Policy Name: Membership Criteria	**Policy Number:** 2.1
Section: Institutions – 2	**Date Revised:** March 15, 2013

2 Institutional membership

Institutional 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.

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

Policy Name: Applying for Membership	**Policy Number:** 2.2
Section: Institutions – 2	**Date Revised:** March 15, 2013

2.2 Applying for membership

The Alliance reviews institutional membership applications twice monthly. The institutional membership application is available on the Alliance public website (http://www.allianceforclinicaltrialsinoncology.org). 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 receive a letter 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.

Policy Name: Membership Activation	**Policy Number:** 2.3
Section: Institutions – 2	**Date Revised:** March 15, 2013

2.3 Membership activation

If the Board of Directors approves the Membership Committee's recommendation for approval, applicants will receive a letter of approval status with additional information. Alliance staff will activate institutions after all roster, regulatory and financial documentation has been received. 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. 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

The Alliance complies with the NCI's Unified Site Code Policy (http://ctep.cancer.gov/highlights/site_code_policy.htm). A site must be included on the roster if one or more of the following criteria are met:

- Direct receipt of CTEP agent
- Enrollment of patients/research participants
- Institution's whose employees, representatives, and/or agents are authorized to obtain informed consent from patients
- Direct receipt of federal funds
- Directly responsible for submission of data to the study sponsor or their designee

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 1572 forms for all investigators; certification that all investigators have received training in human subjects protection; documentation that the institution has a procedure in place to notify patients of new information regarding toxicities and outcome; and all new members have acknowledged understanding of the Individual Scientific Misconduct Policy (see section 3.4).

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.

2.3.3 Financial documentation

Financial documentation 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 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 at the affiliates.

Responsibilities are listed below. An affiliate institution has its 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 the affiliate 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.

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 affiliate 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 Drug Management Authorization Section. 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 (http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm) for more specific investigational drug information.

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 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.

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.

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.

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 and that the physicians who oversee the conduct of Alliance studies disclose potential conflicts of interest.

2.5.2 Affiliate member principal investigator

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

The principal investigator (PI) for an affiliate institution is responsible for the conduct of Alliance activities at an Alliance institution and for the integrity of all data submitted from the 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
- 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 Cytogeneticist

2.5.4.1 Approval for M.D./Ph.D. cytogeneticist

An institution must have an approved cytogeneticist before patients may be registered to a cytogenetic study. Patients may not be registered to a cytogenetic study until the institutional cytogeneticist receives approval from the principal investigator for cytogenetic studies and the chair of the Karyotype Review Committee. In the absence of an Alliance-approved cytogeneticist, institutions may not enroll patients on studies requiring cytogenetic review. If an institution is on cytogenetic probation and the cytogeneticist leaves, upon arrival and subsequent approval of a new cytogeneticist, the institution is taken off probation.

2.5.4.2 Cytogenetic probation

Institutional performance is evaluated every six months by the principal investigator for cytogenetic studies in consultation with the chair of the Karyotype Review Committee. A letter from the principal investigator is generated that informs the institutional cytogeneticist, institutional principal investigator, and the Institutional Performance Evaluation Committee (IPEC) that the institution has been placed on cytogenetic probation. If 50 percent or more of the cases entered on cytogenetic studies are found to be inadequate, the institution is put on cytogenetic probation. While on cytogenetic probation, the institution may still enter patients on cytogenetic studies. If at the time of the next review (six months later) it is found that 75 percent or more of the cases are adequate, the institution is taken off probation.

If the institution fails to meet the threshold of 75 percent adequacy, the institution's privileges to enroll patients on cytogenetic studies may be suspended. A letter from the principal

investigator for cytogenetic studies is sent to the institutional cytogeneticist, institutional principal investigator, and IPEC in the instance in which an institution has been suspended from enrolling patients on cytogenetic studies. Only the principal investigator for cytogenetic studies and the chair of the Karyotype Review Committee may change an institution's cytogenetic probationary status.

Policy Name: OHRP Assurances	**Policy Number:** 2.6
Section: Institutions – 2	**Date Revised:** March 15, 2013

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 Alliance must have documentation that there has been prospective review, at least annual continuing review, and review of significant protocol updates. 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.

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 requirements

Any substantive changes of information concerning risks or alternative procedures and/or translational research contained in the model informed consent document must be justified in writing by the investigator. Investigators must forward copies of such changes, with their justifications, to the Alliance for review.

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. 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 will not collect these IRB approvals but will review during institutional audits. 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.

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 OHRP.

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 NCTN 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.

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 of the NCI maintains oversight responsibility for the network group and cancer center CCOP 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 (http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm). The CTMB Guidelines may be referenced for any policies and procedures that are not specified within the Institutional Audits Policy.

CTMB staff reviews all site visit 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 Clinical Trials Monitoring Branch may make specific recommendations for action if they do not believe the action taken by the group or cancer center 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 on-site audits conducted of member institutions and their affiliates/CCOPs examine a meaningful and random sample of the following:

- Clinical records and abstracts
- X-ray films and other radiographic 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 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 if feasible based on accrual. Initial audits are conducted on-site. Routine audits will generally be scheduled within 30-36 months after the previous audit.

Institutions remain at risk for audit even if their membership in the Group is withdrawn or terminated since they have made a commitment to long-term follow-up of patients with provision of good quality data according to the study schedule.

For affiliates, an on-site audit may be conducted by the main member institution utilizing the same on-site audit procedures used by the Alliance. Each main member must appoint an audit liaison to manage the affiliate audits. The audit liaison should be a member of Alliance who is versed in the Alliance's audit policies. All audit liaisons should have previous auditing experience and are required to participate in training sessions and/or modules. The audit team should consist of physicians and CRPs from the main member. 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 three or more studies with IND agents since the previous audit.

2.8.5.2 Scheduling audits for CCOPs and CCOP components

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

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

If an institution's membership or participation in Alliance is withdrawn or terminated, continued long-term follow-up of enrolled patients and the collection of good quality data according to the study schedule are required. Therefore, these institutions remain eligible for an audit. The selection of withdrawn/terminated institutions for audit will be determined by the audit program manager, the chair of the Audit Committee, and the chief administrative officer. The selection will be based on the number of total patient cases and protocols with emphasis on important or pivotal trials, have a large number of patients in follow-up, or are not meeting acceptable quality standards for follow-up data.

2.8.5.3 Case/protocol selection

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

A **minimum** number of cases equivalent to 10 percent of patients accrued since the last audit will be reviewed. The 10 percent of cases reviewed apply to each participating site being audited. For selection purposes, the 10 percent of chosen cases will always be rounded up. For selection of patient cases the following apply where appropriate: (1) 10 percent Group/CCOP cases, (2) 10 percent of Group/CCOP "endorsed" cases, and (3) 10 percent of "non-endorsed" credited to the Group or CCOP. 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 audit consisting at a minimum of informed consent and eligibility. However, if the unannounced cases only receive a limited review, then these cases do not count towards the minimum of 10 percent.

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

2.8.5.4 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 for the audit is sent to the institution at least one month prior to the audit to allow adequate time to prepare for the audit.

2.8.5.5 Materials for review

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 may be verified against the primary medical record.

IRB approvals, annual re-approvals, all required amendment approvals, and safety reports, are reviewed. A sample of at least three consent forms are carefully reviewed and compared with the model consent form for required elements. NCI Drug Accountability Record Forms (DARFs) for at least three IND drugs are reviewed where applicable, including if possible one or more unannounced drugs. DARFs are also crosschecked with at least one patient case for each of these drugs.

2.8.5.6 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.

Each main member or CCOP 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.

2.8.6.1 Prior to audit

The institution prepares for the audit by gathering all source documentation pertaining to the selected cases.

For the selected protocols, the institution provides (a) the Institutional Review Board documents for approvals, re-approvals, amendment approvals, and relevant reports of expedited adverse event reports, and (b) the current version of the protocols and most recently IRB-approved informed consents in use at the institution.

Records regarding the disposition of investigational drugs, specifically agent order receipts, return drug receipts, and the NCI Drug Accountability Record Forms, must be available. The pharmacy should be alerted that the auditors will conduct an on-site inspection of investigational agent storage, security, and records. In addition, pharmacy procedures should be in place to ensure that the person prescribing the Division of Cancer Treatment and Diagnosis (DCTD)-agent is an investigator registered with the Pharmaceutical Management Branch (PMB) and/or the prescription is co-signed by the registered investigator.

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 and informed consent content requirements, (2) drug accountability and pharmacy compliance including the use of NCI DARFs, 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 major and lesser deficiencies.

For each component rated as **Acceptable Needs Follow-up** or **Unacceptable**, the institution is required to submit a written response and/or Corrective and Preventive Action (CAPA) plan to the audit program manager. A copy of the written response/corrective and CAPA plan, along with an assessment by the Alliance audit staff of the response/corrective action plan, is forwarded to the CTMB by the audit coordinator within 45 days of the date the final audit report was entered into the CTMB Audit Information System. Each audit report indicates the date the Alliance must receive the response/corrective action plan. If the plan is not received and approved by the date indicated in the audit report, patient registration is 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 recommended when the result is designated Acceptable, Needs Follow-up.

2.8.7.1.1 Major and lesser deficiencies

Deficiencies are categorized as either "major" or "lesser"; examples are provided in the appropriate sections. Deficiencies too trivial to warrant comment are not put in the report. 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.

Major deficiency: a protocol variance that makes the resulting data questionable or represents a significant noncompliance with regulatory requirements.

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 minor 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 http://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring_coop_ccop_ctsu.htm) for complete details concerning IRB documentation and informed consent content.

Certain documents, such as NCI DARFs, local informed consent forms, and/or IRB approval documentation, may be requested for review prior to the audit day.

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. The institution must have a copy of the CIRB Facilitated Review Acceptance Form. The Alliance auditors will review the acceptance form and the local informed consent. The local institution must obtain all documentation of CIRB approvals. Since the local IRB has assumed responsibility through facilitated review, these documents (hard copy or downloaded into a local electronic database) must be present at the time of the audit.

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. The protocol must be approved by each institution's human subjects committee. Every institution must also 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 IRB approvals with the IRB chair's signature and date, and annual re-approvals for each audited protocol and approval 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.

Major IRB deficiencies may include but are not limited to:

- Protocol never approved by IRB.
- Initial IRB approval documentation missing.
- 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 safety report of unanticipated problems as defined by OHRP policy (see appendix 6 of CTMB Guidelines).
- Lack of documentation of full IRB approval of a protocol amendment or action letter that affects more than minimal risk or IRB approval is greater than 90 days after 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 have completed therapy.

Amendments that are only editorial (e.g., change in contact information, editing of sentences for completeness/structure) are exempt from the 90-day requirement.

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.

Any substantive changes of information concerning risks or alternative procedures and/or translational research contained in the model informed consent document must be justified in writing by the investigator. Investigators must forward copies of such changes, with their justifications, to the Alliance regulatory staff for review.

Major 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 updates or failure to revise an informed consent in response to an NCI warning letter regarding risks that require a change to the informed consent.
- Omission of one or more required informed consent elements required by federal regulations. The informed consent document for trials initiated on or after March 7, 2012, must also include the following statement: “A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will

include a summary of the results. You can search this website at any time."

- Multiple cumulative effects of minor problems for a given informed consent.

2.8.7.2.3 Assessing the IRB and Informed Consent Content

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 audit assessment categories

Acceptable	• No deficiencies identified. • Few lesser deficiencies identified. • Major deficiencies identified during the audit that were addressed and/or corrected **prior to** the audit patient case listing notification for which documentation exists and no further action is required by the Alliance, the institution, or the principal investigator because no similar deficiencies have occurred since the Corrective and Preventive Action (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.
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	• Multiple major deficiencies identified. • A single major flagrant deficiency found. • 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 the total number of major deficiencies cited is 20 percent 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 three or more studies with IND agents since the previous audit.

The Drug Accountability Record Forms (DARFs) must be maintained by all institutions conducting clinical trials with NCI-supplied investigational drugs. The FDA requires investigators to establish a record of the receipt, use, and disposition of all drugs designated as investigational for the purposes of the protocol. The NCI, as a sponsor of clinical trials, must assure that the FDA requirements are met. Therefore, the NCI requires a standardized investigational drug accountability recording system. Each investigator who has filed a 1572 form should receive from the NCI a booklet entitled "Investigational Drug Accountability Record" explaining the requirements in detail.

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 registered with PMB, DCTD, NCI. Procedures must be place in the pharmacy and followed to ensure that the person prescribing the DCTD-agent is an investigator 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 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 tables 2-2 through 2-9 are guidelines for assessing compliance and noncompliance with drug accountability, use of NCI DARFs, and storage regulations for CTEP-sponsored trials using agents supplied by CTEP.

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

Compliance	Non-Compliance
• Maintain accurate records of the disposition of all CTEP supplied agents using NCI DARFs. • Agents supplied by the Pharmaceutical Management Branch (PMB) for NCI-sponsored protocols are shipped from PMB directly to the investigator's primary institution or office. • In situations where two or more institutions are operating as a "centralized research base", a centralized pharmacy service can provide pharmacy services (such as agent storage, preparation and accountability) for investigators in the local community, if the investigators designate that pharmacy service as their shipping designee on their FDA form 1572 submitted to PMB; the centralized pharmacy is then permitted to deliver (transport, not re-ship) CTEP supplied investigational agents to the investigators' offices, clinics, or other institutions. • Agents may be dispensed, delivered, and accounted for at the treatment site in response to an individual patient's treatment order or a prescription for a single dose; in this situation, there is no need for satellite accountability records. • If the physician's office, clinic, research staff, or other institution receives or obtains a multiple day or overnight storage supply of CTEP supplied investigational agents, the DARF is maintained at the appropriate location.	• Inability to track the receipt, use and disposition of DCTD/DCP supplied investigational agents. • NCI DARF not maintained. • Inability to track the agent because of omissions. • Paper and/or electronic DARFs do not contain all information or are not completed as required on NCI DARF; paper printout is not identical to the NCI DARF. • Incorrect agent, dose, or dates dispensed, incorrectly prepared drug, and/or incorrectly documented. • Registered patients who have received IND agents are not recorded on DARF. • Systematic incorrect entries on the DARF. • NCI DARF not kept on timely basis. • There are erasures or "whiteouts". • Corrections are not lined out, initialed and dated. • Agent has been transferred to an investigator who is not registered with PMB, DCTD, NCI. • CTEP supplied investigational agents are repackaged and/or reshipped to other investigators, patients, or locations by mail or express carrier.

Table 2-3. Accessing compliance for DARFs protocol and drug specific

Compliance	Non-Compliance
• Agents received from PMB, DCTD are used only for patients entered onto an approved DCTD-sponsored protocol. • Each agent accounted for separately by protocol. • An agent used for more than one protocol must have a separate DARF for each protocol. • Multi-agent protocols have a separate DARF for each agent. • Separate accountability forms maintained for each different strength or dosage form of a particular agent. • A separate DARF is used for each patient, if stated in the protocol (double-blinded studies). • Appropriate documentation of drug dispensing to multiple patients of multi-dose medication on separate lines of the DARF.	• Patients identified on DARF are not registered patients. • Substitution with any non-DCTD supplied agents, including commercial agents. • Agents supplied for clinical trials used for pre-clinical or laboratory studies without written approval of PMB. • Lack of source documentation to verify agent supplies distributed to investigators or administered to patients. • Each agent not accounted for separately by protocol. • One DARF used for more than one protocol. • One DARF for a multi-agent protocol. • One DARF used for multiple strengths or dosage forms of an agent. • DARF incorrectly used (single DARF used for multiple patients for double blinded study; multiple dose vials recorded for one patient instead of multiple patients, or multiple doses recorded on a single line of the DARF).

Table 2-4. Accessing compliance for satellite records

Compliance	Non-Compliance
• DARF used at each location where doses for multiple patients are received and dispensed and/or stored overnight (such as satellite pharmacy, physician's office, or other dispensing areas) and available for site auditor. • Satellite and control records match.	• No satellite DARFs in use when required or not available for review. • Satellite and control records are not accurately maintained. • Satellite and control records do not agree.

Table 2-5. Assessing compliance for NCI DARFs kept as primary transaction record

Compliance	Non-Compliance
• Agent order receipts (Shipment Record of Clinical Drug Request, NIH 986-1) retained and available for review. • Documentation on DARF of other agent transaction such as agent returns or broken vials. • Transfer of DCTD investigational agents between institutions is approved or authorized by PMB. • Balance on DARF matches supply.	• Agent order receipts (Shipment Record of Clinical Drug Request, NIH 986-1) not retained or not available for review. • Lack of documentation of other agent transactions. • Agents have been borrowed. • Transfer Investigational Drug Form (NIH-2564) not used when transferring agent. • Quantities not accounted for; shelf counts and inventories do not match. • No written documentation from PMB of approval for transfer of agent.

Table 2-6. Assessing compliance for return of drug to NCI

Compliance	Non-Compliance
• Return to DCTD/DCP agents (a) that are outdated, or (b) that are unusable; within 90 days from when agent expired or became unusable. • For studies that are completed or discontinued, return DCTD/DCP agents to the NCI, transferred to another NCI protocol (with PMB approval), or agent destroyed per site's local destruction policy; all appropriately conducted. • Return to DCTD/DCP agents within 90 days of study closure; and Return Form is maintained. • Patient returns of IND supplied agents are not recorded on DARFs unless agents are supplied as double blinded.	• DCTD/DCP agent not returned to NCI; not transferred to an appropriate NCI protocol; or agent not destroyed per site's local destruction policy. • Failure to maintain Return Form. • DCTD/DCP agents not returned for patients in follow-up when no DCTD/DCP agent is being administered. • Patient return of IND supplied agents are recorded on the DARF for non-double blinded studies.

Table 2-7. Assessing compliance for agent storage

Compliance	Non-Compliance
• Each investigational agent stored separately by protocol. • An agent used for more than one protocol kept in separate physical storage for each protocol. • Agent stored under proper conditions (such as refrigerator or freezer) with validation documentation.	• IND not stored separately by protocol. • Agents used for more than one protocol combined in storage. • Agent not stored under proper conditions.

Table 2-8. Assessing compliance for adequate security

Compliance	Non-Compliance
• A secure area is an area that can be locked with a minimum of people having access (the key or combination). • Storage areas shall be accessible only to an absolute minimum number of specifically authorized employees; when it is necessary for unauthorized persons to be present in or pass through, an authorized person must provide adequate observation of the area.	• Agent stored in insecure dispensing area. • Unauthorized people having access to a secure area without supervision.

Table 2-9. Assessing compliance for authorized prescription(s)

Compliance	Non-Compliance
• Investigator ordering and/or dispensing agents is registered with PMB, DCTD, NCI or co-signs for others prescribing agents. • Procedures are in place in the pharmacy and followed to ensure that person prescribing the DCTD-agent is an investigator registered with PMB and/or the prescription is co-signed by the registered investigator.	• Agent prescribed by a person not registered by PMB as an investigator, or order was not co-signed by registered investigator. • Pharmacy does not have procedures in place to ensure person prescribing the agent is registered with PMB or prescription was not cosigned by registered investigator.

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, CCOP, 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, CCOP 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	• Inability to track the disposition of DCTD-supplied investigational agents. • Multiple non-compliant categories identified.

2.8.7.4 Review of patient case records

Assessment of patient cases should include verification of appropriately signed consent form (using the originally signed form when possible), all eligibility criteria and a substantial proportion of drug and/or treatment doses and laboratory values or diagnostic studies required to document toxicities, especially those representing critical treatment periods. These are verified on-site using patient source documents.

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.

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, lab slips and/or printouts, chart 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).

Auditor review of source documentation through electronic medical records and electronic imaging is allowable. The site must facilitate auditor review using the electronic medical records system.

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 **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 major and lesser deficiencies

See below tables 2-11 through 2-16 for examples of major and lesser deficiencies.

Table 2-11. Examples of informed consent deficiencies

MAJOR DEFICIENCIES (Not limited to list below)	LESSER DEFICIENCIES (Not limited to list below)
• Consent form missing. • Consent form not signed and dated by the patient. • Consent form does not contain all required signatures. • Consent form signed after patient registered or started on treatment. • Consent form used was not the current, IRB-approved version at the time of registration. • Consent form not protocol specific. • Consent form does not include updates or information required by IRB. • IRB approved translated informed consent form available but not used to consent patient who is not proficient in reading and speaking English (according to local IRB policy). • Re-consent not obtained as required. • Consent of ancillary studies not executed properly.	• Signature is dated by someone other than the patient.

Table 2-12. Examples of eligibility deficiencies

MAJOR DEFICIENCIES (Not limited to list below)	LESSER DEFICIENCIES (Not limited to list below)
• Patient did not meet eligibility criteria* and/or eligibility requirements were not obtained within the timeframe as specified by the protocol. • Unable to confirm eligibility due to missing documentation.	
* Exception: Patient deemed ineligible based on laboratory/pathology reports following registration and changes based on central review of material.	

Table 2-13. Examples of treatment deficiencies

MAJOR DEFICIENCIES (Not limited to list below)	LESSER DEFICIENCIES (Not limited to list below)
• Incorrect agent/treatment used. • Additional agent/treatment used which is not permitted by protocol. • Dose deviations ≥ 10% for drug(s). • Dose modifications unjustified. • Drug treatment incorrectly administered, calculated or not adequately documented (e.g., doses not adjusted for toxicity). • Unjustified delays in treatment.	• Dose deviations of drug(s) >5% and <10%. • Dose not recalculated per protocol.

Table 2-14. Examples of disease outcome/response deficiencies

MAJOR DEFICIENCIES (Not limited to list below)	LESSER DEFICIENCIES (Not limited to list below)
• Inaccurate documentation of initial sites of involvement. • Tumor measurements/evaluation of status or disease not performed/documented according to protocol. • Protocol-directed response criteria not followed. • Claimed response (PR, CR) cannot be verified or auditor could not verify the reported response. • Failure to identify or report disease progression/relapse.	• Response (PR, CR) verified but not as specified in protocol.

Table 2-15. Examples of toxicity deficiencies

MAJOR DEFICIENCIES (Not limited to list below)	LESSER DEFICIENCIES (Not limited to list below)
• Grades, types, or dates/duration of serious toxicities inaccurately characterized or recorded. • Toxicities cannot be substantiated. • Follow-up studies necessary to assess toxicities not performed. • Failure to report or delayed reporting of a toxicity that would require filing an Adverse Event Report (AER) or reporting to the Group. • Recurrent under- or over-reporting of toxicities. • Failure to report Grade 4 or 5 adverse event(s). • Repetitive failure to report Grade 2 or 3 adverse events. • Recurrent failure to report surgical morbidity/mortality directly related to study intervention. • Extended delay in filing reportable adverse events according to protocol and NCI guidelines.	• Infrequent failure to report Grade 2 or 3 adverse events.

Table 2-16. Examples of general data management quality deficiencies

MAJOR DEFICIENCIES (Not limited to list below)	LESSER DEFICIENCIES (Not limited to list below)
• Recurrent missing documentation, e.g., charts. • Protocol specified laboratory tests not documented. • Protocol specified diagnostic studies including baseline assessments not done, not reported, or not documented. • Protocol-specified research studies not done or submitted appropriately. • Frequent data inaccuracies. • Errors in submitted data. • Delinquent data submission > 6 months. • Use of “liquid erasure product” in a primary record or CRF.	• Few data inaccuracies or errors in data submitted. • Delinquent data submission >3 but <6 months.

2.8.7.4.2 Assessing the findings from patient case records

The following categories in table 2-17 should be used in assigning a final assessment to this component of the audit.

Table 2-17. Patient case records audit assessment categories

Acceptable	• No deficiencies identified. • Few lesser deficiencies identified. • 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, CCOP Research Base, CTSU, the institution, or the principal investigator. No further action is necessary because no similar deficiencies have occurred since the CAPA 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	• Multiple major deficiencies identified. • A single major flagrant deficiency found. • Excessive number of lesser deficiencies identified.

The Alliance uses an algorithm (table 2-18) 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). This sum is then divided by 100. 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 2-18. 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 *line 4 by* 100. 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 manager, 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. All members of the audit team and the principal investigator or designee of the institution being audited must be present at the exit interview. Additional personnel may be present at the discretion of the principal investigator. The exit interview with the principal investigator is a requirement of the audit. An appropriate amount of time should be set aside for this discussion.

The exit interview should provide an opportunity for immediate dialogue, feedback, audit team recommendations, 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, CCOP Research Base or CTSU. 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 (three to five patients).

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 including 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, the lead clinical research professional, and the affiliate principal investigator 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 plan, and gives a due date or due dates when the corrective plan(s) must be received.

- 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. An electronic copy of an optional response template is available on the Alliance website.

- If a CAPA plan is determined to be unsatisfactory, and/or if additional information or documentation is required, the audit program manager will contact the principal investigator, the lead clinical research professional, and affiliate principal investigator 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 manager, 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 manager, 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. 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, the lead clinical research professional, and the affiliate principal investigator.

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.

Policy Name: Continuing Alliance Membership	**Policy Number:** 2.9
Section: Institutions – 2	**Date Revised:** March 15, 2013

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) 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

New affiliates must achieve at least five patient registrations per year.

Affiliates that do not fulfill their accrual requirement of five registrations per calendar year, based on a three-year rolling average, 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 -14 to +15.

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 2-19 through 2-21 outline the parameters for each primary area (quality, timeliness, and group participation).

Table 2-19. IPEC scoring for quality

Parameter	Values	Points
Ineligibility (% of patients with eligibility review completed that were deemed ineligible)	>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)	<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
	<1%	1

Table 2-20. IPEC scoring for timeliness

Parameter	Values	Points
Data submission (% of eCRFs submitted on time)	<75%	-2
	75%-80%	-1
	80%-85%	0
	85%-90%	1
	>90%	2
Response to Queries (% of issued queries that were resolved on time)	<75%	-2
	75%-80%	-1
	80%-85%	0
	85%-90%	1
	>90%	2
Specimen Submission (% of **baseline** samples received on time)	<75%	-2
	75%-80%	-1
	80%-85%	0
	85%-90%	1
	>90%	2

Table 2-21. 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

Policy Name: Institutional Probation	**Policy Number:** 2.11
Section: Institutions – 2	**Date Revised:** March 15, 2013

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 affiliate 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 affiliate of probationary status and to work with the affiliate member 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.

2.11.4 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.

2.11.4.1 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 affiliate 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 an affiliate 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 percent 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 percent 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.

Policy Name: Institutional Retention of Study Records	**Policy Number:** 2.12
Section: Institutions – 2	**Date Revised:** March 15, 2013

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.