2   Institutional membership

Members of the Alliance will be institutions meeting all requirements for membership, which include accrual, data quality and timeliness, adherence to Alliance policies and procedures, and participation in Alliance scientific activities. See the Alliance Bylaws for additional details. Institutional member networks consist of a main member with or without affiliates or components.

2.1   Membership criteria

Refer to the Alliance Bylaws sections 1-4 for qualifications for prospective members.

The Membership Committee considers the following aspects in their evaluation of prospective members:

- Multi-disciplinary institutional resources for clinical trials
- Scientific interests
- Prior clinical research experience
- Level of participation in cancer research cooperative group trials
- Patient population
- Prior institutional performance evaluation metrics
- Satisfactory audit results
- Other regulatory considerations

Policy Name: Applying for Membership	**Policy Number:** 2.2
Section: Institutions – 2	**Date Revised:** January 1, 2018

2.2   Applying for membership

The Alliance reviews institutional membership applications monthly or as needed. The institutional membership application is available on the Alliance public website under the Membership tab (http://www.allianceforclinicaltrialsinoncology.org).   An application will be reviewed by the Membership Committee only if the institution has an active NCI ID and FWA. The Membership Committee evaluates the completed applications for appropriateness of facilities, institutional resources and past performance in clinical research. Following a decision by the Membership Committee, applicants will be notified of approval status. If the Membership Committee approves the application, it then submits its recommendation for approval to the Board of Directors for vote. Refer to the Alliance Bylaws section 5 for additional details regarding the membership evaluation procedure.

Affiliate applications can be approved by the Membership Committee without Board approval.

2.3   Membership activation

If the Board of Directors approves the Membership Committee's recommendation for approval, applicants will receive a notification of approval status with additional information. Alliance staff will activate the member on the Alliance roster in the Cancer Trials Support Unit (CTSU) Regulatory Support System (RSS) and the Clinical Trials Monitoring Branch (CTMB)-Audit Information System. Alliance staff will manage the PI and Lead CRP roles in the institution roster(s). The Lead CRP will add persons and person roles to the institution roster via the NCORP Management System (NCORP SYS) or CTSU Roster Update Management System (RUMS). Upon activation of Alliance membership, the institutional network will be granted access to the Alliance website and Alliance Web applications. Alliance members will have access to clinical trials on the CTSU menu.

2.3.1   Roster

2.3.1.1   A site must be included on the roster if it meets the following definition of engagement in research as defined by OHRP (45 CFR part 46).   An institution is engaged in a particular non-exempt human subjects research project when its employees or agents for purposes of the research project obtain:

1. Data about the subjects of the research through intervention or interaction with them
2. Identifiable private information about the subjects of the research, or
3. The informed consent of the human subjects for the research

2.3.1.2   **NCI Tiers**

The Alliance adheres to the institution membership structure as mandated by the NCI. There are four types of member networks that are structured based on their funding mechanism. The member networks can have up to 3 levels (tiers) of member types:

- Tier 1 members of Lead Academic Performance Site (LAPS) and NCI Community Oncology Research Program (NCORP) represent the administrative offices of the member network. Tier 1 of the Main member networks (non-LAPS, non-NCORP) can either be an administrative office of a health system (if approved by CTSU) or an accruing institution.

- Tier 2 members include affiliates of Main members, NCORP components, and LAPS Main member, LAPS affiliates, LAPS Integrated components as identified in the LAPS grant. LAPS can also have aligned affiliates. Aligned affiliates are institutions/performance sites that are affiliated with the LAPS network but are not included in the LAPS grant. The Alliance Operations Center grant provides the per case payments for aligned affiliates.
- Tier 3 members are sub-component/sub-affiliates. A sub-component or sub-affiliate is an institution or practice site that shares the same FWA, IRB, governance structure, employees of either a Tier I or Tier II member. An example of a sub-affiliate is a physician practice that has a primary clinical site and has additional office locations where the same physicians treat patients. The primary clinic site is the parent and the additional locations are sub-affiliates.

2.3.2   Regulatory documentation

Regulatory documentation includes: documentation that the institution has a current Federalwide assurance (FWA) with the Office for Human Research Protections (OHRP); current Food and Drug Administration (FDA) 1572 forms and financial disclosure forms (FDFs) for all investigators; and certification that all investigators have received training in Human Subjects Protection (HSP) and Good Clinical Practice (GCP).

NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. Registration is accomplished via the NCI Registration and Credential Repository (RCR). Additional details can be found on the NCI/CTEP website.

2.3.3   Financial documentation for institutions

Financial documentation for institutions includes a services agreement signed by the principal investigator and institutional official and W-9 form confirming correct legal name and tax-ID of the institution.

2.4 Responsibilities of a main member

The principal investigator will be required to sign a membership agreement that includes a summary of key policies and procedures, including conflict of interest, scientific misconduct, membership accrual requirements, confidentiality, audit requirements, institutional performance and publications.

The main member institution is responsible for all aspects of conducting Alliance clinical trials within its network. The main member is responsible for monitoring the conduct of a study both at the main member and all sites within its network.

Responsibilities are listed below. Affiliate and sub-affiliate institution have their own unique characteristics but each main institution must be sure that mechanisms are in place so that these responsibilities are met.

2.4.1 Communications

The main member institution must confirm that all research staff have access to the Alliance electronic distribution of information. This information includes new protocols, addenda, memos, letters, and miscellaneous items from the Alliance. The Alliance clinical research office at the institution is frequently located in the oncology or hematology department of a hospital or medical school and it is vitally important that a good communications network is established so that Alliance members from other modalities (e.g., pathology, radiation oncology, surgery, transplant, imaging, correlative sciences) receive information on a timely basis regarding Alliance protocols, meetings, and other relevant topics. It is the responsibility of the main member to assure that their network institutions have the same type of communications network established to distribute information to all disciplines within the affiliate.

2.4.2 Electronic communication

The Alliance makes use of electronic mail and the website to provide information to its members. It is the responsibility of the main member to confirm that participants are able to access this information. The Alliance requires all members to have a unique e-mail address. All network and site PIs, Co-PIs, Lead CRPs and Secondary Lead CRPs are required to receive broadcast emails.

2.4.3   Management of network data

Data forms should be submitted according to specifications in the protocol. The main member is responsible for the data quality and timeliness of their network sites.

If an affiliate institution changes main member networks, the new main member becomes responsible for the timely submission of data for all Alliance patients at the affiliate institution, including patients registered through the previous main member.

A main member institution is responsible for collection of data for patients at an affiliate institution even if that affiliate is dropped from the network. The Institutional Performance Evaluation Committee (IPEC) includes, in its evaluation of a main network, patients from dropped affiliates who are still in the evaluation window.

2.4.4   Investigational drug handling

All affiliates order drugs directly from either the NCI or from a private source as specified in the protocol. However, the main member is responsible for ensuring that all federal regulations regarding investigational drugs are adhered to by the main member and the affiliates. Annually, each Alliance investigator must sign a FDA Form 1572 stating that the investigator will adhere to the federal regulations and each main member should confirm that its investigators are in compliance and have a current FDA Form 1572 on file with the Pharmaceutical Management Branch. Each institution that orders drugs is responsible for any protocol specific requirements related to drug ordering and shipping. Refer to the Investigator's Handbook on the NCI/CTEP website for more specific investigational drug information. See also Section 12, Investigational Product.

2.4.5   Human subjects protection

The main member is responsible for ensuring that all federal regulations are adhered to regarding protection of human subjects. No patient may be entered on a study until the protocol has been reviewed and approved by the IRB of record for the institution where the patient is being treated. Alliance protocols also require a patient to sign an informed consent and the registering institution must confirm that the informed consent has been signed before the patient can be registered to the study. Protocol-specified research interventions, including interventions conducted at a facility external to the registering institution, must be covered under an IRB approval.

2.4.6 Training

The main member serves as a resource for institutional personnel to further their understanding of clinical studies and to expand and encourage participation in the studies. Training programs should be provided for all personnel. The Alliance conducts education and training sessions during the Alliance Group meetings and posts educational resources on its website. All Alliance members are encouraged to participate in these training opportunities.

2.5 Institutional roles and responsibilities

2.5.1 Main member principal investigator

2.5.1.1 Network responsibilities

The main member principal investigator (PI) is responsible for the conduct of Alliance activities at a main member institution and for the integrity of all data submitted from the institution's affiliate network. The PI is ultimately responsible for the conduct of research and regulatory compliance at affiliate institutions. The PI is responsible for managing the funds to support the work of the Alliance at their institution, and receive other funds from the Alliance in support of Alliance activities.

The obligations of institutional membership are set forth elsewhere in these policies. It is the job of the PI to ensure that these are met by all institutions in the network or to correct deficiencies in institutional performance that are documented by Alliance mechanisms, set forth elsewhere in these policies.

Each main member institution shall also have a co-principal investigator, who shall assume responsibility in place of the principal investigator if for any reason the principal investigator is unable to perform duties required for Alliance institutional membership.

Each affiliated institution in a network must name a responsible principal investigator. This PI may be the main member PI or another investigator responsible for clinical trial conduct at the affiliate institution with oversight from the main member PI.

2.5.1.2 Institutional responsibilities

Membership in Alliance is granted to an institution not an individual. It is the institution's responsibility to ensure that the Alliance research program is vigorously and competently administered at that institution, and to recommend to the group chair and Membership Committee, as appropriate, changes in the institutional PI. Although the Membership Committee considers the qualifications of PIs when approving institutions for membership in the Alliance, and must acknowledge changes in PI when proposed by the institution, the Alliance is not involved in

the nomination or selection process which occurs at the institutional level.

The PI receives Alliance communications concerning activities at his/her institution, or appoints individuals to act on behalf of the PI for these purposes. The PIs name individuals from their institutions as authors on Alliance publications, according to Alliance guidelines on publication. The PI takes responsibility for the performance of their institution's interdisciplinary team of Alliance participants, and for the introduction of new scientists to Alliance activities. The PI ensures that specialists from relevant oncology disciplines are available within the institution to support the activities of Alliance; makes certain that the institution meets minimum accrual standards required to maintain Alliance membership; and oversees all aspects of data and specimen management for Alliance studies within the institution. The PI also ensures that Alliance studies are conducted with appropriate attention to the protection of human subjects in research, all applicable regulations and that the physicians who oversee the conduct of Alliance studies disclose potential conflicts of interest. The PI ensures that the delegation of authority and tasks is documented and that research personnel are adequately trained.

2.5.2 Affiliate member principal investigator

The principal investigator (PI) for an affiliate institution is responsible for the conduct of Alliance activities at an Alliance institution, human subjects protection and the integrity of all data submitted from the institution.

These responsibilities are similar to the responsibilities of the principal investigator at the main member institution.

2.5.3 Clinical research professionals

Clinical research professionals (CRPs) at an Alliance institution may include clinical research associates (CRAs), surgical CRAs, oncology research nurses, and others. In general, responsibilities for CRPs at an Alliance institution include the following:

- Obtain IRB approval for Alliance protocols, consent forms, annual continuing review, and any protocol amendments that require IRB approval

- Obtain patient consent (and re-consents, when appropriate) for participation in Alliance studies
- Maintain study-specific regulatory and training files
- When authorized, register consented eligible patients to Alliance studies.
- Submit accurate protocol-required data, specimens and supporting documents according to protocol requirements
- Maintain a research record of supporting documents for each Alliance patient
- Participate in Alliance audits at the institution
- Maintain a patient notification policy

2.5.3.1 Lead CRP

Each Alliance institutional network must designate a lead CRP to receive and distribute communications from the Group and be the primary clinical research professional contact for the network. A secondary CRP should be designated to serve as a backup to the lead CRP. Institutional responsibilities of the lead CRP vary by network.

2.5.4 Withdrawn or terminated institutions

If an institution is withdrawn from the Alliance or terminated by the Alliance, the institution will remain responsible for data submission until such time that there are no longer patients in treatment or follow up, or the patient(s) are transferred to another Alliance member. The main member remains responsible for data from withdrawn affiliates.

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2.6 Office for Human Research Protections assurances

2.6.1 Assurances

The regulations require that each institution engaged in the conduct of research involving human subjects provide a written assurance of compliance that it will comply with the requirements set forth in these regulations. The document is referred to as an assurance. Each assurance sets forth the commitment of the institution to employ the basic ethical principles of the Belmont Report and to comply with the regulations. There are several kinds of assurance documents. Where an independent investigator is to provide an assurance of compliance to OHRP the document is called an agreement.

Under the Department of Health and Human Services (HHS) human subjects protection regulations at 45 C.F.R. 46.103, every institution engaged in human subjects research supported or conducted by DHHS must obtain an assurance of compliance approved by the Office for Human Research Protections (OHRP).

All institutions applying for membership in the Alliance that do not currently have an assurance must obtain a Federalwide Assurance (FWA). The institution is responsible for ensuring that all institutions and investigators engaged in its U.S. federally supported human subject research operate under an appropriate OHRP or other federally approved assurance for the protection of human subjects.

2.6.2 Reporting institutional assurance compliance

The institution's FWA must be included with the member's roster information and remain current. Alliance must have documentation that there has been prospective review, at least annual continuing review, and review of significant protocol updates.

2.7　Institutional Review Boards

Each Alliance member institution must have an approved institutional review board (IRB) under the HHS Regulations for the Protection of Human Subjects (45 CFR 46) in order to enter patients on Alliance protocols. The IRB must follow the federal regulations regarding IRBs. The IRB must also be registered with the Food and Drug Administration (FDA). If the NCI Central Institutional Review Board (CIRB) is utilized by the local IRB through facilitated review, the CIRB is considered the IRB of record.

At the time of institutional audit, the performance of the IRB with respect to review of Alliance protocols and protocol amendments is evaluated. In addition, consent forms used within the institution are examined in order to determine whether they meet the standards required by OHRP. For institutions using CIRB, documentation of CIRB approvals including the CIRB Facilitated Review Acceptance Form will be reviewed, as well as the local informed consent form.

The Alliance may take various actions including suspension of accrual by an institution when it receives information from any source alleging that an IRB fails to comply with federal regulations. In such instances, Alliance informs the CTMB and an audit team may be assembled by staff at the CTMB, in conjunction with OHRP and the Office of Research Integrity (ORI).

2.7.1　Reporting and review requirements

As noted above, the Alliance must have documentation that there has been prospective review, at least annual continuing review and the review of significant protocol updates. IRB approval documentation is submitted to the CTSU. This information is entered into the CTSU/RSS database and is referred to when a patient is being registered. Documentation must state the type of review, list the protocol number (and if it is a review of a protocol update, it must list the protocol update number) and an IRB member or administrator must sign it. The protocol number and the update number, if applicable, must be clearly documented. Initial and continuing review documents must be submitted to the Cancer Trials Support Unit (CTSU) and Alliance staff will access the information in the CTSU database.

Annual continuing review must continue as long as patient data are being submitted. However, if no patients are currently receiving treatment and only data are being submitted, the Alliance accepts expedited review. Institutions must continue to submit studies that are not yet terminated to their IRB for continuing review. The Alliance audit team confirms that informed consent was obtained after initial review and that appropriate continuing review and significant protocol updates have taken place.

Policy Name: Institutional Review Boards	Policy Number: 2.7
Section: Institutions – 2	Date Revised: January 1, 2018

2.7.2 Federal record-keeping requirements for IRBs

The institutional review board that reviewed the study must keep records and minutes of the review per the federal guidelines. Institutions retain their discretion to organize and store IRB records in any manner that is consistent with the requirements of HHS regulations at 45 CFR 46.115. Electronic storage is acceptable as long as all records are accessible for inspection and copying by the Alliance, OHRP, FDA and other regulatory agencies, as applicable.

2.8 Institutional audits

2.8.1 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).

2.8.2 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.

2.8.3   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.

2.8.4   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

2.8.5   Scheduling of audits

2.8.5.1   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.

2.8.5.2   **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.

2.8.5.3 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.

2.8.5.4 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.

2.8.5.5 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.

2.8.5.6   **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.

2.8.5.7   **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.

2.8.6   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:

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

2. Current versions of requested protocols.

3. 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.

4. 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.

5. 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.

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

7. 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.

2.8.7   Conduct of an Alliance audit

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

2.8.7.1   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.

2.8.7.1.1 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.

2.8.7.2 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.

2.8.7.2.1 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 a 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.

2.8.7.2.2   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

2.8.7.2.3 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

2.8.7.2.4 Assessing the IRB, ICC and DTL

The following categories outlined in table 2-1 should be used in assigning a final assessment to the IRB/ICC component of the audit.

Table 2-1. 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, <u>and</u> 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.

2.8.7.3   **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.

2.8.7.3.1 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 2-2. 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)	• NCI DARF not maintained or not maintained completely, accurately or on a timely basis
• Oral study-supplied agents are documented on the Oral DARF	• Oral NCI DARF not maintained for oral study-supplied agents, not maintained completely, accurately or on a timely basis
• NCI DARFs are utilized to track cancer control/imaging study-supplied agents, or other accountability log captures the same information as NCI DARF	• 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) contains all required information; paper printout of eDARF is identical to NCI DARF	• 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
• Corrections on DARFs are lined out, initialed and dated with no erasures and whiteouts; corrections on eDARFs are documented	• Erasures or "whiteouts" on paper DARF
• Agent was dispensed to a registered patient/study participant and documented on the appropriate DARF	• Corrections are not lined out, initialed and dated on paper DARF
• Appropriate documentation of multi-dose vial agent dispensing to multiple patients/study participants on separate lines of the DARF	• Corrections are not appropriately documented on eDARF in electronic inventory system
• Patient/study participant returns of oral study-	• Study-supplied agent dispensed to a registered patient/study participant and not recorded on the

supplied agents are documented on the oral DARF	• appropriate DARF
• Patient/study participant returns of non-oral, non-patient-specific agent supplies are *not* documented on the 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
• Patient/study participant returns of non-oral, patient-specific agent supplies are documented on the DARF	• Dispensing of study-supplied agent to a non-registered patient/study participant recorded 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	• Patient/study participant returns of oral study-supplied study agents *not* documented on the Oral DARF
• [For NCI-sponsored Study] Study Agent has been transferred to an authorized investigator and/or protocol with CTEP approval	• 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 2-3. 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	• Substitution of any study-supplied agent, with non-study supplied study agent, including commercial agents
• Protocol using multiple study-supplied agents have a separate DARF for each agent	• DARF maintained by lot #
	• One DARF used for more than one protocol
• Separate DARFs are maintained by protocol, study agent, strength, 'dosage form' (e.g., oral, injectable), and by ordering investigator	• One DARF used for a protocol using multiple study agents
• A separate patient-specific DARF is maintained for each patient/study participant on a patient-specific supply study, as directed by the protocol	• 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

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Table 2-4. 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 2-5. 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 2-6. 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

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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

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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

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Table 2-7. 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 2-8. 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 2-9. 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

2.8.7.3.2 Assessing the accountability of investigational agents and pharmacy operations

The following categories in table 2-10 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 2-10. 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.

2.8.7.4   **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.

2.8.7.4.1 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)

2.8.7.4.2 Assessing the findings from patient case records

The following categories in table 2-11should be used in assigning a final assessment to this component of the audit.

Table 2-11. 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 2-12) 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 2-12. 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.

2.8.7.5   **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.

2.8.8   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.

2.8.9   Audit review

2.8.9.1   **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.

2.8.9.2 **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.

2.8.9.3 **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.

2.8.9.4 **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.

2.9. Continuing Alliance membership

The Alliance Bylaws outline procedurally how Alliance membership status is evaluated. Each institutional member is re-evaluated for performance in Alliance activities by the Membership Committee semi-annually. The Alliance Institutional Performance Evaluation Committee (IPEC) reviews institutional performance semi-annually. All Alliance institutions are subject to periodic audits. The Membership Committee receives reports from the IPEC, the Audit Committee, and other committee reports as needed to evaluate institutional status. Based on the information received from the various sources, the Membership Committee recommends:

- Continue institutional membership
- Suspend patient registration privileges until specific deficiency is corrected
- Change to probationary status
- Mandated change in membership type or expulsion
- Expulsion from the Alliance

Institutions must annually achieve the required number of patient registrations per year (15 for main member networks, and five for affiliates) based on a rolling three-year average.

2.9.1. Main members

Main members that do not fulfill the accrual requirement of 15 patient registrations per year, based on a three-year rolling average, for two consecutive calendar years will be subject to having their membership type changed to an affiliate in the year following the second year that the three-year rolling average was below 15 patient registrations. They would be allowed four months to find a main member with which to affiliate. It is understood that any affiliates of the main member would also need to find a new main member. If the affiliation agreements cannot be executed in this time frame, the main member (and their affiliates/sub affiliates) will be dropped from participation in Alliance.

At the spring Alliance meeting, the main members likely to be affected by this policy will receive a warning letter from the Membership Committee. Prior to the fall Alliance meeting, main members will be informed of the recommendation for a change in membership type and be given the opportunity to appeal at the fall Board of Directors meeting.

The Membership Committee may recommend exceptions to the Board of Directors for approval. If an exception is granted or an appeal is approved, the affected institution will be granted a grace period of one year. If the network does not meet their accrual requirement at the end of the grace period, the network will be subject

to having their membership type changed to an affiliate, without an opportunity to appeal. If the main member and/or their affiliates do not find another main member with which to affiliate by the end of the grace period, their Alliance membership will be terminated, as of January 1st in the year following the grace period.

2.9.2. Affiliates

Affiliates must achieve at least five patient registrations per year based on a three-year rolling average. Affiliates that do not fulfill their accrual requirement for two consecutive calendar years, will be subject to having their Alliance membership terminated, as of January 1st of the year following the three-year period. At the spring Alliance meeting, the affiliate members likely to be affected by this policy will receive a warning letter. Prior to the fall Alliance meeting, main members will be informed of the recommendation for a change in membership type and be given the opportunity to appeal at the fall Board of Directors meeting. The Membership Committee will include a list of at-risk affiliates to the Board of Directors for approval.

2.10 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.

2.10.1 Institutional Network Performance Evaluation Scoring System

Below tables 2-20 through 2-22 outline the parameters for each primary area (quality, timeliness, and group participation).

Table 2-20. 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) i.e.: # baseline samples received intact during the report period / # baseline specimens received during the report period	<97%	-1
	97-99%	0
	>99%	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)	>3%	-1
	1-3%	0
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).	<1%	1

Table 2-21. IPEC scoring for timeliness

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

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

Table 2-13. 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

2.11 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.

2.11.1 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 2.10) for additional information.

2.11.1.1 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.

2.11.1.2 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

2.11.2 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.

2.11.3 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 Office of the Group Chair within 30 days of the notice. The Office of the Group Chair 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.

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.

2.11.3.1   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 operations 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.

2.11.4 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.

2.12 Institutional retention of study records

The following definitions apply in this policy:

- **Research records** are usually maintained by the investigator or research staff, may be separate from the hospital records, and may contain the original signed informed consent form and copies of key protocol parameters.
- **Source documents** include original patient medical records, hospital charts, lab printouts, radiological reports, correspondence, scans, X-rays, patient-completed forms, etc.
- **Flow sheets and case report forms** are created by the Alliance, completed by the institution, and submitted from the participating sites to the Alliance Statistics and Data Center.

The registering institution identified at registration, or, in the case of a transfer, the institution that accepts the responsibility for the patient, is responsible for maintaining and keeping all regulatory and original source documentation.

If the study treatment does not include investigational agents, then the research records (except for signed informed consent) and Alliance case report forms and flow sheets may be discarded after the study has been terminated. The institutional review board that reviewed the study must keep records and minutes of the review per federal guidelines and their own institutional policies.

If the study includes investigational agents, then in addition to the above requirements, records may only be destroyed two years after the New Drug Application (NDA) or Biologic License Application (BLA) has been approved or withdrawn, or the Investigation New Drug (IND) has been withdrawn/closed. The pharmacy at the institution must keep the ordering records for each agent per the federal requirements and the disposition of the investigational agent must be documented in the drug accountability form.

Source documentation, including the informed consent forms, should be retained indefinitely at the registering institution. In many instances, the signed informed consent form is included in the research records and not in the medical records. The Alliance does not collect signed informed consent forms. If the original signed informed consent form is not charted to hospital source documentation and is maintained in the research records, the signed informed consent form must be removed before the research record is destroyed and retained as would be done for source documents.

2.13 Non-member Collaborators

Non-member collaborators (NMCs) are institutions or networks that participate on Clinical Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) sponsored protocols but are not full member institutions of the Alliance or a participating organization. Most non-member collaborators with the Alliance are international organizations.

In addition to their own country's regulations, International groups must comply with US federal regulations such as:

- Obtaining Federalwide assurance (FWA) with the Office for Human Research Protections (OHRP); and

- Obtaining State Department Clearance. The Alliance will submit State Department Clearance to the NCI on behalf of the international collaborator.

NCI policy also requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. Registration is accomplished via the NCI Registration and Credential Repository (RCR). Additional details can be found on the NCI/CTEP website.

2.14   Participation in AFT

The Alliance adheres to the institution membership structure as mandated by the NCI. The structure includes:

- Tier I members include the LAPS and NCORP administrative offices or umbrella organizations and rostered (non-LAPS, non-NCORP) main members.

- Tier II members include LAPS main members, LAPS Integrated Components (satellite sites of the LAPS main member), NCORP Affiliates, and affiliates of rostered main members

- Tier III members are sub-affiliates. The sub-affiliates are satellites of either a Tier I or Tier II institution and must be owned by the Tier I or Tier II institution and have the same FWA.

The Tier I or Tier II institution and sub-affiliates or integrated components are one entity with multiple locations and considered as a package. Enrollments by these site types are included in the Tier I or Tier II site of which they are a satellite. Accrual and participation in AFT for Tier III sites and integrated component are based on the standing of the Tier I or Tier II package.

Alliance members in good standing may participate in AFT trials. Good standing is defined as meeting the membership accrual requirements and without probation. Member networks must maintain a 3-year average of 15 membership credits and Tier II members, including NCORP affiliates must earn 5 membership credits per year based on a 3-year average before the site(s) can be considered for participation in AFT.

2.14.1   Provisionary Members

Provisionary member networks can participate in AFT trials with approval from the Chief Administrative Officer once the member network has accrued 15 patients per year and prior to the acceptance as a full member.

Once the member network has been approved to participate in AFT, Tier II members within the provisionary member network can participate in AFT *if* the site earns 5 membership credits per year. Tier II sites but cannot participate in AFT until the network has been approved, even if the affiliate has met the affiliate level accrual requirement.

2.14.2   Members on Probation

AFT sanctions for members placed on probation for either IPEC or Audit will coincide with the Alliance sanctions. Specifically:

Policy Name: Participation in AFT	**Policy Number:** 2.14
Section: Institutions – 2	**Date Revised:** July 24, 2019

Immediate: No sanctions

1st Year Anniversary: Member will not be selected to participate in additional AFT studies.

2nd Year Anniversary: Accrual to AFT studies will be restricted until the site meets 15 NCTN membership accrual credits. The remaining accrual can be a mix of AFT and NCTN but not to exceed 50% of the average annual NCTN accrual as per Alliance policy.

3rd Year Anniversary: Membership will be terminated.

Policy Name: AFT Membership Accrual Credits	**Policy Number:** 2.15
Section: Institutions – 2	**Date Revised:** July 24, 2019

2.15 AFT Membership Accrual Credits

Enrollments to AFT studies are included in the Main member accrual totals in years in which the Main member meets or exceeds the Alliance accrual requirements via NCTN enrollments credited to the Alliance and are in good standing. AFT accrual will be included in the total accrual only in years in which the NCTN average was met.

2.15.1 Provisionary Members

AFT accrual will not be included in the total Alliance membership accrual during the provisionary period has ended. AFT accrual will be counted once the member has full status and will be retroactively applied.

2.15.2 Affiliate Accrual

Affiliate AFT accrual will be included in the affiliate and main member totals accrual only in years in which the NCTN average was met by the affiliate.