit is mandatory for any component rated as **Unacceptable**. Depending on the individual circumstances a re-audit may also be scheduled when the result is designated Acceptable, Needs Follow-up.

17.5.7.1.1 Critical, Major and lesser deficiencies

Deficiencies are categorized as either “critical”, "major" or "lesser"; examples are provided in the appropriate sections. An exhaustive list of examples is not given, but the examples are intended to guide the reviewers in their assessment and categorization of specific deficiencies. Deficiencies too trivial to warrant comment are not included in the report.

Critical deficiency: any condition, practice, process or pattern that adversely affect the rights, safety or well-being of the patient/study participant and/or the quality and integrity of the data; includes serious violation of safeguards in place to ensure safety of a patient/study participant and/or manipulation and intentional misrepresentation of data

Major deficiency: a protocol variance that makes the resulting data questionable.

Lesser deficiency: a deficiency that does not affect the outcome or interpretation of the study and is not described as a major deficiency. An unacceptable frequency of lesser deficiencies is treated as a major deficiency.

17.5.7.2 Review of IRB documentation and informed consent content

See section 5.2 of the CTMB Audit Guidelines for complete details concerning IRB documentation and informed consent content.

17.5.7.2.1 IRB documentation

Before a patient enters a study, all federal requirements for the protection of human subjects must be met. Every institution must have documentation of IRB approval.

Maintaining a separate chronologic file for correspondence regarding IRB information for each protocol is recommended so that information regarding annual renewals and changes in protocols is readily available for audit review.

Documentation of initial IRB approvals with the IRB chair's signature and date, annual re-approvals for each audited protocol and approval for amendments should be available at the site visit for review by the audit team. The same is true for IRB review of safety reports. If an institution being audited is covered by another institution's IRB, the written agreement should be available for review.

For institutions that use the NCI Central Institutional Review Board (CIRB) as their IRB of record for particular trials, the following items must be provided for auditing:

1. Initial approval letter from CIRB to the Principal Investigator (PI) for study activation
2. CIRB Approval of the Annual Signatory Institution Worksheet About Local Context
3. Documentation that IRB approval was obtained prior to patient registration
4. Reporting of any unanticipated problems, serious non-compliance and/or continuing non-compliance problems per OHRP/FDA policy
5. Other correspondence with CIRB such as annual re-approvals, protocol amendments, etc.

Critical IRB deficiency:

- Any finding identified before or during an audit that is suspected to be fraudulent activity

Major IRB deficiencies may include but are not limited to:

- Initial approval by expedited review for protocols requiring full board review per OHRP guidelines.
- Expedited re-approval for situations other than approved exceptions.
- Registration and/or treatment of patient prior to full IRB approval.
- Re-approval delayed more than thirty days, but less than one year.
- Registration of patient on protocol during a period of delayed re-approval or during a temporary suspension (i.e., Request for Rapid Amendment).
- Missing re-approval.

- Expired re-approval.
- Internal reportable adverse events reported late or not reported to the IRB.
- Failure to submit or submitted after 90 days, any reportable external safety report to the IRB that is considered an unanticipated problem as defined by OHRP, unless there is an IRB policy that does not mandate reporting of external safety reports.
- Lack of documentation of IRB approval of a protocol amendment or action letter that affects more than minimal risk or IRB approval is greater than 90 days after the Network Group's notification; this includes a Request for Rapid Amendment (RRA) resulting from an action letter indicating temporary suspension of accrual with expedited review permitted.

Lesser IRB deficiencies may include but are not limited to:

- Protocol annual re-approval delayed less than 30 days.
- Delayed re-approval for protocol closed to accrual for which all patients/study participants have completed therapy.

17.5.7.2.2 Informed consent content (ICC)

The audit team verifies that the most recent IRB-approved local informed consent document for at least three protocols (if the number of protocols allows) contains the elements required by federal regulations. In addition, each of the three informed consent documents should be checked to ensure they contain the risks and alternatives listed in the model informed consent document approved by the NCI. If CTSU case(s) are reviewed, at least one local informed consent document should be reviewed for content

Risks, opt in/opt out Alliance-specific translational research questions and alternatives to study treatment may not be added or deleted from the model informed consent document.

If the site identifies a **significant** error in risk (e.g. missing risks, or risks erroneously attributed to the drug), the responsible investigator must send an email

to the protocol coordinator listed on the study cover page and the Alliance regulatory group providing written justification for correction of the identified error. The Alliance will determine if a protocol amendment is required to address the issue.

Institutions using the NCI Central Institutional Review Board (CIRB) as their IRB of record must follow the NCI-CIRB policy regarding acceptable and prohibited ICD modifications.

Critical ICC Deficiency:

- Any finding identified before or during an audit that is suspected to be fraudulent activity

Major ICC deficiencies related to informed consent content (does not represent an all-inclusive list of the major deficiencies that may be found):

- Omissions of one or more risks/side effects as listed in the model informed consent document.
- Omission of one or more revisions to the informed consent per protocol amendment or failure to revise an informed consent in response to an NCI action letter regarding risks that require a change to the informed consent.
- Omission of one or more required informed consent elements required by federal regulations.
- Changes made to the informed consent document not approved by the IRB of record.
- Multiple cumulative effects of minor problems for a given informed consent.

Lesser ICC Deficiencies:

- When the CIRB is the IRB of record, failure to have the informed consent document locally implemented within 30 days of notification (posted on the CTSU website)
- IRB approved informed consent document with incorrect version date

17.5.7.2.3 Review of the Delegation of Task Log (if applicable)

The Clinical Investigator (CI) is held responsible for the conduct of a clinical trial and may delegate activities/duties associated with the clinical trial to his/her staff. In such a case, a Delegation of Task Log (DTL) must be maintained and include anyone who contributes significant trial-related duties. This log is generated and maintained by institution and protocol by the CI via the DTL link on the CTSU website.

Auditors will request the DTLs for appropriate protocols and review for implementation and maintenance.

Critical DTL Deficiency:

- Any finding identified before or during an audit that is suspected to be fraudulent activity

Major DTL Deficiency:

- Performing tasks not assigned to individual
- Failure to keep DTL current
- Individual not listed on DTL

17.5.7.2.4 Assessing the IRB, ICC and DTL

The following categories outlined in table 17-1 should be used in assigning a final assessment to the IRB/ICC component of the audit.

Table 17-1. IRB/ICC/DTL audit assessment categories

Acceptable	• No deficiencies identified. • Few lesser deficiencies identified. • Any major deficiencies identified during the audit that were addressed and/or corrected **prior to** the audit for which a written and dated CAPA plan exists, and no further action is required by the Alliance, or NCORP, 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. In any case, the Alliance will provide the CTMB with a copy of the CAPA plan at the time the final audit report is submitted or by the date follow up is due.
Acceptable Needs Follow-up	• Multiple lesser deficiencies identified. • Major deficiencies identified during the audit but not corrected and/or addressed **prior to** the audit.
Unacceptable	• A single critical deficiency identified. • Multiple major deficiencies identified. • Excessive number of lesser deficiencies identified.

Alliance uses an algorithm as a guideline to determine the final assessment for the IRB/ICC component of an audit. The Alliance tallies the total number of items that are reviewed for a particular IRB/ICC review. IRB records for each protocol that are reviewed and each individual consent reviewed are considered separate items. If a single critical deficiency is identified or if the total number of major deficiencies cited is 20 % or greater of the total items that are reviewed for this segment of the audit, the IRB/ICC component of the audit is rated **Unacceptable**.

While this algorithm is used to assess the majority of IRB/ICC audit ratings, exceptions may be made by the Audit Steering Committee in consultation with the chair of the Audit Committee and the Chief Administrative Officer.

17.5.7.3 Review of accountability of investigational agents and pharmacy operations

An effort will be made to audit a pharmacy on-site at least every other audit, including a re-audit if the deficiencies are related to drug inventory and/or security and the institution has registered patients on one or more studies with IND agents since the previous audit.

Agent accountability and storage procedures described in this section are required under federal regulations and NCI policy for

NCI-supplied study agents (by PMB/CTEP or designated company/Group for DCP and imaging agents). See NCI/CTEP policies under the Agent Management section of the CTEP/PMB website.

An Oral NCI Investigational Agent (Drug) Accountability Record Form (Oral DARF) has been created and all transactions with oral agents must be recorded on this DARF. Agent transactions for formulations other than oral must be recorded on the NCI Investigational Agent (Drug) Accountability Record Form (DARF).

A waiver statement allowing use of electronic DARFs (eDARFs) has not been issued by the NCI and the NCI does not endorse any eDARF pharmacy package. Institutions that choose to use an electronic accountability system must ensure the database is capable of producing a paper printout that is identical to the NCI DARF. Electronic accountability system database limitations are not valid reasons for improper accountability documentation according to NCI policy.

All protocols that use investigational drugs, or commercially available drugs for an investigational purpose when designated by the protocol, must have a specific drug supply for use with that protocol only. This means there may be several supplies of the same drug, each designated for use for only one protocol. Separate NCI DARFs for each study listed by study number must be kept. Multi-agent protocols require a separate NCI DARF for each agent. Each different strength or dosage of a particular agent must also have a separate NCI DARF. For open-label studies, multiple patients may be treated with one drug and each drug receipt and dispensing date is to be recorded on that NCI DARF. DARFs cannot be patient-specific, except in the instance where the drug is being compared with a placebo in double-blind fashion and is supplied per patient by NCI. Refer to the NCI/CTEP Investigator's Handbook for information on drug accountability and the NCI regulations for accountability of investigational agents.

Auditors are required to inspect the drug logs and tour the area where the investigational drugs are stored (on-site audits). The pharmacy (if one participates in the handling of protocol drugs) must also be visited to evaluate storage and security compliance. Arrangements should be made with the staff pharmacist for the audit

team to visit the pharmacy area. If no pharmacy is used, drug-handling procedures in the clinic/office must be audited.

The investigator ordering and/or dispensing agents (or co-signing for others) must be currently registered with PMB, DCTD, NCI. Procedures must be in place in the pharmacy and followed to ensure that the person prescribing the DCTD-agent is an investigator currently registered with PMB and/or the prescription is co-signed by the registered investigator.

17.5.7.3.1 Guidelines for conducting the review

Because of the difficulty categorizing critical, major and lesser deficiencies related to investigational drug accountability and storage, auditors will determine the rating of this component based on the findings of compliance to the required procedures for drug accountability and storage.

The following table lists compliant and non-compliance issues for the review of accountability of investigational agents and pharmacy operations.

Table 17-2. Assessing compliance for NCI DARFs completely and correctly filled out

Compliance	Non-Compliance
• Maintain complete, accurate and timely records of agent disposition of all study-supplied agents using NCI Investigational Agent (Drug) Accountability Record Forms (DARFs) • Oral study-supplied agents are documented on the Oral DARF • NCI DARFs are utilized to track cancer control/imaging study-supplied agents, or other accountability log captures the same information as NCI DARF • Paper and/or electronic DARFs (eDARFs) contains all required information; paper printout of eDARF is identical to NCI DARF • Corrections on DARFs are lined out, initialed and dated with no erasures and whiteouts; corrections on eDARFs are documented • Agent was dispensed to a registered patient/study participant and documented on the appropriate DARF • Appropriate documentation of multi-dose vial agent dispensing to multiple patients/study participants on separate lines of the DARF • Patient/study participant returns of oral study-	• NCI DARF not maintained or not maintained completely, accurately or on a timely basis • Oral NCI DARF not maintained for oral study-supplied agents, not maintained completely, accurately or on a timely basis • Lack of a DARF(s) to verify cancer control/imaging study supplied agents are administered to patients/study participants • Paper and/or electronic DARFs (eDARFs) do not contain all information or are not completed as required; paper printout of eDARF is not identical to the NCI DARF • Erasures or “whiteouts” on paper DARF • Corrections are not lined out, initialed and dated on paper DARF • Corrections are not appropriately documented on eDARF in electronic inventory system • Study-supplied agent dispensed to a registered patient/study participant and not recorded on the

supplied agents are documented on the oral DARF • Patient/study participant returns of non-oral, non-patient-specific agent supplies are *not* documented on the DARF • Patient/study participant returns of non-oral, patient-specific agent supplies are documented on the DARF • [For NCI-sponsored Study] An institution or centralized pharmacy service (Control) may receive NCI-supplied study agent directly from NCI and is permitted to deliver (transport, not re- ship or repackage) NCI-supplied study agent to the institution's Satellite Dispensing Areas • [For NCI-sponsored Study] Study Agent has been transferred to an authorized investigator and/or protocol with CTEP approval	• appropriate DARF • Multiple dose vials not used for more than one patient/study participant and/or doses not documented correctly on separate lines of the DARF • Dispensing of study-supplied agent to a non-registered patient/study participant recorded on the DARF • Patient/study participant returns of oral study-supplied study agents *not* documented on the Oral DARF • Patient/study participant returns of non-oral, non-patient-specific agent supplies are documented on the DARF • Patient/study participant returns of non-oral, patient-specific agent supplies are not documented on the DARF • [For NCI-sponsored Study] NCI-supplied study agents are repackaged and/or reshipped to other investigators, patients, or locations by mail or express carrier • [For NCI-sponsored Study] Study agent has been transferred to an unauthorized investigator or protocol without CTEP approval

Table 17-3. Assessing compliance for DARFs protocol and study agent specific

Compliance	Non-Compliance
• Only study-supplied agents used to treat patients/study participants and study-supplied agents not used for other purposes • Protocol using multiple study-supplied agents have a separate DARF for each agent • Separate DARFs are maintained by protocol, study agent, strength, 'dosage form' (e.g., oral, injectable), and by ordering investigator • A separate patient-specific DARF is maintained for each patient/study participant on a patient- specific supply study, as directed by the protocol	• Substitution of any study-supplied agent, with non-study supplied study agent, including commercial agents • DARF maintained by lot # • One DARF used for more than one protocol • One DARF used for a protocol using multiple study agents • One DARF used for multiple agent strengths, dosage forms, or ordering investigators • Single DARF used for multiple patients/study participants on study when patient-specific DARF should be maintained • Study-supplied agent used for pre-clinical or laboratory studies without written approval by NCI

Table 17-4. Assessing compliance for satellite records

Compliance	Non-Compliance
• Satellite Dispensing Area DARF is used at each location where study-supplied agent is received from the Control dispensing area and is stored more than a day • Satellite Dispensing Area records are available the day of the audit • Satellite Dispensing Area and Control records match and are accurately maintained • Unused and un-dispensed study-supplied agent is documented on Satellite Dispensing Area DARF as returned to Control for disposition (i.e., transfer, return and/or to be locally destroyed)	• No satellite DARFs in use when required • Satellite DARFs not available at the time of the audit • Satellite and Control records do not match or are not accurately maintained • Unused and un-dispensed study-supplied agent is not documented as returned to Control dispensing area; Satellite Dispensing Area is inappropriately transferring and/or locally destroying study-supplied agent

Table 17-5. Assessing compliance for NCI DARFs kept as primary transaction record

Compliance	Non-Compliance
• Study-supplied agent order receipts/ documentation (paper or electronic) are retained and available for review • Documentation on Control DARF of study- supplied agent transactions such as agent returns, authorized agent transfers or authorized agent local destruction • Balance on DARF matches physical inventory • [For NCI-sponsored Study] Written documentation of NCI authorization for transfer of study-supplied agent between investigators, protocols or institutions or for local destruction of unused/un-dispensed NCI-supplied study agent is maintained (paper or electronic)	• Study-supplied agent order receipts/documentation are not retained or not available for review • Lack of documentation on Control DARF of study-supplied agent transactions and local destruction • Quantities not accounted for in physical inventory; quantity does not match DARF • [For NCI-sponsored Study] No written documentation of NCI authorization of transfer or local destruction of NCI-supplied study agent maintained

Table 17-6. Assessing compliance for return of drug to NCI

Compliance	Non-Compliance
• Return of unused/un-dispensed NCI-supplied study agent to NCI or locally destroyed with NCI authorization when notified study agent is no longer suitable for clinical use; Return Form or local destruction authorization is maintained • Return of unused/un-dispensed NCI-supplied study agent to NCI or locally destroyed with NCI authorization or transferred to another NCI protocol (with NCI approval), when studies are complete or discontinued. Return Form	• Unused/un-dispensed NCI-supplied study agent is not returned, not transferred to an appropriate NCI protocol or not destroyed within 90 days of notification from NCI; NCI- supplied study agent is locally destroyed without NCI authorization or not locally destroyed per local institution's destruction policy • Agent returned to PMB that should have been destroyed on-site or agent returned to PMB that

or local destruction authorization is maintained • NCI-supplied study agent is returned, transferred or locally destroyed within 90 days of study completion, when requested by the NCI, or when patients/study participants are in follow-up and NCI-supplied agent is not being administered • [For Non-NCI sponsored Study] Study agent final disposition of inventory is documented on DARF	was not supplied by PMB • Failure to maintain Return Form or documentation of authorized local destruction; no written NCI authorization for transfer or local destruction • Unused/un-dispensed NCI-supplied study agents not returned, transferred or locally destroyed within 90 days when patients/study participants are in follow-up and no NCI-supplied study agent is being administered [For Non-NCI sponsored Study] Study agent final disposition of inventory is not documented on DARF

Table 17-7. Assessing compliance for agent storage

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

Table 17-8. Assessing compliance for adequate security

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

Table 17-9. Assessing compliance for authorized prescription(s)

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

17.5.7.3.2 Assessing the accountability of investigational agents and pharmacy operations

The following categories in table 17-10 should be used in assigning a final assessment to this component of the on-site audit. CTMB strongly recommends an "on-site" audit be conducted every other 3-year cycle. The main member, NCORP, or the Alliance may conduct an on-site pharmacy inspection.

Table 17-10. Pharmacy audit assessment categories

Acceptable	• Compliance found for all categories. • Any non-compliant item identified during the audit that was addressed and/or corrected prior to audit for which a written and dated Corrective and Preventive Action (CAPA) plan exists and no further action is required by the Network Group, NCORP Research Base, CTSU, the institution, or the principal investigator. No further action is necessary because no similar non-compliance issues have occurred since the CAPA was implemented. However, this approach may not be applicable if the non-compliance is associated with a safety concern and determined that further action is necessary.
Acceptable Needs Follow-up	• Category found non-compliant during the audit, which was not corrected and/or addressed prior to the conduct of the on-site audit.
Unacceptable	• A single Critical Non-compliance finding • Multiple non-compliant categories identified. • Inability to track the disposition of NCI-supplied study drug
No Assessment Required	• No IND or NCI-supplied study drug is in stock or in use during the audit period. • This designation applies under the following two conditions: • The review of the pharmacy consists of only security, storage and review of pharmacy procedures to ensure investigator has an active PMB registration. • Review of security, storage and pharmacy procedures were found to be compliant.
Limited Review Needs Follow-up	• Non-compliance identified under Pharmacy and audit was limited to review of storage, security and/or pharmacy procedures; and CAPA plan or follow-up response is requested.

17.5.7.4 Review of patient case records

Alliance patient data submitted by the institution to the Statistics and Data Center (SDC) are compared to patient source documents so that the submitted data will be verified against the primary medical record.

Assessment of patient cases should include:

1. Properly signed and dated consent documents (using the original consent documents when possible), including documentation of the consent process
2. All eligibility criteria
3. Correct treatment and treatment sequence
4. Evaluation of disease outcome/tumor response
5. Reporting of adverse events related to treatment
6. General quality of the data submitted, supporting documents uploaded and required/optional specimens submitted

Data that could likely affect every major study endpoint described in the protocol objectives and statistical sections are reviewed using primary documents either by the audit team or as part of central data review.

Auditing Patient Cases for Studies in Medidata RAVE
Targeted Source Data Verification is a system utilized by auditors reviewing patient records to electronically record audit activity directly in iMedidata Rave (Rave) for those studies using Rave to manage patient clinical data.

Source documents should be independently verifiable. Copies of Group study forms generally are not considered to be primary source documents. The use of flow sheets as primary source documentation is strongly discouraged, except for flow sheets that are signed, dated and accepted as part of the official institutional medical record. Primary laboratory reports, progress notes, etc., are considered adequate. Documentation of oral drug administration

should be included in the patient's primary record independent of the flow sheet (e.g., notation in progress notes or photocopy of prescription, as well as documentation in the NCI Drug Accountability Record Form where appropriate).

Per GCP requirements, corrections to paper source documents are to be done by a single line through the error, initials of the person making the corrections, and the date of correction. The correction on CRFs should be supported by the source data. For unusual changes, a brief explanation should be given. If there is conflicting information in the source documents, the PI should indicate in a study note which information was used and why those data were chosen.

Auditor review of source documentation through electronic medical records and electronic imaging is allowable. A staff member must be present to assist with navigating through the system.

Per FDA regulations, the medical record should contain documentation in the case history for each study volunteer that the study consent document was explained to the patient, questions were answered, and informed consent was obtained. This documentation should be included in a progress note, nurse's note, or elsewhere in the medical record to verify informed consent was obtained.

The CTMB Guidelines section 5.4 allows for missing documentation in the patient case review at the time of the audit to be submitted to the audit team after the audit. The audit team leader will provide the site with a list of unconfirmed items at the exit interview. The missing documentation must be submitted in one submission to the audit team leader within one week following the audit.

A **critical deficiency** is defined as any finding identified before or during an audit that is suspected to be fraudulent activity

A **major deficiency** is defined as a variance from protocol-specified procedures that makes the resulting data questionable.

A **lesser deficiency** is a deficiency that is judged to not have a significant impact on the outcome or interpretation of the study and is not described above as a major deficiency. **An unacceptable**

frequency/quantity of lesser deficiencies should be treated as a major deficiency in determining the final assessment of a component.

17.5.7.4.1 Examples of critical, major and lesser deficiencies

Informed Consent-Critical Deficiencies

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

Informed Consent-Major Deficiencies

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

- Consent of ancillary/advanced imaging studies not executed properly

Eligibility – Critical Deficiency

- Any finding identified before or during an audit that is suspected to be fraudulent activity

Eligibility – Major Deficiencies

- Review of documentation available at the time of the audit confirms patient/study participant did not meet all eligibility criteria and/or eligibility requirements were not obtained within the timeframe as specified by the protocol
- Documentation missing; unable to confirm eligibility [Exception: Patients deemed ineligible based on laboratory/pathology reports following registration and changes based on central review of material.]

Treatment – Critical Deficiencies

- Any finding identified before or during an audit that is suspected to be fraudulent activity
- Incorrect agent/treatment/intervention used

Treatment – Major Deficiencies

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

documented

- Timing and sequencing of treatment/intervention not per protocol
- Unjustified delays in treatment/intervention

Disease Outcome/Response – Critical Deficiency

- Any finding identified before or during an audit that is suspected to be fraudulent activity

Disease Outcome/Response – Major Deficiencies

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

Adverse Events – Critical Deficiency

- Any finding identified before or during an audit that is suspected to be fraudulent activity

Adverse Events – Major Deficiencies

- Failure to report or delayed reporting of an

adverse event that would require filing an expedited Adverse Event (AE) report or reporting to the Group

- Adverse events not assessed by the investigator in a timely manner (per protocol)
- Grades, types, or dates/duration of serious adverse events inaccurately recorded
- Adverse events cannot be substantiated
- Follow-up studies necessary to assess adverse events not performed
- Recurrent under- or over-reporting of adverse events

General Data Management Quality – Critical Deficiency

- Any finding identified before or during an audit that is suspected to be fraudulent activity

General Data Management Quality – Major Deficiencies

- Recurrent missing documentation in the patient/study participant records
- Protocol-specified laboratory tests not done, not reported or not documented
- Protocol-specified diagnostic studies including baseline assessments not done, not reported or not documented
- Protocol-specified research/advanced imaging studies not done or submitted appropriately
- Frequent data inaccuracies
- Errors in submitted data
- Delinquent data submission (> 6 months delinquent is considered a major deficiency; a 3-6 month delinquency is considered a lesser deficiency)

17.5.7.4.2 Assessing the findings from patient case records

The following categories in table 17-11should be used in assigning a final assessment to this component of the audit.

Table 17-11. Patient case records audit assessment categories

Acceptable	• No deficiencies identified. • Few lesser deficiencies identified and no follow-up is requested • Any major deficiency identified during the audit that was addressed and/or corrected **prior to** the audit for which a written and dated Corrective and Preventive Action (CAPA) plan exists and no further action is required by the Alliance, NCORP Research Base, the institution, or the principal investigator because no further deficiency has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a deficiency is associated with a safety concern and determined that further action is necessary (to be discussed with CTMB liaison). In either case, CTMB must receive a copy of the CAPA at the time the final report is submitted.
Acceptable Needs Follow-up	• Multiple lesser deficiencies identified. • Major deficiencies identified during the audit but not corrected and/or addressed **prior to** the audit.
Unacceptable	• A single critical deficiency identified. • Multiple major deficiencies identified. • Multiple lesser deficiencies of a recurring nature found in a majority of the patient cases reviewed.

The Alliance uses an algorithm (table 17-12) as a guideline in assessing the final rating for the patient case review. The number of patients reviewed is multiplied by six (there are six categories in the patient case review; informed consent, eligibility, treatment, disease outcome/response, adverse events, and general data quality). The number 100 is divided by the product. The result is the point value assigned to each lesser deficiency. Each major deficiency is worth double the point value that is assigned to a lesser deficiency. The point value for all major deficiencies and lesser deficiencies should then be added. This sum is then subtracted from 100 in order to determine the final rating score.

- A final rating score of less than 70 is considered an unacceptable assessment for the patient case review segment of the audit.
- A final rating score of less than 77 is considered unacceptable for a re-audit.

Table 17-12. Final rating for the patient case review

Algorithm	Line
Number of patients.	*1.* _____
Number of lesser deficiencies.	*2.* _____
Number of major deficiencies.	*3.* _____
Multiply *line 1* by 6, which is the number of categories. This is the **number of items**.	*4.* _____
Divide 100 by *line 4*. This is the **point value for each lesser deficiency.**	*5.* _____
Multiple *line 5* by 2. This is the **point value for each major deficiency**.	*6.* _____
Multiple *line 2* by *line 5*. This is the **score for lesser deficiencies**.	*7.* _____
Multiple *line 3* by *line 6*. This is the **score for major deficiencies**.	*8.* _____
Add *lines 7* and *8*. This is the **total deficiency score**.	*9.* _____
Subtract *line 9* from 100. This is the **final rating score**.	*10.* _____

While this algorithm is used to assess the ratings of the majority of patient case review audits, the group chair or designee, in consultation with the Chair of the Audit Committee, Audit Program Director, and Chief Administrative Officer, may make exceptions.

A minimum number of four patient cases are required for utilization of the algorithm.

The audit ratings for audits with less than four patient cases will be assessed on a case-by-case basis.

17.5.7.5 Exit interview

At the conclusion of the visit, the audit team conducts an exit interview. It is expected that the Principal Investigator or designee and designated staff be present at the exit interview. Additional personnel may be present at the discretion of the principal investigator. An appropriate amount of time should be set aside for the audit team to review with the institution the preliminary

findings, items reviewed "off-site", and recommendations from the audit team.

The exit interview should provide an opportunity for immediate dialogue, feedback, clarification, and most importantly, education.

During this interview, specific problems or questions are discussed. The list of unconfirmed items should be reviewed and provided to the PI and/or lead CRP by the audit team leader. General issues of concern and the major deficiencies should be brought to the attention of the institution staff. It is very important to discuss these issues and to allow the principal investigator to provide clarifications or explanations that could have a direct influence on the final report submitted to the NCI.

17.5.8 Re-audits

A re-audit is mandatory for any component rated as **Unacceptable** if the institution continues to participate in the Alliance or NCORP Research Base. It is not necessary that the re-audit be conducted on-site. Depending on the nature of the deficiencies that resulted in the Unacceptable rating, the re-audit may be conducted as an off-site review. A re-audit should be done no later than one year after an Unacceptable audit or when sufficient patients have been accrued.

If only the IRB or pharmacy component is rated Unacceptable, an off-site re-audit of that component may be conducted depending on the nature of the deficiencies. Unacceptable pharmacy audits for security or shelf balance issues will be conducted on-site.

If the patient case review component is rated Unacceptable, re-audits must be conducted on-site. In such cases, the IRB/ICC and pharmacy components will also be audited. On a case-by-case basis, complete re-audits (three components) may be conducted after an Unacceptable rating in only the IRB/ICC or pharmacy component.

17.5.9 Audit review

17.5.9.1 Audit evidence of scientific misconduct

The audit team leader must notify the Alliance Chief Administrative Officer, or in his/her absence another designated person within the Office of the Group Chair, immediately if the audit team uncovers any evidence of systematic or apparently

deliberate submission or intent to submit false data to the Alliance. The Chief Administrative Officer immediately notifies the Group Chair, the Chair of the Audit Committee, and CTMB of this occurrence. See also section 3.4, Individual Scientific Misconduct Policy.

If still on site and it is practical to do so, the audit team will immediately takes steps to preserve the evidence of false data submission and undertake expansion of the audit to gather additional information. A re-audit with an augmented team which may include NCI, Office of Research Integrity (ORI), and FDA representatives will be scheduled by Alliance in cooperation with the appropriate federal agencies.

Any data irregularities identified through quality control procedures or through the audit program that raise any suspicion of intentional misrepresentation of data must be immediately reported to the Alliance Chief Administrative Officer who will report suspicions or findings to the Group Chair, the Chair of the Audit Committee, and the NCI. The CTMB must be notified immediately by telephone of any findings suspicious and/or suggestive of intentional misrepresentation of data and/or disregard for regulatory safeguards for any of the three (IRB/ICC, pharmacy, and patient case) components of an audit. It should be emphasized the irregularity/misrepresentation does not need to be proven and a reasonable level of suspicion suffices for CTEP notification. It is also essential that involved individual(s) and/or institutions follow their own institutional misconduct procedures in these matters.

17.5.9.2 Action taken based on audit results

For audits where the findings indicate poor data quality or noncompliance with regulatory requirements, Alliance may take a variety of actions depending on the scope and severity of the problem.

- The PI and institution's staff is advised of the problems encountered during the audit and advised of ways to improve performance.

- If the Alliance is not satisfied that the problems are correctable, it may choose to terminate the membership or affiliate status of the institution.

- Audit reports are reviewed by Alliance audit staff and then forwarded to the principal investigator, outlining the assessment of the audit and any recommendation for action to be taken. If an institution has received an Unacceptable rating in any of the three components (IRB/ICC, pharmacy, patient case), or Acceptable Needs Follow-up (ANFU) with a re-audit requirement, the Audit Committee will also receive an electronic copy of the report.

- The principal investigator and the lead clinical research professional receive final audit reports a maximum of 70 days after an audit takes place. Included with the Final Audit Report is a cover memo that states the audit ratings, explains which deficiencies must be addressed with a written corrective and prevention plan and gives a due date.

- The CAPA plan must include measures for prevention of deficiencies in the future. A response confirming correction of a specific deficiency (e.g., submission of a data form or adverse event report) is insufficient without an overall corrective plan. In many cases, corrective action may entail a review of policies and procedures, additional training of clinical research staff and/or communication with the IRB regarding procedures and timelines. In addition, preventative plans need to be included to ensure the issues do not re-occur and double-check systems are in place.

- If a CAPA plan is determined to be unsatisfactory, and/or if additional information or documentation is required, the Audit Program Director will contact the principal investigator and the lead clinical research professional to obtain an additional response. If the request(s) for an additional response are not answered in a timely fashion, patient registration privileges at the institution may be suspended.

- The CAPA plan is due 15 business days from the date the report was distributed.

- An unacceptable rating in the IRB/ICC, patient case review, or pharmacy sections of the audit is evaluated on a case-by-case basis by the Chief Administrative Officer and/or Group Chair and may also warrant immediate suspension of registration privileges depending upon the evaluation. Registration privileges are reinstated upon receipt of a CAPA plan and

approval of the plan by the Audit Program Director, in consultation with the Chief Administrative Officer.

- If an institution fails to provide an acceptable CAPA plan for one or more audit components rated as Acceptable Needs Follow-Up or Unacceptable within 45 days of when the Final Audit Report was initially distributed, written notice will be provided to the principal investigator that the corrective action is overdue, and a five day working grace period will be granted for the submission of the CAPA plan. If a CAPA plan is not received within this five-day grace period, patient registration privileges may remain suspended. If the institution is an affiliate, patient registration privileges for the main member may also be suspended at this time.

- If the CAPA plan is not submitted within the five-day grace period, it must include a written explanation from the PI that explains the reason for the delay. The suspension of patient registration privileges will not be lifted until an acceptable CAPA plan is submitted and approved by the Audit Program Director, in consultation with the Chief Administrative Officer, and is forwarded and reviewed by the CTMB.

17.5.9.3 Report submission to CTMB

Report of preliminary audit findings must be submitted to the CTMB within one working day of completing the audit. Critical and Major deficiencies should be described. This report is not intended to be a complete or exhaustive list of all deficiencies contained in the final audit report.

The Alliance audit program staff is responsible for submitting all audit reports and related correspondence to the CTMB. If the CTMB has any comments or questions, the audit staff is notified. The audit staff forwards CTMB comments, if appropriate, to the principal investigator and the lead clinical research professional.

17.5.9.4 Changes to the Alliance database subsequent to audit

The Statistics and Data Center staff receive copies of audit reports. The SDC staff is responsible for determining if data changes may be required based on audit findings.

17.6 Institutional Network Performance Evaluation

The Alliance membership networks will be evaluated twice yearly coinciding with the Alliance Meetings in three primary areas: quality, timeliness, and group participation. Points will be assigned based on multiple parameters, as shown below. The points will be added to derive an overall score. An overall score can range from -15 to +16.

A network with an overall score below 0 in any evaluation period requires review by the Institutional Performance Evaluation Committee (IPEC) for potential action, including warning or probation. As stated in the Institutional Probation Policy (section 2.11), a network with an overall score of -1 to -5 will receive a warning for substandard performance. The IPEC may recommend probation if a network meets one of the following criteria:

- Two successive evaluation periods with substandard overall scores of -3 or less.
- One evaluation period with substandard overall score of -6 or less.
- Three successive evaluation periods with substandard scores of -2 for timeliness.

17.6.1 Institutional Network Performance Evaluation Scoring System

Below tables 17-13 through 17-15 outline the parameters for each primary area (quality, timeliness, and group participation).

Table 17-13. IPEC scoring for quality

Parameter	Values	Points
Ineligibility (% of patients with eligibility review completed that were deemed ineligible) i.e.: # patients ineligible / # patients evaluated NOTE: This includes all patients evaluated who were accrued by the membership on RAVE trials (patients are not filtered by date of registration to the trial).	>3%	-1
	1-3%	0
	<1%	1
Main member audit (for each component—IRB/ICC, pharmacy, patient case—the most current audit results of acceptable, acceptable needs follow-up [ANFU] or unacceptable will be evaluated)	Unacceptable	-2
	ANFU	0
	Acceptable	2
Specimen condition (% of samples intact out of all samples received)	<90%	-1
	90-95%	0
	>95%	1

Early termination of follow-up (% of patients deemed lost to follow-up, withdrew consent for follow-up or deemed canceled, i.e., protocol treatment not received) i.e.: # patients that terminated follow-up early / # patients that were accrued by the membership NOTE: This includes all patients accrued by the membership on RAVE trials (patients are not filtered by date of registration to the trial).	>5%	-1
	3-5%	0
	<3%	1

Table 17-14. IPEC scoring for timeliness

Parameter	Values	Points
Data submission (% of eCRFs submitted on time) i.e. # forms received on time during report period / total of # forms that were due during the time period plus # forms due before the time period that are still outstanding Baseline forms are given a 15-day grace period after the target date. Treatment forms are given a 30-day grace period after the target date. Follow up forms are given a 60-day grace period after the target date.*	<75%	-2
	75% - <80%	-1
	80% - <85%	0
	85% - <90%	1
	≥90%	2
Response to Queries (% of issued queries that were resolved on time) i.e. # query responses received on time during report period / total of # query responses that were due during the time period plus # query responses due before the time period that are still outstanding Queries are given a 30 day grace period after the target date.*	<75%	-2
	75% - <80%	-1
	80% - <85%	0
	85% - <90%	1
	≥90%	2
Specimen Submission (% of primary and mandatory samples received on time)	<75%	-2
	75% - <80%	-1
	80% - <85%	0
	85% - <90%	1
	≥90%	2

* The grace period for timeliness is based on standards developed by an NCI working group.

Table 17-15. IPEC scoring for group participation

Parameter	Values	Points
Audit participation by physicians and clinical research professionals (CRPs) in the past two years	No participation	0
	MD or CRP participation	1

17.7 Institutional probation

The Alliance is committed to ensuring that Alliance member institutions meet high quality standards in the conduct of clinical research and the protection of human subjects. Alliance monitors compliance to federal regulations and Alliance guidelines through various mechanisms, including on-site audits and institutional performance evaluations. The criteria for institutional probation set forth below allow Alliance to identify and monitor institutions that have demonstrated substandard performance, with the goal of improving performance at institutions on probation.

17.7.1 Probation based on institutional network performance evaluation

The Institutional Performance Evaluation Committee (IPEC) reviews the performance of main member networks according to the *Institutional Network Performance Evaluation Scoring System.* The main member networks will be evaluated twice yearly in three primary areas: quality, timeliness, and group participation. Please see the Institutional Network Performance Evaluation Policy (section 17.6) for additional information.

17.7.1.1 Criteria for warnings of substandard institutional network performance

Prior to a recommendation for probationary status, the IPEC may issue warnings to networks with substandard overall scores of -1 to -5 during one evaluation period.

17.7.1.2 Criteria for IPEC recommendation of probation of main member networks

The IPEC may recommend probation to the Membership Committee if a network meets one of the criteria below.

- Two successive evaluation periods with substandard overall scores of -3 or less
- One evaluation period with substandard overall score of -6 or less
- Three successive evaluation periods with substandard scores of -2 for timeliness

17.7.2 Recommendation of probation for an affiliate member

In rare circumstances, IPEC may recommend probation of an affiliate, if it is determined that the substandard overall score for two consecutive evaluation periods is attributable to a particular affiliate.

If the network is underperforming in more than one area, IPEC considers the entire network to be underperforming and recommends probation for the entire network.

17.7.3 Probationary process

The intent of the probationary process is to provide a network the opportunity to improve its Alliance clinical research program, and regain status as an Alliance member in good standing.

The Institutional Performance Evaluation Committee reviews the performance of main members and affiliates using established criteria. The chair of IPEC notifies the principal investigator (PI) in writing of the conclusions of the IPEC.

The IPEC may recommend to the Membership Committee that an institutional network be placed on probation based on substandard performance. Following review and discussion, the Membership Committee votes to determine whether to recommend to the Board of Directors that an institutional network be placed on probation.

The Membership Committee shall communicate the recommendation of probation to the PI of the main member network so evaluated, at a date no later than 30 days prior to the scheduled Board of Directors meeting. The network PI may appeal the recommendation to the Board of Directors before a final decision is rendered. The Board of Directors shall make the final decision and a simple majority shall indicate final approval of recommendations.

After the Board of Directors votes to place a network or individual network sites on probation, the group chair or designee (e.g., chief administrative officer) notifies in writing the main member principal investigator of probationary status, the deficiencies cited, and the penalties associated with probationary status. The group chair or designee copies an institutional official (e.g., dean, executive vice president, cancer center director, hospital director) who is responsible for oversight of the Alliance program.

The principal investigator is required to submit a response and a detailed site improvement plan to the quality management staff within 30 days of the notice. The quality management staff may be involved in the development of the site improvement plan in conjunction with the institution. The institutional site improvement plan should address key infrastructural issues contributing to poor performance. Alliance leadership may suspend patient registration privileges if a satisfactory site improvement plan is not received.

During the probationary period, accrual will be closely monitored by the Alliance with increased utilization of quality control procedures at the time of patient registration and timely review of data submission. The member institution may also be assigned a mentor by the Alliance.

Until the probationary status is lifted, the Alliance does not recognize the institution(s) as a member in good standing. Institutions that do not resolve issues responsible for probationary status within one year following an extension of probationary status, and who cannot successfully resolve such issues by changing to another membership level, will be expelled from Alliance. The Membership Committee shall communicate the recommendation to the PI of the main member network so evaluated, at a date no later than 30 days prior to the scheduled Board of Directors meeting. The network PI may appeal the recommendation to the Board of Directors before a final decision is rendered. The Board of Directors shall make the final decision and a simple majority shall indicate final approval of recommendations for lifting of probationary status or one-year extension of probationary status. A two-thirds vote is required for a change in institutional membership level or expulsion of a member from the Alliance. Institutions who are expelled from Alliance may re-apply for membership no sooner than three years after the date of expulsion. See section 8 of the Alliance Bylaws.

All correspondence regarding probationary status of affiliates is addressed to the main member network PI. It is the responsibility of the network PI to inform the individual network institution of probationary status and to work with the institution to develop an appropriate corrective action plan.

The IPEC, Membership Committee, and Board of Directors are scheduled to review probationary status semi-annually. The Audit Committee will report unacceptable audit results to the IPEC and the Membership Committee, as appropriate.

17.7.3.1 Implications of probationary status

The implications of probationary status for Alliance participation and membership depend on the level of membership and duration

of the probationary status. At each anniversary of a network or network institution probation, the IPEC, Membership Committee, and Board of Directors review the status of the cited institution and votes by majority on the progression of the sanctions according to the following schedule.

Immediate

If the network is placed on probation and the institution has a voting seat on the Board of Directors, the PI does not vote at the Board of Directors meetings. If a network institution is place on probation, the PI retains the privilege to vote at the Board of Directors meetings.

The Alliance quality management staff will work closely with the institution to assist in resolving the issues that resulted in a probationary status.

Year 1 Anniversary

The network's accrual privileges are limited according to the following guidelines.

- A main member network is limited to registering 15 patients per calendar year, or 50 % of the rolling three-year annual average (up to 100 patient registrations), based on calendar years, whichever is greater. The accrual limitation will be in effect until probation is lifted.
- If the cause for probation is data driven, network accrual privileges may temporarily be limited to 15 patient registrations until the data issues are resolved. Upon resolution of data issues the probationary accrual limitations (15 patient registrations or 50 % of annual average whichever is greater) are in effect until probation is officially lifted.
- An affiliate that is placed on probation is not permitted to register more than five patients per year.

Year 2 Anniversary

Expulsion. The Board of Directors may vote to terminate membership of the network or affiliate in the Alliance. See section 8 of the Alliance Bylaws regarding conditions for expulsion.

17.7.4 Probation based on unacceptable audits

In compliance with the CTMB Guidelines, if a participating institution (main or affiliate) is deemed unacceptable for the same audit component(s) on two consecutive audits, the institution will be placed on probation. Probationary status may be conferred by the Office of the Group Chair, in conjunction with the Audit Committee. This may occur prior to and separate from the IPEC, Membership Committee, and Board of Directors deliberations. The group chair and chair of the Audit Committee will notify the Membership Committee when probationary action has been taken as a result of unacceptable audits and request an affirmative vote as appropriate. Audit ratings are included in the IPEC criteria for institutional evaluation.

Following a second unacceptable audit for the same audit component, the group chair or designee (e.g., chief administrative officer) notifies in writing the main member principal investigator of probationary status, the deficiencies cited and the penalties associated with probationary status. The group chair or designee copies an institutional official (e.g., dean, executive vice president, cancer center director, hospital director) who is responsible for oversight of the Alliance program.

The principal investigator is required to submit a response and a detailed site improvement plan to the group chair or designee, within 30 days of the notice. The Office of the Group Chair and audit personnel may be involved in the development of the site improvement plan in conjunction with the institution. The institutional site improvement plan should address key infrastructural issues contributing to poor performance. The group chair or designee may suspend patient registration privileges, if a satisfactory site improvement plan is not received.

During the probationary period, accrual will be closely monitored by the Alliance with increased utilization of quality control procedures at the time of patient registration and timely review of data submission. The member institution may also be assigned a mentor by the Alliance.