Policies and Procedures

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Alliance for Clinical Trials in Oncology
Policies and Procedure

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1 Introduction

The Alliance for Clinical Trials in Oncology (Alliance) was created in 2011 by the merger of three National Cancer Institute (NCI) funded cancer cooperative groups: American College of Surgeons Oncology Group (ACOSOG), Cancer and Leukemia Group B (CALGB), and North Central Cancer Treatment Group (NCCTG). Per the Alliance Constitution, the missions of the three component cooperative groups were joined in the new **vision statement**:

"To reduce the impact of cancer on people by uniting a broad community of scientists and clinicians from many disciplines, committed to discovering, validating and disseminating effective strategies for the prevention and treatment of cancer."

The Alliance receives grant funding from the National Cancer Institute (NCI). The Alliance is one of the Network Groups for the NCI National Clinical Trials Network (NCTN) and serves as a research base for the NCI Community Oncology Research Program (NCORP). The Alliance complies with the NCTN and NCORP Program Guidelines, related NCI policies and procedures and the Code of Federal Regulations (CFR). As an NCTN and NCORP Group, the Alliance utilizes centralized NCI systems for the management of clinical trials. Alliance strives to develop and execute studies in response to overall NCTN priorities.

1.1 Specific aims

The Alliance is founded upon more than 60 years of cooperative group experience, and is designed to meet the current challenges of cancer clinical and translational research. The Alliance is an experienced multi-institutional cancer clinical trials group that provides a comprehensive and highly efficient clinical trials infrastructure, access to experienced collaborators across all disciplines of oncology clinical trials research, and a diverse portfolio of trials for patients with breast, gastrointestinal, genitourinary, respiratory, central nervous system, hematological malignancies, and selected rare tumors.

As in integral component of the National Clinical Trials Network (NCTN), the Alliance has the leadership, experience, infrastructure, and member commitment required to achieve the scientific, operational, and collaborative aims outlined below.

1.1.1 Scientific aims

Alliance scientific programs conduct trials of highest possible clinical and translational impact that define new standards of care for patients with cancer. Programs have the following specific aims:

1. To conduct multimodality studies of adult cancers that include novel approaches to treatment and evaluation of patient outcomes based upon improved understanding of the molecular pathogenesis of these diseases

2. To develop strategic innovation in advanced technology for specific research areas (eg, advanced imaging methods/agents, radiotherapy) and the testing of innovative concepts and tools in prospective, multi-institutional clinical trials.

3. To develop treatments specific for molecularly defined disease subsets

4. To develop and implement novel clinical trial designs that facilitate evaluation of target-directed therapies

5. To introduce imaging response as a biomarker to direct therapy

6. To improve treatment outcomes by studying psychosocial adaptation to cancer, symptom management, and cancer survivorship

7. To study the unique therapeutic, psychosocial, economic, functional, and biological features of cancer in special populations including those with rare tumors, the older adults, underrepresented minorities, and those who are economically disadvantaged

8. To incorporate innovative science and procedural advances into clinical trials.

1.1.2 Operational aims

The Alliance infrastructure is a fully integrated system that is optimally designed to serve the NCTN and NCORP research community. The Alliance operations units have the following specific aims:

1. To optimize clinical trial efficiency and implement innovative approaches in data collection and sharing including special populations and patients currently underrepresented in clinical trials

2. To support a broadly based institutional member research network that includes a balance of academic and community researchers of all disciplines who are committed to conducting high impact cancer clinical trials

3. To provide operational capabilities for clinical and translational trials that are efficient, innovative, and make maximal use of available resources to achieve accurate and timely clinical trials results

4. To maintain responsible stewardship of important public resources, including clinical trials data and outcome-linked biospecimens, so that these can be used to conduct the best possible cancer treatment discovery and biomarker validation research

5. To train the next generation of investigators to meet the continuing challenges of cancer clinical and translational research

1.1.3 Collaborative aims

The Alliance is committed to collaborating with the NCI and all NCTN members to achieve the overall goals of the NCTN. Specific aims for collaboration include the following:

1. To closely integrate with our corresponding Statistics and Data Management Center in all aspects of trial operation through jointly developed policies and procedures for clinical trial development and conduct

2. To participate to the fullest possible extent in clinical trials planning and management committees convened by the NCI including the Disease/Modality Specific Steering Committees, the Group Banking Committee, and other planning groups

3. To collaborate with other network groups, cancer centers, , and selected organizations outside of the NCTN to optimally leverage available resources to achieve NCTN scientific objectives

4. To promote accrual to all NCTN trials among its institutional members

5. To practice responsible resource sharing in order to achieve the goals of the NCTN as a whole.

1.2 Overview of program structure

As outlined in the Alliance Constitution and Bylaws, the primary governance body of the Alliance is the Board of Directors, which represents the group's institutional members. The Alliance is led by the group chair, with assistance from the group vice chair. The Alliance is also supported by five program directors/principal investigators, each responsible for a specific program integrating discipline-related science and operational functions across all disease committees. The Executive Committee represents the Board of Directors and assists the group chair in planning and coordinating group activities.

The Alliance structure is disease-centered, with multi-modality involvement and significant input from both academic- and community-based researchers, full involvement of patient advocates, and routine participation of mentored junior investigators (see table 1-1). The group chair is responsible for the conduct and quality of scientific activities and efficient operation of the Alliance, represents the Alliance in its business with the NCI and other parties, and serves as the spokesperson for Alliance. The group chair directs eight multidisciplinary disease committees and six modality committees, and is responsible for central administration, finance, quality assurance and membership services.

Table 1-1. Alliance program structure

	Operations Center		Programs				
			Statistics and Data Management	Central Protocol Operations	Translational Research	Cancer Control	Procedure-Based Therapy
Operations Units	• Group Administration • Finance • Membership Services		• Data Collection & Management • Systems Integrations & Support • Information Systems	• Protocol Office	• Integrated Biorepositories	• NCORP Research Base	• IROC
Scientific Committees	• Breast • Experimental Therapeutics and Rare Tumors • Gastrointestinal • Genitourinary • Leukemia • Lymphoma • Myeloma • Neuro-oncology • Respiratory	• Clinical Research Professionals • Oncology Nursing • Patient Advocate • Transplant & Cell-Based Therapies	• Biostatistics • Computational Genomics & Bioinformatics		• Pharmacogenomics & Population Pharmacology • Pathology & Laboratory Medicine	• Cancer in the Older Adult • Health Disparities • Health Outcomes • Prevention • Community Oncology • Symptom Intervention • Cancer Care Delivery Research	• Imaging • Radiation Oncology • Surgery • Interventional Oncology (Working Group)
Administrative Committees	• Audit • Conflict of Interest • Constitution & Bylaws • Data and Safety Monitoring • Ethics	• Institutional Performance Evaluation • Membership • Pharmacy • Publications		• Data Sharing	• Biorepository		• Program Steering

In addition to the traditional modalities of surgery, radiation oncology, medical oncology, pathology and biostatistics, Alliance research is enriched by involvement of patient advocates, oncology nurses, community oncologists, and specialists in imaging, laboratory medicine, information technology, bioinformatics, outcomes and comparative effectiveness research, research ethics, and disparities research. In order to productively manage this deep scientific scope, Alliance uses a program approach that provides a structure to support researcher involvement and innovation in these many fields, yet maintains operational efficiency.

The Alliance includes five programs, each led by an Alliance program director who operates under the direction of the Group Chair to manage scientific, administrative, and operational activities of the group (see figure 1-1). Specifically, each program includes an operational unit and one or more scientific or administrative committees that report directly to the program director. Each program effectively interacts with the disease committees, and the program director is responsible for ensuring optimal integration of their program's activities into study development and execution. For example, each disease committee requires the involvement of biostatistics (Statistics and Data Management Program), protocol development and study concept review (Central Protocol Operations Program), biomarker development and biorepository support (Translational Research Program), and cancer control research and community oncology participation (Cancer Control Program). The fifth program, the Procedure-Based Therapy Program (PBTP), initiates new study concepts that involve procedure-based therapy (i.e., surgery, radiation oncology, intervention oncology) as the primary therapy, as well as collaborates with individual disease committees that involve one of these types of therapy. For example, if a study under the Genitourinary Committee involves an imaging substudy, the Imaging Committee (under PBTP) provides input during development of the subtsudy and assigns an imaging co-chair for the study. The program-based structure of the Alliance is an innovative approach to management of cooperative group research. The Alliance programs create an interactive environment that fosters integration across disciplines and operational units, and has proved to be a highly effective structure for maximizing efficiency.

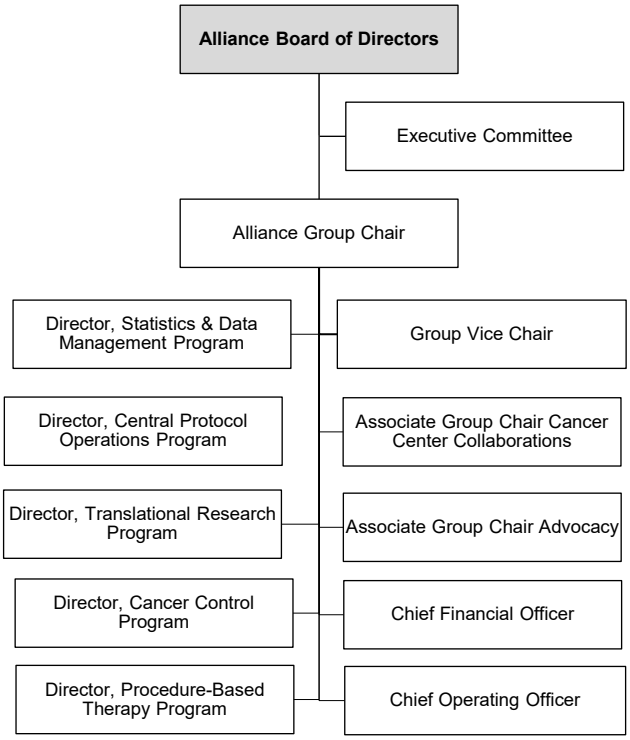


Figure 1-1 Alliance Leadership

1.2.1 Operations Center

The Operations Center is responsible for administrative and fiscal affairs. This includes support for scientific leadership, administrative committees, membership services, regulatory compliance/audits, travel, meetings, financial services and research & grants administration. As part of the Operations Center, Research & Grants Administration coordinates a per-case payment program, using funds provided by the NCI and other federal agencies, to defray the costs incurred by institutions in treating and following patients on the group's clinical trials. The Operations Center is the communications hub of the Alliance, providing regular distribution of information essential for the conduct of group business to participating members, NCI, regulatory agencies (e.g., Food and Drug Administration (FDA), Office of Human Research Protections (OHRP), Institutional Review Board (IRB)), other NCTN groups and the general public. The office organizes all group meetings, coordinates communications, education and training, maintains the Alliance website, and produces a variety of publications, including a monthly newsletter.

In addition to the group chair, senior leaders provide support to Alliance members through this office (see figure 1-1). The group vice chair stands in for the group chair for any responsibility within the Office of the Group Chair. The associate group chair for Cancer Center Collaborations ensures that Alliance research is optimally linked to cancer center clinical and translational programs. The associate group chair for Advocacy promotes patient advocacy initiatives.

Staff working within the Operations Center are associated with either the Boston or Chicago hub offices. Additional affiliate staff are located at various institutions throughout the United States. The COO, CFO and the group vice chair share responsibility for overseeing all administrative functions of the Operations Center, including administrative operations, grant preparation, communications, education and training, member roster tracking, audit and regulatory compliance monitoring, budget, financial, and regulatory operations staff and their areas of responsibility.

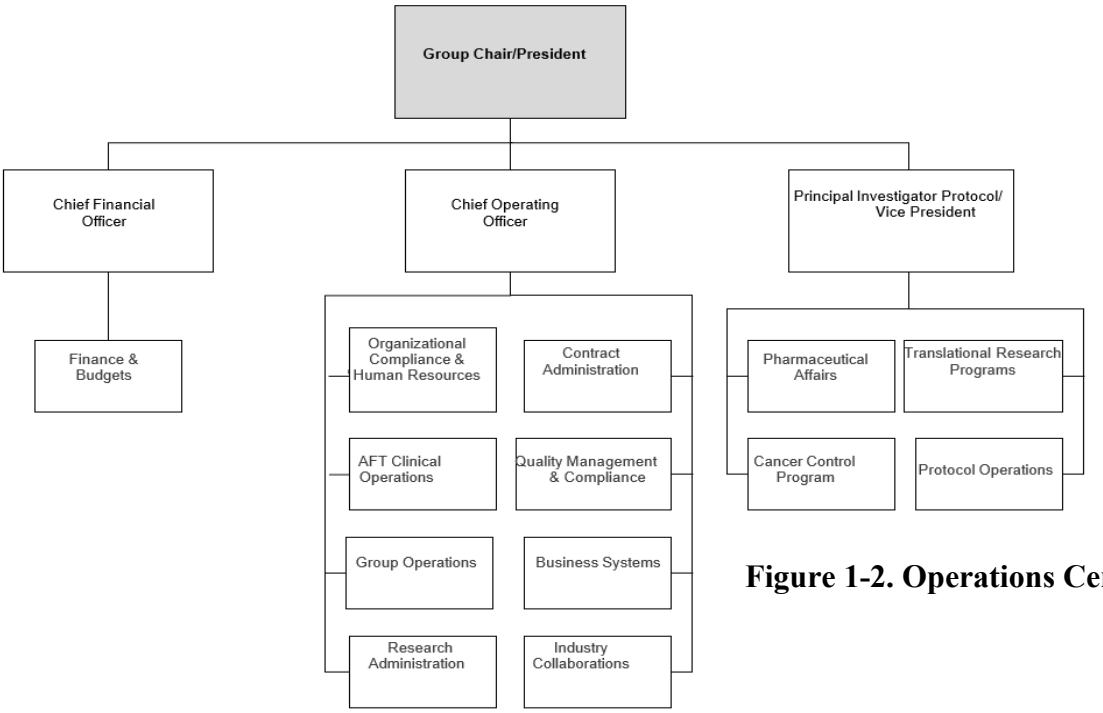


Figure 1-2. Operations Center

1.2.2 Statistics and Data Management Program

The Alliance Statistics and Data Management Program, also referred to as the Statistics and Data Management Center (SDMC), supports the activities of the group by achieving the highest standards for the conduct of clinical trials in terms of study design, statistical methodology, data collection and management, data sharing, protection of patients and their data, and regulatory compliance. The SDMC also strives to continually improve the efficiency of Alliance systems and processes.

Two scientific committees, Statistics and Computational Genomics and Bioinformatics, serve as core resources for Alliance investigators at all stages of the study process from design to analysis and reporting. These scientific teams are also responsible for developing innovative statistical and bioinformatic design and analytical plans to ensure reproducible research and improve the efficiency of Alliance coordinated trials.

In addition to its scientific committees, the Alliance SDMC houses key operational units for data collection & management, registration & site support, and information systems. The SDMC is primarily located at the Mayo Clinic in Rochester, MN with few faculty members and Masters level Statisticians at outside institutions. Figure 1-3 illustrates the SDMC organizational and leadership structure.

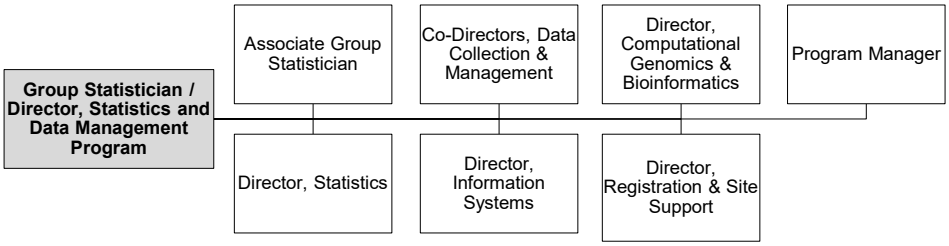


Figure 1-3. Statistics and Data Management Program

1.2.3 Central Protocol Operations Program

The Central Protocol Operations Program oversees the development and maintenance of all study protocols generated by Alliance scientific committees. Staff members manage the complex process of study protocol development, including scientific team coordination, study concept review and prioritization, which includes collaboration with the Translational Research Program (TRP) for their scientific review, NCI submission, protocol document development and maintenance, and study budgeting. In addition, staff members coordinate study-specific logistics such as biomarker study funding (including collaboration with TRP to prepare BIQSFP applications), pharmaceutical and regulatory affairs (e.g., drug distribution and IND reporting), other regulatory logistics (e.g., NCI CIRB submission and credentialing) and implementation of accrual management plans. This process adheres to NCI NCTN Operational Efficiency Working Group (OEWG) timelines and the NCORP Concept/Protocol Efficiency Timelines, which are carefully monitored by Protocol Operations Office staff. The Protocol Office also posts protocols and other study-related documents on the CTSU web site for downloading by sites and serves as focal point of communication for both study chairs and investigators throughout Alliance member institutions.

Once a protocol is activated, Protocol Office staff implement protocol amendments and other protocol communications, maintain all regulatory support documentation, and serve on numerous NCI committees that work to improve the cooperative group process. The Central Protocol Operations Program represents the interests of the group in many study-specific negotiations with the NCI, pharmaceutical firms, other network groups, international collaborators, and the public. Figure 1-4 illustrates the Protocol Office staff and their areas of responsibility.

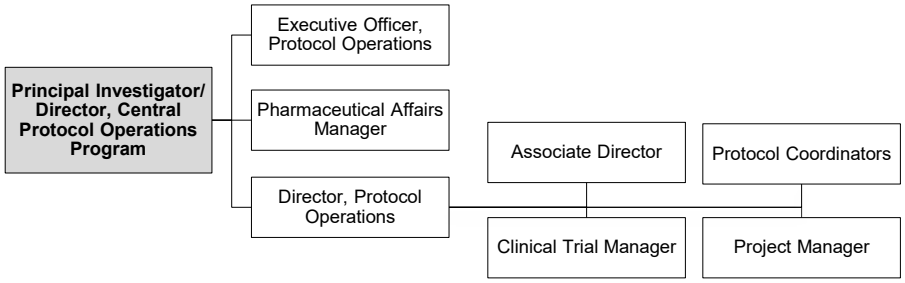


Figure 1-4. Central Protocol Operations Program

1.2.4 Translational Research Program (TRP)

With the advent of molecularly driven oncology, the Translational Research Program is essential for the development and execution of trials performed by each Alliance disease and modality committee of both NCTN and NCORP trials. The TRP facilitates the scientific agenda by supporting the basic and translational researchers who work within Alliance committees. The TRP director, in collaboration with the chairs of disease committees, names translational research leader(s) for each disease and modality. These individuals work within the TRP to ensure optimal integration of translational endpoints and biospecimen collection into Alliance trials. These researchers also promote successful collaboration between Alliance committees and researchers within Specialized Programs of Research Excellence (SPOREs), cancer centers, and other research groups. In addition, discipline committees within the TRP, such as Pharmacogenomics and Population Pharmacology, Translational Bioinformatics, and Pathology provide both scientific input and operational support for Alliance translational research. Figure 1-5 illustrates the TRP senior leadership roles.

A key TRP operational component involves management of biospecimens resources collected during Alliance clinical trials. The TRP coordinates the Alliance integrated biorepositories, an operations unit with locations at The Ohio State University, Washington University Medical Center, the Mayo Clinic, and Brigham and Women's Hospital. The TRP also manages a network of molecular reference laboratories that provide specialty services that are required for Alliance research

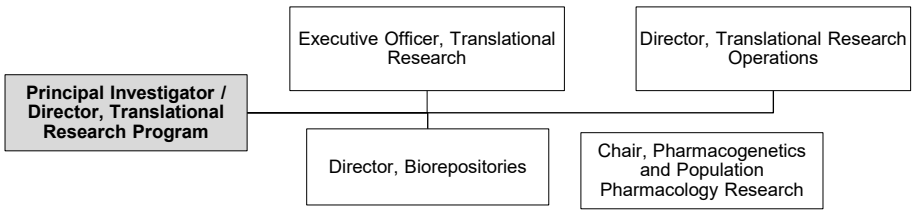


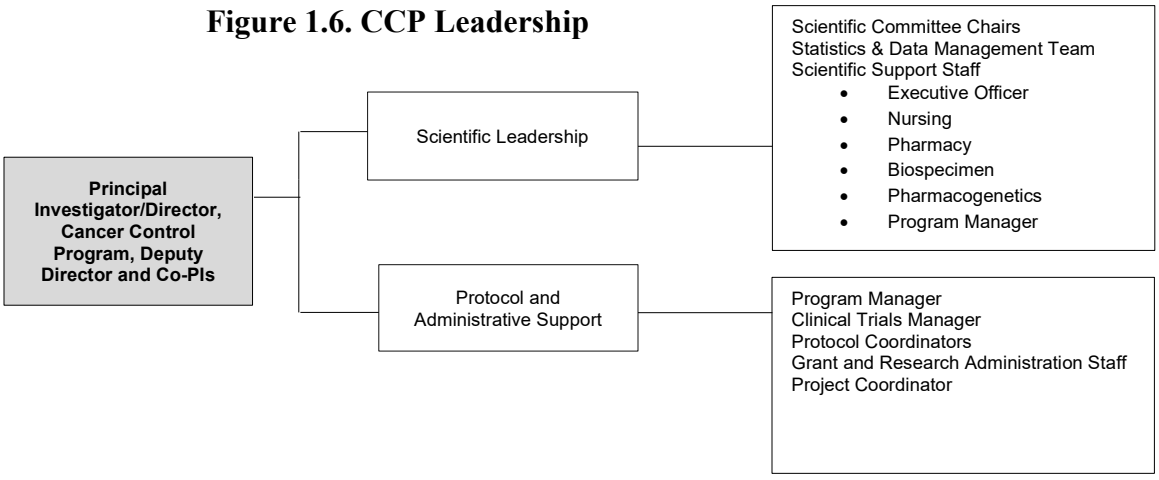
Figure 1-5.Translational Research Program

1.2.5 Cancer Control Program

Research in cancer control is integrated throughout the scientific programs and operations of the Alliance. The Cancer Control Program serves as the research base for the NCI Community Research Oncology Program (NCORP), as well as non-NCORP community oncology members. There are six scientific domains of the Cancer Control Program (CCP): Cancer Prevention, Symptom Intervention, Health Outcomes, Cancer in the Older Adult, Health Disparities and Cancer Care Delivery Research (CCDR). The Office of Director for Cancer Control oversees administrative components of the Cancer Control Program, including Leadership, Community Oncology Membership Services (including the Community Oncology Committee), Administrative/ Operations, and Pilot Projects/Consulting. Research conducted by the scientific committees of the Cancer Control Program is integrated with the Alliance disease committees and TRP so that each Alliance treatment study can be leveraged as appropriate to include cancer control endpoints. This integration occurs by placement of cancer control researchers and community oncology members in disease and modality committees. In addition, a leadership team reviews each Alliance trial concept for opportunities to contribute to cancer control research, for example, incorporation of health outcomes endpoints to a treatment trial. Cancer Care Delivery Research is currently restricted to NCORP sites only, as they are funded to conduct these trials.

The activities of the Cancer Control Program are central to the work of the Alliance. In particular, the Cancer in the Older Adult, Health Disparities, and Health Outcomes Committees are essential for achieving the goals of the cancer treatment trials program. Figure 1.6 illustrates CCP leadership roles. In addition, the Community Oncology Committee is responsible for ensuring participation by community oncology leaders in treatment trial and translational research study design and execution. A community oncology co-chair is required for every protocol.

Figure 1.6. CCP Leadership



1.2.5.1 NCORP Specific Aims

The overarching aim of the Alliance National Cancer Institute Community Oncology Research Program (NCORP) Research Base is to reduce the burden of cancer by conducting high-quality multidisciplinary, multi-site interventional and observational clinical trials, as well as database analyses. The NCORP places special emphasis upon issues affecting minority, underserved and older adult patient groups, and upon building strong collegial relationships with NCORP Community sites and Minority/Underserved Community sites. There are three specific aims within the overall research base:

1. To reduce the incidence and prevalence of clinically significant cancers

   In support of aim 1, Alliance NCORP will a) identify patients at greatest risk for developing specific cancers and detecting early stage disease amenable to curative therapies; b) employ effective pharmaceutical interventions in high risk patients; and c) develop effective strategies to alter behaviors that increase cancer risk.

2. To alleviate the symptoms of cancer and the toxicities of cancer treatment, and

   In support of aim 2, NCORP will seek to: a) understand the pathophysiology and natural history of cancer symptoms and to identify factors that increase the risk of such symptoms; and b) find approaches to prevent and treat such symptoms.

3. To improve the delivery of cancer care in community and academic practices.

   In support of aim 3, NCORP will focus upon three strategies; a) evaluate practice-level changes to improve cancer care delivery; b) appraise factors that contribute to cancer's negative financial impact on patients/caregivers and develop interventions to reduce this financial toxicity; and c) implement patient-reported data in routine cancer care delivery.

   In support of each of the three primary aims, four cross cutting themes have been identified. First, Alliance NCORP will focus on the identification and elimination of disparities in cancer incidence, morbidity, and mortality. Strategies to

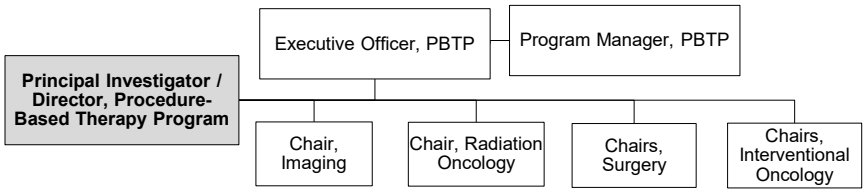
reduce disparities are 1): to conduct stand-alone and companion trials to assess and/or intervene to improve health disparities and to examine existing data in the Alliance to assess and/or monitor disparities among populations that experience disparities; and 2) to provide education strategies for and monitoring of accrual of underserved and minority populations to Alliance studies. Second, we seek to improve cancer outcomes in older patients utilizing the following strategies: 1) to improve survival and minimize morbidity (including maintenance of function and quality of life in older patients with cancer; 2) to delve into the clinically relevant variables related to aging and their impact on cancer outcomes; and 3) to improve accrual of older adults to cancer clinical trials. Third, the Alliance NCORP will conduct health outcomes research to improve our understanding of the patient experience from the vantage point of disease, treatment, and survivorship, focusing on 3 research priorities: 1) to embed patient-reported outcomes (PROs) in Alliance clinical trials, when appropriate; 2) to conduct novel PRO methodology research; and 3) to develop and assess the optimal use of technology in health outcomes assessment. Fourth, the Alliance NCORP will vigorously engage community oncologists and patient advocates in study development and conduct, building upon existing strong, collegial relations with NCORP Community and Minority/Underserved Community sites. Moreover, although mentoring has been an ongoing strength within the Alliance NCORP, training the next generation of NCORP cancer investigators will receive even greater attention.

1.2.6 Procedure-Based Therapy Program

Cross-committee collaboration is an essential cornerstone among disease, cancer control, translational research, and statistics and data management areas. The Procedure-Based Therapy Program (PBTP) addresses the unique features and challenges of developing new approaches to treating localized disease and includes developing strategies to optimize the contributions of standard approaches to surgery, radiation therapy, and interventional oncology to multimodality cancer treatment. Examples of these include minimally invasive surgery, brachytherapy, radiofrequency ablation, endoscopic surgery and ablation, wearable monitoring devices, and implantable drug delivery systems. Figure 1-7 illustrates PBTP leadership roles.

The mission of the PBTP is to improve the lives of cancer patients by achieving the multidisciplinary collaboration required to meet the unique challenges of developing and testing new devices and procedure-based cancer management approaches. The program also aims to leverage the emerging field of image analysis to bring forward novel imaging biomarkers that can inform on patient outcome, tailor procedure-based interventions and personalize patient care. The Program is comprised of a Steering Committee and four scientific committees: Radiation Oncology, Imaging, Interventional Oncology, and Surgery.

Figure 1-7. Procedure-Based Therapy Program



1.2.7 Member institutions

Membership in a network group is required for enrollment of patients on group protocols. Alliance member networks may be Lead Academic Participating Sites (LAPS) or NCORP networks. LAPS and NCORP institutional networks receive grants from the NCI to support their infrastructure and participation in NCI-funded clinical trials. Non-LAPS and non-NCORP institutions receive per-case payments from the Alliance NCI-grants to support their clinical trial participation.

A principal investigator and a co-principal investigator, who are responsible for managing the site according to all Alliance and NCTN policies, lead Alliance member institutions. Membership evaluation involves assessment of each site's current and past clinical trials accrual, audit history, and staff structure to support clinical trials and requires that each potential member agree to adhere to the policies and procedures of the Alliance.

1.3 Committees

Alliance organizational structure, as defined in its Constitution and Bylaws, calls for its research agenda to be driven by a number of scientific committees, whose activities are supported by administrative committees with research infrastructure needs executed by operations units. Alliance is a large and diverse organization, working across many institutions. To permit optimal leadership and accountability, the group is structured into programs (see section 1.2). The assignment of Alliance committees and operations units to the group chair and to the programs is shown in table 1-1.

1.3.1 Scientific committees

Alliance trials are conducted by scientific committees of two types: disease committees and modality/discipline committees. Disease committees serve as the primary site of study concept generation. Modality/discipline committees foster cross-disease participation of a modality or discipline in Alliance research. Scientific committee chairs are either proposed by the group chair or, for those committees within Alliance programs, are nominated by the appropriate program director. The Alliance Executive Committee approves all chair appointments. Each scientific committee chair names several vice chairs, who are also approved by the Executive Committee. Committee members are appointed by the committee chair with input from the vice chairs and from modality/discipline committee leaders.

Diversity of leadership and membership is built into the scientific committee structure. The committee leadership (chair plus several vice chairs) must include representatives from medical oncology, surgical oncology (for solid tumor committees), radiation oncology, translational research, and transplantation (leukemia and myeloma committees). Alliance disease committees include, at a minimum, two representatives each from the disciplines of medical oncology, surgical oncology (solid tumor committees), translational research, radiation therapy, community oncology practices and young investigators (those within five years of fellowship completion), as well as patient advocates and liaisons from Cancer Control committees, as applicable.

Alliance research is supported by a number of committees that ensure participation of essential modalities and disciplines in trial design and execution. As cancer research has become more complex and specialized, the number and variety of these committees has increased. Several committees play important roles in designing and executing Alliance trials. Some modality/discipline committees, however, are not sites of study concept development, but instead provide focal points for member involvement, enable collaboration and increase the impact of Alliance trials by promoting interactions with key member groups.

1.3.2 Administrative committees

Administrative committees conduct business as required to ensure the effective and ethical operation of the Alliance. Administrative committees reporting directly to the Board of Directors include the following: Membership, Institutional Performance Evaluation, Audit, and Constitution and Bylaws. The chairs of each of these committees are proposed by the group chair, and approved by the Board of Directors. Administrative committees reporting directly to the Executive Committee include: Data and Safety Monitoring Board, Conflict of Interest, and Publications.

Policy Name: Membership Criteria	**Policy Number:** 2.1
Section: Institutions – 2	**Date Revised:** December 16, 2024

2 Institutional membership

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

2.1 Membership criteria

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

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

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

2.2 Applying for membership

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

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

2.3 Membership activation

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

2.3.1 Roster

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

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

2.3.1.2 **NCI Tiers**

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

- Tier 1 members of Lead Academic Performance Site (LAPS) and NCI Community Oncology Research Program (NCORP) represent the administrative offices of the member network. Tier 1 of the Main member networks (non-LAPS, non-NCORP) can either be an administrative office of a health system (if approved by CTSU) or an accruing institution.
- Tier 2 members include affiliates of Main members, NCORP components, and LAPS Main member, LAPS affiliates, LAPS

Integrated components as identified in the LAPS grant. LAPS can also have aligned affiliates. Aligned affiliates are institutions/performance sites that are affiliated with the LAPS network but are not included in the LAPS grant. The Alliance Operations Center grant provides the per case payments for aligned affiliates.

- Tier 3 members are sub-component/sub-affiliates. A sub-component or sub-affiliate is an institution or practice site that shares the same FWA, IRB, governance structure and employees of either a Tier I or Tier II member. An example of a sub-affiliate is a physician practice that has a primary clinical site and has additional office locations where the same physicians treat patients. The primary clinic site is the parent and the additional locations are sub-affiliates.

2.3.2 Regulatory documentation

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

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

2.3.3 Financial documentation for institutions

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

2.4 Responsibilities of a main member

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

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

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

2.4.1 Communications

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

2.4.2 Electronic communication

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

2.4.3 Management of network data

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

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

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

2.4.4 Investigational drug handling

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

2.4.5 Human subjects protection

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

2.4.6 Training

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

2.5 Continuing Alliance membership

The Alliance Bylaws outline procedurally how Alliance membership status is evaluated. Each institutional member is re-evaluated for accrual requirements and 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.

2.5.1 Main members

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

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

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

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

2.5.2 Affiliates

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

2.6 Institutional roles and responsibilities

2.6.1 Main member principal investigator

2.6.1.1 Network responsibilities

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

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

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

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

2.6.1.2 Institutional responsibilities

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

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

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

2.6.2 Affiliate member principal investigator

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

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

2.6.3 Clinical research professionals

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

- Obtain IRB approval for Alliance protocols, consent forms, annual continuing review, and any protocol amendments that require IRB approval
- Obtain patient consent (and re-consents, when appropriate) for participation in Alliance studies

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

2.6.3.1 **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.

2.6.4 Withdrawn or terminated institutions

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

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2.7 Office for Human Research Protections assurances

2.7.1 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.

2.7.2 Reporting institutional assurance compliance

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

2.8 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. Each Alliance member institution in the United States must utilize the CIRB as the IRB of record for studies that are activated after March 1, 2019.

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).

2.8.1 Reporting and review requirements

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

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

2.8.2 Federal record-keeping requirements for IRBs

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

2.9 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. Signed informed consent documents must be retained for at least two (2) years after termination of the study. 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 for a minimum of two (2) years at the registering institution.

2.10 Non-member Collaborators

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

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

- Obtaining Federalwide assurance (FWA) with the Office for Human Research Protections (OHRP); and
- Obtaining State Department Clearance. The Alliance will submit State Department Clearance to the NCI on behalf of the international collaborator.

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

2.11 Participation in AFT

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

- Tier I members include the LAPS and NCORP administrative offices or umbrella organizations and rostered (non-LAPS, non-NCORP) main members.
- Tier II members include LAPS main members, LAPS Integrated Components (satellite sites of the LAPS main member), NCORP Affiliates, and affiliates of rostered main members
- Tier III members are sub-affiliates. The sub-affiliates are satellites of either a Tier I or Tier II institution and must be owned by the Tier I or Tier II institution and have the same FWA.

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

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

2.11.1 Provisionary Members

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

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

2.11.2 Members on Probation

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

Immediate: No sanctions

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

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

3rd Year Anniversary: Membership will be terminated.

Policy Name: AFT Membership Accrual Credits	**Policy Number:** 2.12
Section: Institutions – 2	**Date Revised:** December 16, 2024

2.12 AFT Membership Accrual Credits

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

2.12.1 Provisionary Members

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

2.12.2 Affiliate Accrual

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

3 Participants

Individual members of the Alliance fall into three categories: institutional, staff (Alliance operations, statistics and data management), and special member.

3.1 Participant Categories

Institutional members belong to an Alliance member institution and are involved with Alliance studies. This category includes the following**:**

- Principal investigators
- Investigators in all modalities and disciplines
- Pharmacists
- Clinical research professionals and oncology nurses
- Coordinators (e.g., pharmacy, radiation oncology, imaging, surgery, pathology)
- Cytogeneticists
- Administrative staff
- Laboratory researchers
- Fellows in oncology-related disciplines

Alliance staff may be located at an Alliance institution, but are responsible for group functions, including network group management, protocol development, regulatory affairs, statistical support and management of group data. This category includes Alliance operations and program staff as follows:

- Statistics and Data Management Center
- Operations Center
- Central Protocol Operations Program
- Cancer Control Program
- Procedure Based Therapy Program
- Translational Research Program
- Biorepositories

Special members are not located at an Alliance institution but interact with other Alliance participants in group activities. This category includes the following:

- Laboratory personnel handling Alliance samples at a non-Alliance institution
- Imaging/RT personnel evaluating data from Alliance studies
- Active participants relocated to non-Alliance member institutions (e.g., a study chair who has moved to a non-Alliance institution but is continuing to serve as chair)
- Patient advocates

- Investigators who participate in Alliance committees or studies but are not located at Alliance institutions
- Consultants who provide advice to Alliance leadership/committees within their area of expertise but do not actively participate in the research of the research programs of the group
- Data and Safety Monitoring Board (DSMB) members
- Representatives from federal agencies (FDA, NIH, etc)

3.2 Membership and participant registration

3.2.1 Applying for membership and registration

The institutional membership application is available on the Alliance public website (http://www.allianceforclinicaltrialsinoncology.org).

The lead Clinical Research Professional (CRP) or Secondary Lead CRP is responsible for adding and withdrawing all institutional members via CTSU Roster Update Management System (RUMS) or NCORP-SYS.

NCI policy requires all persons participating in any NCI sponsored clinical trial to register and renew their registration annually. Registration is accomplished via the NCI Registration and Credential Repository (RCR). RCR utilizes five person registration types:

- **Investigator (IVR)** — MD, DO, or international equivalent
- **Non-Physician Investigator (NPIVR)** — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD)
- **Associate Plus (AP)** — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., RUMS, OPEN, RAVE, TRIAD)
- **Associate (A)** — other clinical site staff involved in the conduct of NCI-sponsored trials
- **Associate Basic (AB)** — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems

All Investigators (IVRs), Non-Physician Investigators (NPIVRs), and Associate Plus (APs) are required to obtain Human Subjects Protocol and Good Clinical Practice (GCP) Training to be in compliance with the NIH. The training provider, course title, completion date, and expiration date, if applicable, and the provider's training certificate must be uploaded in the NCI Required Training subsection of the NCI Biosketch.

All persons applying for Alliance membership must obtain an NCI/CTEP-I.D me account, access the RCR system, and complete an annual NCI person registration.

Additional details are available on the CTEP website https://ctep.cancer.gov/investigatorResources/default.htm. Alliance leaders and committee chairs may request special membership for an individual. The request is sent to the Operations Center.

3.2.2 Alliance person database

The CTSU maintains a database of all Alliance individual members in the Regulatory Support System (RSS).

The institutional principal investigator and the lead CRP are responsible for ensuring that the roster of institutional members is accurate and up-to-date, utilizing the CTSU Roster Update Management System (RUMS) and providing timely notification to Alliance of changes to PIs and lead CRPs.

Alliance staff claim individual members as "persons" in the Alliance roster and ensures the accuracy of the Alliance person roster.

The Alliance may release portions of the roster to persons who are not Alliance members upon approval by the Alliance group chair or designee. Individuals who wish to request the roster should send a request and justification to the chief operating officer.

3.3 Traveling on official Alliance business

Alliance members whose travel expenses are paid by an Alliance grant must follow federal guidelines regarding reimbursement of travel expenses. Each institutional grants and contracts office that reimburses travel has its own policy regarding how federal travel funds are to be reimbursed. Please refer to the specific grants and contracts office of the institution that is funding travel expenses for instructions on how to file expense reports.

For information on travel support available from the Alliance, see the Alliance Travel Policy (refer to the Alliance website under Meetings). In addition to support for travel to group and committee meetings, the Alliance also provides travel support for the institutional audit program.

3.4 Individual scientific misconduct

The integrity of Alliance data is dependent upon the work of many individuals at all levels of the group. No event is more damaging to the reputation of the clinical research that Alliance and the other network groups perform than the discovery of submission of false or fraudulent data. Inclusion of such data in our analyses may invalidate the scientific conclusions reached. These invalid conclusions may result in the setting of inappropriate medical practice standards consigning large groups of patients to inferior therapy. Moreover, the violation of the trust between the patient and the healthcare team by such an event will erode the relationships required for conduct of clinical trials and harm the public's perception of all medical investigations. As such, evidence of any systematic or intentional attempt to submit false data of any sort to the Alliance will be dealt with in the most rapid and vigorous manner possible. In addition to withdrawing Alliance membership from those affected, and suspending accrual from the institution(s), the Alliance will assist appropriate governmental bodies in the prosecution of the individuals involved.

The Alliance publicizes its policies concerning scientific misconduct in a variety of forums, including the group meeting sessions, the group newsletter, and other means. Specific training sessions in ethics for investigators, clinical research professionals, statisticians, and other personnel are offered.

This training includes instructions on means whereby Alliance members can bring possible instances of scientific misconduct to the attention of those required to investigate it, how to deal with improper data that may have been recorded, and how to correct, if necessary, the scientific record based upon data that are inaccurate.

3.4.1 Receipt of allegations of scientific misconduct

Individuals who have been asked to falsify data or who believe they have knowledge that others are falsifying data must inform the Chief Operating Officer (COO) at the Alliance as soon as possible via whatever means (phone, letter, fax, e-mail, personal contact) is practical. The COO completes a detailed accounting of the notification. If this notification occurs by phone, the COO asks the party making the call if a witness to the call is desired. The policies of Alliance and NCI require a thorough investigation of any allegation of scientific misconduct while at the same time taking whatever actions are reasonable and proper to preserve the confidentiality of the informant and, until misconduct is proven, to protect the reputation of those accused. Although anonymous calls for the purpose of notification are discouraged since they may lead to less effective resolution of the matter, they are, nevertheless, accepted. This notification does not supersede or replace any notification also required by the institution from which the report originates. Alliance participants should contact the grants and contracts offices of their institutions to ascertain the correct procedures for reporting such matters at their institution.

3.4.2 Processing of allegation within Alliance

Upon receipt of an allegation of scientific misconduct, the COO immediately brings the matter to the attention of the group chair or, in the absence of the group chair, the group vice chair.

When notification is complete, the group chair, group vice chair, or CO O immediately contacts the Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch to report the incident. Subsequent to this notification, other actions may be required. These may include the immediate suspension of accrual to protocols in the involved institution and further investigation (see below).

3.4.3 Investigation of the allegation

In concert with NCI or other agencies, Alliance develops and implements a plan to investigate the allegation. This investigation usually consists of a thorough audit (see section 2.8).

The terms to be used by various committees and officers in connection with the investigation of possible episodes of scientific misconduct have been deliberately chosen to remove any restriction or impediment to whatever action Alliance committees, Executive Committee and Board of Directors may eventually choose to take in a given case. The Alliance may take action against a participant or institution independently whether or not the individual is found guilty in civil or criminal proceedings by others.

The terms used in the audit section of these policies to define institutional performance are used to describe adherence to protocol as well as the quality of data and other submitted materials. In this section we distinguish between erroneous data that result from unintentional mistakes and omissions, and data that are systematically erroneous or untrue.

It is acknowledged that in any process as complex as clinical research occasional errors of many sorts may occur. These may include typographical mistakes, miscalculations of numeric data, omissions of tests, doses, or procedures, delays of treatments, etc. These events when encountered are characterized by the terms used in the audit section and may generate actions concerning the institution as specified elsewhere in these policies.

Falsification of information is to be distinguished from inaccuracies arising from sources noted in the preceding paragraph. Examples include an ineligible patient falsely made eligible, a non-responding patient said to have responded, an abnormal laboratory result made normal, omitted doses of treatment said to have been given, etc. When wrong information is provided systematically, intent to deceive may be inferred. Occasional divergences of opinion among investigators are to be expected in any clinical trial, and data

arising from such divergences are to be distinguished from those that are systematic attempts to deceive. When necessary, the Alliance Audit Committee, Institutional Performance Evaluation Committee, Membership Committee, Executive Committee, and Board of Directors render judgment as to whether a given problem represents scientific misconduct and take appropriate actions as defined elsewhere in these policies.

Notwithstanding procedures for revoking membership, halting institutional accrual, or taking other action as defined in these policies or in the Alliance Constitution and Bylaws, the Alliance group chair takes immediate action as defined here when allegations or proof of scientific misconduct occurs within Alliance.

3.4.4 Actions to be taken if allegation of scientific misconduct is proved

If false data have been submitted to the Alliance Statistics and Data Management Center, the data are segregated and reviewed. The SDMC staff is responsible for determining what data changes may be required (see also section 2.8).

3.4.5 Publication and retractions

If the data have been used in any analyses in preparation of an abstract, the abstract will be revised, if possible, based on a new analysis without the suspect data, or a disclaimer will be offered during the presentation of the revised data. If such data have been used for preparation of a manuscript, the paper will be withdrawn until a new analysis can be conducted. If the manuscript with the false data has been published, the journal will be asked to publish a retraction and re-analysis at the earliest possible time.

It is understood that correction of published information derived from flawed data is of great importance to the public and the scientific community. The Alliance will issue such corrections to relevant journals within 30 days of the time that false data are discovered, or with CTEP consent, whenever a re-analysis can be completed. In addition Alliance has agreed to make its computer data and documentation available to CTEP for analysis when necessary in a national health emergency.

3.4.6 Actions against individuals

An allegation of scientific misconduct may result in immediate action on the part of the group chair to suspend patient registrations by a participant or a member institution. Subsequently, possible actions relevant to institutions occur through usual committee processes described elsewhere in these policies.

Allegations of scientific misconduct by individuals are brought by Alliance staff, the Audit Committee, or others to the Alliance Executive Committee for investigation. Those accused may be asked to appear before the Committee. In such matters, because of the possibility of injury to patients or the public health, time is of the essence. The Executive Committee sets the schedule for the appearance and testimony of the accused. On the basis of the investigation, the Committee may either take no action or may make recommendations to the Alliance Board of Directors. Recommendations to the Board may include severing the membership of the accused, removing the accused from study chairmanship or authorship, censure, or any other action the Executive Committee feels is appropriate.

The accused is provided with the written recommendation of the Executive Committee to the Board. At the meeting of the Board, or in writing prior to the meeting, the accused may offer a rebuttal of the Executive Committee recommendations, but may not offer evidence not previously considered by the Executive Committee. The Board acts on the recommendation of the Executive Committee, accepting it, rejecting it, or changing it, as the Board deems appropriate.

3.4.7 Confidentiality

The action of the Board is final and is a matter of record. It is documented in the minutes of the Board and communicated to the relevant Alliance institution. The deliberations of the Board, the Executive Committee, evidence and audits collected by the committees of the group, and the statements of the accused are held confidential by the Alliance. However, any and all evidence of misconduct is shared with the NCI and/or other appropriate governmental bodies.

3.5 Conflict of Interest

3.5.1 Introduction

A financial conflict of interest (FCOI) in research means a significant financial interest that could directly and significantly affect the design, conduct, analysis, or reporting of research. The Alliance for Clinical Trials in Oncology has implemented procedures designed to "promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct, and reporting of research will be free from bias resulting from Investigator financial conflicts of interest.[i]"

3.5.1.1 Policy

This **POLICY** intends to provide well-defined and transparent requirements for disclosures of conflict of interest, the administrative processes for reviewing the disclosures, and procedures for identifying potential, perceived, and actual conflicts of interest. This POLICY will identify when a management plan will be implemented, when an Investigator may be precluded or limited from participation in Alliance activities, and for maintaining such records.

3.5.1.2 Scope

The Alliance Study chairs/Co-chairs, Committee chairs/Vice chairs, Board of Directors, Executive Committee, Group leaders, Data and Safety Monitoring Board, Main Member Principal Investigators, Institutional Investigators, members of the Statistics and Data Center, and Alliance operations staff members, including Executive Officers, must comply with this POLICY.

3.5.1.3 Disclosure

3.5.1.3.1 Disclosure Requirements

Financial arrangements >$5000 per year must be disclosed and submitted as outlined in this POLICY. Disclosures are for the 12 months preceding the date of the disclosure. An Alliance Conflict of Interest form must be completed before participation in research activities and attending group meetings. and at least annually and more depending on the role within the Alliance. For example, Study leaders are required to submit Conflict of Interest disclosure forms before study activation and annually until the study results are published; Authors are required to submit Conflict of Interest disclosure forms before manuscripts will be approved by the Alliance publication committee; and before abstracts can be presented. Conflict of Interest disclosure forms are required before study concept

submission. Updated Conflict of Interest disclosure forms are required to be submitted within 30 days of material changes in financial arrangements.

3.5.1.4 Management of De Minimus and Maximum Thresholds

The Alliance manages financial interests that fall between Public Health Service Policy (PHS) the de minimus threshold and the Food and Drug Administration maximum threshold.[ii]

3.5.1.5 Training

On an annual basis, the Alliance will provide Conflict of Interest training to Investigators and staff by distributing this POLICY. Additionally, this POLICY is available on the Alliance website (https://allianceforclinicaltrialsinoncology.org/P&Ps/Chap3) and will be available during the annual Alliance Group Meetings. The Alliance reserves the right to require additional training, as necessary. Financial Conflict of Interest training and review of the Alliance Conflict of Interest (COI) POLICY is requisite for participation in research activities.

3.5.1.6 Alliance Member Responsibilities

Members should recognize financial arrangements that may be perceived as potential or actual Conflicts of Interest. These include personal investments or other business relationships, including those of the members' Immediate Family and the connection between the Alliance Group structure and the members' involvement. It is expected that material conflicts of interest will be resolved before an individual assumes leadership roles within the Alliance.

3.5.1.7 Roles within the Alliance

Table 3-1. provides general guidance on the management of potential, perceived, or actual Conflicts of Interest based on the roles within the Alliance and the linkage between the Conflict of Interest and the drugs, devices, technology, and/or therapies currently under or will be under investigation by the Alliance.

All Financial arrangements of the Investigator/Individual and those of their Immediate Family Member with shared income of >$5000 per year must be disclosed.

Table 3-1. Alliance Roles and General Management of Financial Conflicts of Interest

ROLE	**GENERAL MANAGEMENT OF FINANCIAL CONFLICTS OF INTEREST (FCOI)** *The Alliance reserves the right to modify the Management of FCOI at any time as it deems necessary*
Group Chair (GC)/ Vice Chair (VC), Program Directors (PD) and Executive Committee Members (EC)	FCOI with financial relationship>$25,000 (such as compensation) per year in a privately held business, and/or equity interest in a publicly traded company sponsor >$50,000 per year, or ≥5% ownership interest (including common stock) in either a privately held or publicly traded business, that has a product currently under investigation, in consideration of investigation or in direct competition with products under investigation with the Alliance must: • Disclose their conflict; and • Recusal from discussions and voting if a topic presents a conflict or an appearance of a conflict
Study Chair/ Study Co-Chair	FCOI with financial relationships>$5000 to ≤$25,000 (such as compensation), and/or equity interest in a publicly traded entity ≤$50,000 per year that has a product/s currently under investigation in a trial in which they serve as a study chair or study co-chair requires the implementation of a Management Plan consisting of the following: • Public disclosure of their conflict at meetings/presentations and for publications when engaged in Alliance activities • A copy of the Investigator's Institutional Management Plan for review by the COI Committee • Depending on the impact of the FCOI, they may be required to recuse themselves from discussions involving the entity in which they have a conflict • The assignment of a non-conflicted study co-chair is required, and the study co-chair or their designees are required to take a significant role in reviewing data and preparing study results for publication or presentation FCOI that have **one** or **more** of the following: the Investigator will be prohibited from serving as a Study Chair or co-chair on the study(while the study is under development, newly activated, or ongoing and accruing subjects) and this will remain in effect for one year following the completion of the study.[iii] • Personal payment >$25,000 per year from an entity in which they have a product/s under investigation in a study in which they have a material role; • Any financial arrangement in which the value of compensation could be influenced by the outcome of

	the study. • Equity interest in a publicly traded entity in which they have a product under investigation in the trial of >$50,000 per year, or ≥5% ownership interest in a public or privately held entity (including common stock) or direct employment with an industry partner. The Management Plan for the Study Chair or Study Co-Chair with a FCOI at the **maximum threshold** will be implemented and include the following: • The Committee chair will appoint a new study chair who is non-conflicted to assume responsibility for study oversight. The new study chair and the study statistician will assume primary responsibility for data management, analysis, and presentation and publication of study results • Public disclosure of their conflict at meetings/presentations and for publications when engaged in Alliance activities • A copy of the Investigator's Institutional Management Plan for review by the COI Committee • Recusal from discussions involving the entity in which they have a conflict.
Disease Discipline and Modality Committee Chairs/ co-Chairs and Vice Chairs	FCOI of >$5000 to ≤$25,000 (such as compensation) and/or an equity interest in a publicly traded by entity ≤$50,000 per year, in which they have a product under investigation in the trial requires the implementation of a Management Plan consisting of the following: • Public disclosure of their conflicts at meetings/presentations and for publications when engaged in Alliance activities • A copy of the Investigator's Institutional Management Plan for review by the COI Committee • Depending on the impact of the FCOI, they may be required to recuse themselves from discussions involving the entity in which they have a conflict FCOIs with **one** or **more** of the following, the Investigator *will be prohibited* from serving as the *Committee Chair (or the Committee co-Chair or Vice Chair)* sponsoring a study (while the study is under development, newly activated, or is ongoing and accruing subjects) and this will remain in effect for one year following the completion of the study. • Personal payment of >$25,000 per year from an entity

	that has a product/s under investigation in the trial in which they have a material role. • Any financial arrangement in which the value of compensation could be influenced by the outcome of the study • Equity interest in a publicly traded entity in which they have a product under investigation in the trial of >$50,000 per year or ≥5% ownership interest in a public or privately held entity (including common stock) or direct employment with an industry partner. The Management plan that will be implemented for a FCOI at the maximum threshold for the Committee Chair (co-Chair or Vice Chair) includes the following: • The Vice-chair or designee will assume responsibility for study oversight • Public disclosure of their conflict at meetings/presentations and for publications when engaged in Alliance activities. • A copy of the Investigator's Institutional Management Plan for review by the COI Committee • Recusal from discussions involving the entity in which they have a conflict
Data Safety Monitoring Board (DSMB)	**At each DSMB meeting:** FCOIs >$5000 to ≤$25,000 (such as compensation) and/or equity interest in a publicly traded entity ≤$50,000 per year that has a product/s in a trial under review: Each member will verbally disclose any conflicts pertinent to studies under review. FCOI >$25,000 (such as compensation) and/or >$50,000 per year or >5% ownership interest including stock options or other forms of equity interest from a public or private entity that has a product/s in a trial under review. Each member will verbally disclose their conflict/s and recuse themself from discussions from the pertinent studies under review
Executive Officers (EO) and Statistics and Data Management (SDMC) Trial Statisticians	FCOIs with **one** or **more** of the following, the individual will no longer be involved with any aspect of the study in which there is a conflict (while the study is under development, newly activated, or ongoing and accruing subjects). This will remain in effect for one year following the completion of the study. • Personal payment of >$25,000 per year from an entity that has a product/s under investigation in the trial in which they have a material role;

	• Any financial arrangement in which the study's outcome could influence the value of compensation • Equity interest in a publicly traded entity with a product/s under investigation in the trial of >$50,000 per year, or ≥5% ownership interest (including common stock), or direct employment with an industry partner Requires: • Public disclosure of conflicts at meetings/presentations and for publications when engaged in Alliance activities. • A copy of the Investigator's Institutional Management Plan for review by the COI Committee
Alliance Operations and SDMC Members	FCOI with financial relationships >$25,000 (such as compensation) per year in a privately held business and/or equity interest in a publicly traded company sponsor >$50,000 per year, or ≥5% ownership interest (including common stock) in either a privately held or publicly traded business that has a product currently under investigation, in consideration of investigation or in direct competition with products under investigation with the Alliance; a Management Plan will be implemented that may include the following: • The individual will no longer be involved with any aspect of the study in which there is a conflict (while the study is under development, newly activated, or ongoing and accruing subjects). • The individual will recuse themselves from any discussions about the trial or trials. • Public disclosure of the conflict/s at meetings/presentations and for publications when engaged in Alliance activities This will remain in effect for one year after the conflict no longer exists.
Main Member Institutional Principal Investigator (Board of Directors), Investigators participating in Alliance studies	The COI committee may request an Institutional management plan from investigators with multiple disclosures of >$5000 or exceeding the threshold from one or more entities.
Institutional Investigator	Financial conflict disclosures of institutional investigators are subject to institutional conflict of interest policies. The Alliance may request a management plan from investigators exceeding thresholds, including documented institutional management plans in compliance with institutional requirements. The Alliance may disapprove of the study participation of institutional investigators exceeding maximum thresholds upon review of the institutional plan to mitigate bias.

3.5.2 Decisions on matters of conflict of interest

It is not possible for this POLICY to provide guidelines for every situation that could give rise to a potential, perceived, or actual conflict of interest. For this reason, the Conflict-of-Interest Committee is broadly charged with using the guidance of the definitions and the roles offered in the tables to arrive at a recommendation that is consistent with regulations and takes all reasonable steps to ensure any potential bias is minimized or eliminated. In this activity, the Conflict-of-Interest Committee members understand the committee has considerable latitude and flexibility with respect to rendering its decisions.

Table 3-2. Definitions

Term:	**Definition**
Conflict of Interest (COI)	A professional, proprietary, and/or financial arrangement on the part of an individual, their spouse, domestic partner, dependent children, and other dependent family members with whom the individual directly shares income, which may directly and significantly affect the design, conduct, analysis, or reporting of research. A COI can be potential, perceived, or actual.
De Minimus Threshold [1]	The Public Health Service (PHS) defines a significant financial interest >$5000 related to the investigator, their spouse, and dependent children that must be disclosed: • For publicly traded entities: the value of any remuneration received from an entity in the twelve months preceding the disclosure is >$5000 per year, and any payment for services not otherwise identified as salary (e.g., consulting fee, honoraria, paid authorship); equity interest includes any stock, stock option, or other ownership interest, as determined through reference to public prices or other reasonable measures of fair market value. • For a non-publicly traded entity: significant financial interest exists if the value of any remuneration received from the entity in the 12 months preceding the disclosure, when aggregated is >$5000, or when the investigator holds any equity interest (e.g., stock, stock options, or other ownership interest); or • Intellectual property rights and interests (e.g., patents, copyrights), upon receipt of income related to such rights and interests. • Reimbursed or sponsored travel related to their institutional responsibilities; however, disclosure does not apply to travel that is reimbursed or sponsored by a Federal, state, or local government agency, an institution of higher education, an academic teaching hospital, a medical center, or a research institute that is affiliated with an institute of higher education. The term does not include the following:

[1] Research means a systematic investigation designed to develop or contribute to generalizable knowledge relating broadly to public health, including behavioral and social-sciences research. The term encompasses basic and applied research and product development. As used in this subpart, the term includes any such activity for which research funding is available from a PHS Awarding Component through a grant or cooperative agreement, whether authorized under the PHS Act or other statutory authority.

	• Salary, royalties, or other remuneration from the applicant institution; • Any ownership interests in the institution if the institution is an applicant under the SBIR Program (42 CFR 50 (F): Promoting Objectivity in Research)
Disclosure requirements	For purposes of this POLICY, a disclosure includes compensation received >$5000 in the 12 months preceding the date of the disclosure.
Financial Arrangement	Anything of monetary value, whether or not the value is readily ascertainable remuneration or in which any person has an ownership or equity interest.
Financial Conflict of Interest (FCOI)	A financial conflict of interest (FCOI) in research may exist whenever an Investigator or immediate family member with shared income has a direct or indirect interest or financial relationship, with an Entity that may conflict, be perceived as conflicting or be inconsistent with the Investigators duties, responsibilities or ability to exercise judgment in any Group Research.
Immediate Family Member	Includes a spouse, domestic partner, dependent children, and other dependent family members with whom the individual directly shares income
Institution	Any domestic or foreign, public, or private entity or organization (excluding a Federal agency) that is applying for or that receives PHS research funding.
Investigator	Any person who is responsible for the design, conduct, analysis, or reporting of research. The investigator must disclose potential conflicts of interest and/or related financial arrangements of any individual with whom the investigator directly shares income (e.g., spouse, children, or domestic partner).
Management of Financial Conflicts of Interest (FCOI)	Taking action to address (FCOI) can include reducing or eliminating the FCOI to ensure, to the extent possible, that the design, conduct, and reporting of research will be free from bias, *See* Management Plan
Management Plan	A documented plan of action is implemented to ensure, to the extent possible, unbiased data collection and to mitigate potential, perceived, or actual conflicts of interest by protecting the integrity of the research surrounding the design, conduct, analysis, or reporting of research conducted by the Alliance.
Material Changes	For purposes of disclosing financial arrangements >$5000, material changes include decreases or

	increases to previously reported amounts or new arrangements not previously reported.
Maximum Threshold	Significant Financial Interests (SFI) is when an investigator cannot be involved in the development and management of a clinical trial. The FDA defines significant financial interest related to the investigator, spouse, and dependent children to include the following: • Payments from the sponsor in >$25,000 per year *during* the research and *for one year after*, not including compensation for research costs. • Any financial arrangement in which the value of compensation could be influenced by the outcome of the study. • Equity interest in a publicly traded corporation >$50,000 a year during the time of research and one year after. Any ownership interest, stock options, or other financial interest in a non-publicly traded company whose value cannot be readily determined through reference to public prices. [iv]
Ongoing Affiliation	Relationship with an entity having a role in the development or sale of a product or technology, including entity/organization holding *patents, trademarks,* or *licenses* for the development or sale of research products.
Public Health Services (PHS)	Public Health Service ("PHS") of the US Department of Health and Human Services, and any components of the PHS to which the authority involved may be delegated, including the National Institute of Health ("NIH").
Professional Interest	Involvement (current or prior) in the development of a product, technology, or service with an entity being studied by the Alliance, or in consideration for Alliance-related activities or where the product, technology, or service competes with a product, technology, or service under consideration by the Alliance. Financial relationships with the entity having a role in the development or sale of a product or technology, including organizations holding *patents, trademarks,* or *licenses* for the development or sale of research products, including service as an *Officer, Director, Trustee, Partner, Employee* or on a *Scientific Advisory Board* or in a similar capacity for such an organization. An entity the investigator is negotiating for or has an arrangement on prospective employment or affiliation or compensation >$5000 annually for services such as *honoraria, consultative services, paid authorship* either by the entity or a third party (medical services companies or

	continuing medical education companies) Receipt of *unrestricted educational grants* of ≥$100,000 over a three-year period for research funding not designated for a particular study or contracted product through their employee institution, i.e., the funds are not managed by the institution but are managed by the investigator. All non-government or non-academic travel reimbursement from a for-profit entity (*See* reimbursed or sponsored travel)
Proprietary Interest	The investigator has a financial interest in the research product being evaluated because the investigator or an Immediate family member has: a). a material interest in the product or technology that may result in financial gain, e.g., the investigator is receiving compensation that could be affected by study outcome, such as compensation that is explicitly greater for a favorable result or the investigator is receiving annual royalties or other compensation at a value exceeding $5000 per year following the commercial sale of the product or technology. Such royalties may be in the form of personal compensation to the investigator or may be used to support the investigator's research. b). an equity interest (including common stock) exceeding $5000 per year, or ≥5% ownership interests (including stock options) in a start-up company, the stock of which is not publicly traded, or options exceeding $5000 per year in a commercial enterprise that will benefit from the sale of the product or technology.
Research	Any Alliance study under development or ongoing that involves the analysis of a drug, treatment, medical device, technique, or technology and any correlative, biological investigation/s related to such protocols, investigations, or analyses, including any type of publication, presentation, or other public disclosure of results.
Reimbursed or Sponsored Travel	Non-government or non-academic travel reimbursement from a for-profit entity for the Investigator and/or Immediate Family Member. For the purposes of this POLICY. the following must be disclosed: the purpose of the trip, sponsor/entity, destination/duration, and any additional information as requested.
Research Product	A drug, treatment, medical device, technique, or technology that will be or is currently under

	investigation by the Alliance.
Significant Financial Interest (SFI)	A Financial Conflict of Interest (FCOI) in research is present when a Significant Financial Interest (SFI) affects or could appear to affect, the professional judgment of a researcher when designing, conducting, or reporting research. For purposes of this POLICY, any remuneration when aggregated >$5000 is considered an SFI.
Sponsor funding the study	For purposes of financial disclosure, "sponsor of the covered clinical study" means the party providing all or some kind of support (funding, drugs, devices, assays, etc.) for a particular study when it was conducted.
Unrestricted research/ educational grant	Receipt of $100,000 or more over a three-year period for research or an educational grant that is not designated for a particular study or educational program. The funds are “unrestricted” and are managed by the investigator. *See* Professional Interest

3.5.3 Review of Disclosure Statements

The Conflict-of-Interest Committee meets no less than twice per year and reviews the disclosure statements. The Committee provides recommendations concerning conflicts of interest to the Alliance Executive Committee.

3.5.4 Actions on conflict of interest

The Executive Committee provides recommendations to the group chair on actions to be taken involving conflicts of interest.

3.5.5 Penalties for failure to observe the conflict-of-interest policy

Lack of compliance with this POLICY is referred to the Alliance Executive Committee. The Executive Committee will conduct and complete a retrospective review within 120 days of identified noncompliance and document its findings. The Executive Committee will recommend appropriate corrective action, which will be presented to the Alliance Board of Directors. The Board of Directors will review the recommendation and will either accept or modify the corrective action. Failure to submit conflict of interest forms or to comply with a Management Plan by individuals subject to this POLICY may result in suspension or termination of Alliance membership privileges, including serving as a study or committee chair.

3.5.6 Public disclosure

Financial conflicts of interest must be disclosed in *any* public presentation of research results. Financial conflicts of interest must be disclosed during Alliance committee meetings, including study development discussions. In addition, the Alliance will make information about financial conflicts of interest publicly available within five business days of a written request to AllianceConflictOfInterest@alliancenctn.org. Questions about this POLICY may be sent to the same address.

3.5.7 Record Retention

Records of all financial disclosures and any actions the Alliance took concerning the disclosures, including the recommendations by the Conflict-of-Interest Committee reported to the Executive Committee, will be maintained for at least three years after the grant has ended.

3.5.8 Reporting Financial Conflicts of Interest (FCOI)

The Alliance reports Financial Conflicts of Interest (FCOI) that could directly and significantly affect the design, conduct, or reporting of NIH-funded research.

The Alliance submits Conflict of Interest disclosures to the Cancer Therapy Evaluation Program (CTEP), as a part of the Central Institutional Review Board (CIRB) Submission. A management plan is provided as appropriate.

The Alliance provides a Financial Conflict of Interest report to the awardee Institution receiving Alliance grants according to the requirements of the Institution.

3.5.9 Alliance Conflict of Interest Committee

The Alliance Conflict of Interest Committee is a volunteer committee appointed by the Group Chair. The Conflict-of-Interest Committee is comprised of Alliance investigators and staff. The committee reviews the financial conflict of interest disclosure forms related to research supported by the Alliance and Alliance for Clinical Trials in Oncology Foundation, reviews the information on the disclosure forms, and provides recommendations to the Executive Committee on Management of Conflicts of Interests identified. The Executive Committee considers these recommendations and may request additional information prior to rendering a decision.

End of Chapter Notes

Examples of Financial Conflicts of Interest

- The investigator or sponsoring committee chair or vice chair has played a substantial role in the prior development of the product or technology being studied by the Alliance.

- An Investigator submits a study proposal using two agents; one is under an IND, and the other is commercially available. The investigator is in the speaker's bureau for the company with the agent under an IND and a consultant for the agent that is commercially available. A third party reimburses the investigator.

- An Investigator's spouse is employed by an organization that has a product frequently used in Alliance research. The spouse has employee stock options with a value of >$150,000. The Investigator is a co-chair of a study that will use an agent from his/her spouse employer. A favorable outcome would add another indication of use for the agent.

Additional Information on Conflict-of-Interest Management Plans

1. Independent review of study by Cooperative Group or Network Group beyond Disease Committee	An independent review of studies by network group leadership beyond the sponsoring committee will be undertaken.
2. Independent Review by NCI	CTEP will be informed of the Management Plan for a Study Chair/ Study (3 below)
3. Independent review by the Data Safety Monitoring Board	Independent review by a Data and Safety Monitoring Board (DSMB) will continue for all phase III trials. For the studies that have a study chair with a conflict, the Management Plan will be shared with the DSMB before the review of the study. A representative from CTEP will participate in DSMB meetings and have access to this information at that time.
4. Trial Management of data Independent of the Study chair	For non-DSMB monitored studies, no aggregate outcome data is shared with the study chair until it is deemed ready for sharing by the trial statistician. The study statistician, the study co-chair or his or her designee, and the professional staff of the Alliance Statistics and Data Management Center will undertake the management of data independently of the study chair.
5.Any Additional measures proposed by the Group	• Public disclosure of conflict of interest at meetings/ presentations and publications • Recusal from deliberations • Sharing Institutional Management Plan • Divestiture of the conflicting interest

General Elements that pertain to assuring unbiased data collection and review in Group Trials for Study Leaders with Conflicts >$5K-$25K (*Taken from the Conflict-of-Interest Policy for NCI/DCTD-Supported Cooperative Group or National Clinical Trials Network Randomized Phase 2 or Phase 3 Clinical Trials,* August 2012)

Other Considerations for the Conflict-of-Interest Committee

- Committee chairs with financial interests in products actively under investigation or proposed in committee-sponsored studies may be required to publicly disclose potential conflicts and/or recuse themselves from relevant discussions.
- Alliance leaders may have individual financial interests related to industry partnerships or other affiliations that do not exceed the threshold of $25,000. However, multiple disclosures of >$5000 are subject to review by the Alliance COI Committee. The Committee may recommend a management plan that includes oversight by co-leaders.
- If all of the key individuals of a study show a significant conflict of interest such that they are ineligible for authorship, the COI committee will be asked to provide a recommendation. Under these circumstances, it is possible the COI Committee will prepare a report for adjudication by the Executive Committee.

Authorship (*See* Publications Policy No 10.0)

- An individual with a conflict of interest may lose authorship rights on a publication. In general, an individual with a significant conflict of interest such that they are ineligible for a study chair or co-chair role cannot serve as either the first, corresponding, or senior (last) author of an Alliance publication.
- When a conflict exists with the Committee chair or Vice-chair, the committee leader may not serve as either first, corresponding, or senior author.
- However, an investigator may be precluded from authorship due to the magnitude and nature of an FCOI. Under this circumstance, the Investigator would likely have had prior notification of this determination.

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[i] 42 CFR 50.603 (F), Promoting Objectivity in Research.
[ii] 42 CFR 50(F); 21 CFR § 54.2 (f), *Conflict-of-Interest Policy* for NCI/DCTD-Supported Cooperative Group or National Clinical Trials Network Randomized Phase 2 or Phase 3 Clinical Trials, August 2012)
[iii] 21 CFR § 54.2 (f) states the FCOI exists during the time the clinical investigator is carrying out the study and for *one year* following the *completion* of the study
[iv] *Id,* Financial Disclosure by Clinical Investigators

4 Committees

4.1 Committees and their function in Alliance

The Alliance has scientific (disease, modality, and discipline) and administrative committees. These committees are responsible for the scientific, administrative oversight and quality assurance activities of the Alliance. The function of each scientific committee is to plan, implement, evaluate, analyze, and report on activities relating to its area of specialization. Each committee shall meet periodically as appropriate. Scientific committees include Disease Committees, whose activities focus upon research related to a particular disease or organ system; Modality Committees, whose activities focus upon optimal involvement of a particular profession; and Scientific Discipline Committees whose activities focus upon integration of particular disciplines in the work of Alliance.

A list of all committees is outlined in the Alliance by-laws.

4.1.1 Disease committees

The Alliance disease committees are responsible for developing and conducting the scientific agenda of the Alliance. They collaborate closely with the modality and discipline committees and many of the Alliance studies are multimodality studies that address more than one research hypothesis.

4.1.2 Discipline committees

The Alliance discipline committees, working in conjunction with the disease committees or on their own, are responsible for studies that focus on new methodologies for treating cancer or minimizing the burden of cancer for individuals and their family members. These committees also develop studies addressing the fundamental biology of cancer, cancer risk assessment and prevention.

4.1.3 Modality committees

The Alliance modality committees develop educational programs and/or provide quality control services and serve as a scientific resource for other committees.

4.1.4 Administrative committees

The Alliance administrative committees are responsible for the administrative and quality assurance activities of the Alliance. Administrative committees shall conduct business as required to ensure the effective and ethical operation of the Alliance.

4.2 How to form a committee

The proposal to form a new scientific committee is brought before the Executive Committee for review and approval. The approval and formation of a new committee are also brought to the attention of the chair of the Constitution Committee, since changes to the Alliance Constitution or Bylaws may be required. If a new committee is approved, the Group Chair names the new committee chair following a leadership search process and approval by executive committee.

The group chair may form administrative, ad hoc committees, and working groups; the Executive Committee must approve these committees and the chairs of newly formed committees.

4.3 Committee membership

The group chair, with the approval of the Executive Committee, names the committee chair. The committee chair nominates the vice-chair for approval by the Group Chair and the Executive Committee and selects committee members. . Members are encouraged to bring their ideas to the committee chair for consideration and let the committee chair know of their interest in being on the committee. Committee membership is rotated at appropriate intervals

4.4 Roles and responsibilities in committees

4.4.1 Committee chair nomination and approval

Committee chairs are either proposed by the group chair or, for those committees within Alliance programs, are nominated by the appropriate program director. All chair appointments are approved by the Alliance Executive Committee. The chair is chosen and their performance is evaluated on the basis of the leadership they can provide to the area of committee responsibility.

4.4.2 Committee Chair Nomination Process

Group Chair names a Nominating Committee Chair and together they select the Nominating Committee members. A Call for Nomination goes out to all Alliance and NCTN members, with a request to submit names of nominees to the Nominating Committee Chair. Following interview and assessments, the nominating committee provides recommendations to the Group Chair. The Group Chair determines the candidate to put forward to the Executive Committee for approval by majority vote. Outgoing committee chair provides advise to nominating committee and is consulted but is not a member of the nominating committee.

4.4.3 Committee chair responsibilities

It is the responsibility of the committee chair to coordinate the activities of the committee and to ensure that the work of the committee is performed in a timely manner.

4.4.3.1 Administration

Committee membership: The committee chair names the members of the committee. The number of members may not exceed the number designated by the group chair. The committee chair is responsible for rotating members off of the committee and adding new ones as needed.

The committee chair nominates the vice chair of the committee to the group chair for the group chair's review and approval. Committee vice-chair appointments are then presented to the Executive Committee for approval. The committee chair also nominates subcommittee and working group chairs , if applicable, to the group chair for the group chair's review and approval. Subcommittees are formed by committee chairs, in order to oversee

and provide guidance by members who have subject matter expertise related to a growing areas of interest. They may convene regularly in order to fulfill goals of the parent committee. Subcommittees must be approved by the Group Chair and Alliance Executive Committee. Working groups are created to research and develop deliverables on specific topics. Working Groups need Group Chair approval, but are sent to the Executive Committee for informational purposes only. Working Groups may be elevated to Subcommittee if the need continues and if so desired by the parent committee chair. This request is submitted to Group Chair and Executive Committee for approval.

Committee liaisons: The committee chair names liaisons to the committee from other committees after discussion with the other committee chair.

Group and committee meetings: The committee chair or designee prepares agendas for committee and group meetings.

The committee chair also identifies invitees to the meetings and requests support for travel, as appropriate.

The committee chair may schedule conference calls as often as needed to accomplish the work of the committee.

Conflict of interest: The committee chair, vice chair, study chair and study co-chair (of studies that have not been published, current and pending studies) are required to complete a conflict of interest disclosure form at least annually (see Alliance Policies and Procedures, section 3.5 Conflict of Interest).

Scientific misconduct: Each participant in the Alliance is expected to review and comply with the section on individual scientific misconduct in the Alliance Policies and Procedures (see section 3.4 Individual Scientific Misconduct).

The committee chair and all investigators are expected to comply with federal guidelines regarding human subjects training requirements.

Annual progress reports: The committee chair prepares an annual progress report for the committee for inclusion in the annual grant progress report that the Alliance must submit to NCI.

Competing renewal report: The committee chair prepares a committee report whenever the Alliance submits a competing renewal application.

4.4.3.2 Protocol development and management

The committee chair assigns study chairs and evaluates study chair performance on an ongoing basis.

The committee chair supervises the protocol process from concept development through publication of results. This includes overseeing the development and review of concepts, submitting concepts to the Study Concept Review Committee, providing input throughout the protocol development process, and reviewing publications including interim agenda reports, abstracts and manuscripts. Committee chairs are responsible for mentoring study chairs and guiding them through the protocol development process, including forms development. The committee chair acts as a mediator if other members of the study team cannot reach resolution on significant issues that arise during the life cycle of a protocol. Committee chairs also participate in the development of protocol amendments as required.

The committee chair reviews study accrual on an ongoing basis and consults with the study team to develop appropriate action plans for studies that are accruing at a slower pace than anticipated.

The committee chair attends DSMB meetings for studies within the committee.

The committee chair participates in study team conference calls as appropriate.

The committee chairs may be contacted by investigators, oncology nurses and clinical research associates when the study chair is unavailable, with questions pertaining to a specific study (e.g., clarification of eligibility, treatment issues). Nobody, including the committee chair, may grant waivers of eligibility criteria.

The committee chair regularly communicates with the data managers. The committee chair may be called on to answer protocol questions in the absence of the study chair.

The committee chair regularly communicates with the statisticians responsible for the committee regarding protocol development, monitoring of ongoing studies and analysis/publication of results.

4.4.3.3 Publications

The committee chair, along with the committee's primary statistician, works with study chairs to complete manuscripts in a timely manner. If the study chair is not able to write a manuscript in a timely manner, then the committee chair discusses with the group chair reassignment of that study to another individual who will be able to write the manuscript.

The committee chair reviews the committee's statistical study summaries before they are distributed to the Alliance.

The committee chair reviews the committee's abstracts/ manuscripts/presentations prior to public distribution.

The committee chair works with his/her counterpart in other network groups to ensure that intergroup studies have a representative from each group that participated in the study.

4.4.3.4 Intergroup collaborations

If appropriate, the committee chair discusses collaboration with his/her counterpart in other national groups.

The committee chair may also explore collaborations with international groups in conjunction with the CPOP office. International groups must comply with the federal regulations of the United States in addition to their own country's regulations.

4.4.3.5 Finances

Travel to Alliance meetings: Committees that do not have a separate grant have travel funds available in the Operations Center from various grants and other sources to support travel to the committee meetings. Travel expense reimbursement policies and frequently asked questions may be found on the Alliance website in the "Meetings" section.

Funding to support research projects: The committee chair works with the committee members and interested participants in the Alliance demonstrating interest in applying for additional

funding. If the project appears feasible, the committee chair asks the person who is responsible for the project to discuss the project with the executive officer and the primary statistician so that appropriate budgets, supporting the efforts of the Alliance operations offices, will be included in the application.

If funding is requested to support a research project, the group chair, appropriate committee chair(s), executive officer, and group statistician are copied on correspondence regarding this project.

Details concerning the proposed funding are included with the concept when it is submitted to the SCRC for review. Some concepts are not approved if no new funds are brought in to finance them. Information about the potential sources of support—federal or non-federal—should appear on the cover sheet that accompanies the concept.

The proposal is submitted to the CPOP office for review of the scientific plan and budgetary requests prior to submitting an application to the NCI or other granting agencies. If the proposal is submitted to a non-federal source, the Alliance Foundation reviews it prior to the submission. Applications to non-profit organizations are submitted from the Alliance Foundation.

All negotiations with industry collaborators are handled by Alliance and Foundation operations staff , not by the investigator or committee chair who proposed the project. The Alliance and the party arrange the details of the drug/device provision directly to group members.

4.4.4 Committee vice chairs

The committee vice chair assists the committee chair in carrying out the responsibilities of the committee and assumes responsibility for the committee when the committee chair is absent. The committee chair nominates candidates for committee vice chairs, who are approved by the Executive Committee.

4.4.5 Subcommittee chairs/cadre leaders

The cadre leader is appointed by the committee chair with the approval of the group chair. The cadre leader coordinates the activities of a subcommittee.

4.4.6 Committee members

Committee members, based on their expertise and interest in that particular area, are appointed by the committee chair with input from the vice chairs and from modality/discipline committee leaders. Principal investigators may nominate Alliance members to the committee for consideration by the committee chair, but only the committee chair appoints the committee members.

Patient advocates are assigned to other committees (besides the Patient Advocate Committee) and advise committees on various aspects of clinical research, providing the patient perspective.

Policy Name: Electing Executive Committee Members	**Policy Number:** 4.5
Section: Committees – 4	**Date Revised:** December 16, 2024

4.5 Electing Executive Committee members

The group chair appoints a nominating committee consisting of at least three individuals, no more than one of whom may be from any single member institution. The nominating committee, after consultation with the chairs of the appropriate modality committee and the cancer control committee, proposes a candidate(s) for vacant positions on the Executive Committee. In addition, individual institutional members may self- nominate or put forth candidate nominations at the time of the election by the Board of Directors. Each position on the Executive Committee is filled by a separate election. When reseating the Executive Committee every three years in conjunction with the BOD, ranked voting may be utilized for each category. Those who are representatives from academic member institutions will be nominated by Principal Investigators of any academic member institution, and those who are representatives from community member institutions will be nominated by Principal Investigators of any community member institution.

Each election is conducted by closed ballot. In the event of a plurality, only the top two candidates are entered into a runoff election.

Each elected representative to the Executive Committee serves a three-year term and may only be elected for three consecutive terms, but is eligible for re-election following a term out of office. The terms of office of the elected members of the Executive Committee overlap to provide continuity of committee activities. See the Alliance Constitution for additional details.

5 Meetings

The purpose of meetings of the Alliance for Clinical Trials in Oncology is to provide a forum to plan, conduct, and share the results of clinical trials research with the membership of Alliance. Meetings are a necessary and vital communication function of the Alliance. Continuing medical education credits may be offered for, clinical research professionals, oncology nurses, and pharmacists, when appropriate.

5.1 Group meetings

Group meetings are held on a biannual basis in the Spring (May) and the Fall (November). Both meetings are open to all Alliance members. Most disease, modality, discipline, and administrative committees meet during the three- or four- day meeting. The disease, modality, and discipline meetings are open to all attendees. Disease, modality, and discipline chairs have the option to have a closed session for their committee members in addition to the open session. This request must be communicated to the meetings manager before a meeting schedule is published. All administrative committee meetings are closed sessions and only open to committee members or invited guests. In addition, several committees may sponsor workshops and educational forums as time and space allows. The group chair sets the agenda for the plenary session.

Outside speakers may be invited to address committees, but are subject to approval by the group chair. Funding may not be available and should be verified with the Operations Center prior to committing financial support for travel and honoraria.

Alliance members receive information regarding group meetings in newsletters and on the Alliance website (http://www.allianceforclinicaltrialsinoncology.org). The travel policies and reimbursement forms are included on the member's side of the Alliance website under the 'Member Services' tab and the heading 'Meetings'.

5.1.1 Attendance

All members who plan to attend a group meeting should complete an online registration form. A registration fee is required for non-member attendees. Attendance records will be maintained at the Operations Center.

Attendees are welcome to go to any open session at the meeting. Attendance at closed sessions is only open to committee members or with approval from the committee chair.

5.1.2 Travel funding for group meetings

Travel funding for attendees is based on the committee rosters. A subset of committee members is selected by the committee chairs to receive funded travel spots and necessary staff are also funded to attend. Travel expenses for all other meeting participants are the responsibility of the participant or their institution. Non-members that have full/partial registration fee covered by the Alliance (e.g., guest speakers, other select attendees) will be given a code for use in the online registration.

5.1.3 Study accrual reports and publications

Reports summarizing the progress of active studies are generated by the Alliance Statistics and Data Center and distributed at the group meeting (at least annually). The summary also includes a listing of published manuscripts and abstracts. The primary purpose of these reports is to inform Alliance meeting attendees as well as the National Cancer Institute of the current status of Alliance research.

5.2 Identification of funded travelers and expense reports

All committee members on a roster are eligible to be funded to attend group meetings. It will be the responsibility of the committee chairs to identify a subset of their committee roster to be funded for group meetings.

5.2.1 Committee member funding and roster updates

Committee chairs must complete and update the "Committee Funding Application sent by the Meetings Manager of the Operations Center, at least three months prior to each meeting. The application link includes the current committee roster as well as past funding and attendance information, where applicable. Committee chairs must submit, via the Committee Funding App link, all roster updates as well as all selections for funded travelers. Committee chairs with supplemental funding from the Alliance for Clinical Trials in Oncology Foundation should submit the names of travelers utilizing these funds at the same time.

If the Committee Funding Application is not updated and received by the deadline, the list of funded travelers will default to the last funded list for that committee. There will be no exceptions or changes after this date.

5.2.2 Travel funding notification

Travelers who are funded by the Alliance or Alliance for Clinical Trials in Oncology Foundation will be notified via invitation email. The invitation email will include information on arranging travel, travel policy, and reimbursement of allowable expenses.

5.2.3 Expense reports

Funded travelers must submit for reimbursement of out of pocket expenses to the Alliance within 180 days of travel. All expenses must comply with the Alliance travel policy. Expenses that do not comply with policy cannot be reimbursed and will be removed from the expense report or adjusted as needed to comply. Given the volume of expense reports, it is not always possible to notify the traveler when this occurs. The attendee will be contacted if the expense report is not completed correctly or if receipts are missing or inadequate.

5.3 Continuing Education (CE) Credit

The Alliance for Clinical Trials in Oncology offers a variety of Continuing Education (CE) credit opportunities. Through sessions occurring at the Alliance's semi-annual Group Meetings, members can receive Society of Clinical Research Associates (SOCRA) and/or Ohio Nurses Association (ONA) Nursing CE credit. Sessions eligible for SOCRA credits may also be eligible for CE credits from the Association of Clinical Research Professionals (ACRP). As a research based organization, the Alliance prioritizes these CE opportunities for the membership and values members' need to develop increased skillsets to further aid in clinical research.

5.3.1 Continuing Education (CE) Requirements

Members interested in receiving CE credits must fill out the registration application, register for their desired sessions, and indicate credit requests prior to the Group Meeting.

CE credits are tracked through the Group Meeting registration system. CE credits and certificates may not be issued if sessions are not designated at the time of registration.

For sessions to count for CE credits members must ensure timely attendance at these sessions. It is the responsibility of the individual member to ensure that attendance is recorded at each session for CE credit.

In order to receive both SOCRA and Nursing credit, an additional required post Group Meeting feedback survey, must be completed within 15 days of the survey's release.

It is the responsibility of individuals interested in acquiring CE credit to complete all required materials. within the allotted timeframe.

5.3.2 Continuing Education (CE) Credit Certificates

Once all the requirements for CE credits are completed, the Alliance provides members with a completion certificate stating the amount of hours/credits individuals have received.

All credit certificates will be sent out after the 15 day deadline and only once participants have completed the required survey.

While the Alliance will provide a certificate citing an individual's total CE hours/credits, it is the responsibility of the member to keep track of Certificate, individual hours/credits and the submission process necessary for each desired CE program.

6 Study protocol

This section of the Policies and Procedures describes Alliance clinical trial characteristics and conduct, including definitions of study types, study team roles, development of a study protocol, and policies relating to study conduct.

6.1 Study types

Each Alliance study is characterized either as a "treatment" study or as a "non-treatment" study.

6.1.1 Treatment studies

Treatment refers to therapy for diagnosed cancer including chemotherapy, surgery, radiotherapy, or other therapy, including adjuvant therapy, as long as it is directed against the cancer.

6.1.2 Non-treatment studies

All other studies are classified as non-treatment, even those for which there is therapy for some secondary condition. Non-treatment studies can stand alone or can be a substudy in treatment studies. Non-treatment studies also include observational studies, symptom intervention or behavioral intervention studies originating from Cancer Control Program (CCP) committees (Prevention, Symptom Intervention, Health Disparities, Health Outcomes, Cancer in the Older Adult and Cancer Care Delivery Research). The primary endpoint in these studies is not cancer treatment.

6.1.2.1 Companion and Substudies

A companion study is conducted in conjunction with one or more treatment or other intervention studies. Companion studies may investigate pharmacology, tumor biology, quality of life, symptom management, economic outcomes, or other areas of interest to the group.

A substudy is typically embedded within another study to reduce administrative and IRB work for participating institutions, decrease the number of consent forms a trial participant must sign, or facilitate translational research. In order to receive a substudy number, the study component should be an objective (or more than one objective) of the main trial, as listed in the protocol document. Substudies with study numbers do not necessarily have to be published at the same time as the parent study, and may be

published as a distinct manuscript. The component should also have a separate study chair who is not the parent study chair listed on the protocol cover page.

6.2 Study participation

Unless otherwise indicated, Alliance studies are open to all members of the Alliance and the NCTN. In accordance with U.S. Department of Health and Human Services (HHS) policy, member institutions must receive CIRB approval prior to registering trial participants on an Alliance study. Some studies may require limited access or establish individual credentialing requirements (see section 7).

6.2.1 Limited access studies

Limited access studies restrict trial participant registration to a specific list of institutions indicated on the protocol cover page. Affiliates or networked institutions may not participate unless specifically stated on the protocol cover page. Main member institution participation does not guarantee affiliate institution participation. An affiliate institution may participate, if listed on the protocol cover page, regardless of whether its corresponding main member institution also participates. The study chair, in consultation with the committee chair, determines the list of limited access institutions.

As per NCI requirements, limited access studies may not include members outside of the Lead Participating Organization. Permission for the addition of institutions outside of the Lead Participating Organization to limited access studies must be obtained from the NCI.

6.2.2 Credentialing

Studies may require credentialing, an authorization before investigators and/or institutions can participate. Credentialing is often conducted at the level of an individual investigator, e.g., a surgeon is credentialed to perform a particular surgical procedure. Institutions may also need to be authorized to participate in a particular study, e.g., an approved transplant institution. Authorizations may be study-specific, and may require fulfillment of additional regulatory requirements. Requirements for credentialing and/or authorization are included within the protocol document.

6.2.3 Non-Alliance members

Members of other network groups may participate in Alliance studies via the CTSU and the Oncology Patient Enrollment Network (OPEN). Requirements for submission of study data and materials are the same as for Alliance members.

6.3 Study team roles and responsibilities

6.3.1 Study chair

The study chair is responsible for proposing the research idea to, and obtaining approval from, the sponsoring committee chair. The study chair works with the committee chair, committee statisticians, appropriate committee members, committee liaisons, and other study team members to refine the concept and, upon review by the Alliance Study Concept Review Committee (SCRC) and approval by the Cancer Therapy Evaluation Program (CTEP) or the Division of Cancer Prevention (DCP), to develop the trial. Trial development includes writing and revising sections of the protocol, participating in conference calls with the study team and CTEP or DCP, and working with statisticians and the data management staff to define the required data elements that must be captured on the case report forms.

The study chair is responsible to address requests for clarification of protocol details and site questions regarding management of patients on the trial (for example, questions pertaining to eligibility, treatment and follow-up), participates in the development of trial amendments, and, timely review of eligibility reviews and case evaluation (see Section 8). For phase 1 trials, the study chair is required to convene regularly scheduled conference calls with the primary statistician, representatives from each participating institution, and other staff as appropriate to evaluate toxicities encountered and to make decisions concerning dose escalation, modification of cohort size, etc.

Upon completion of the primary endpoint, and in conjunction with the primary statistician, the study chair is responsible for ensuring that the results of the study are published or reported to the scientific community in a timely manner.

6.3.1.1 Moving study chair to a non-Alliance institution

If the study chair moves to a non-Alliance institution, the committee chair appoints an Alliance-based study co-chair, if one has not already been named for the study. This study chair may continue to serve in the full capacity as study chair with the agreement of the appropriate committee chair and if no conflicts of interest have arisen because of the move of the study chair. With approval of the Group Chair (or designee) the Study Chair may become a special member of the Alliance.

If the Study Chair moves to industry they will need to be replaced, however the Study Chair may retain authorship rights according to the publication policy.

6.3.1.2 Replacing study chair

Study chairs will have their performance carefully evaluated and will be replaced if performance is not satisfactory. If a study chair is forced to relinquish responsibility for a study, the group chair (or designee) and committee chair will appoint a new study chair and re-assign authorship responsibility.

6.3.2 Study co-chair

It is expected that study co-chairs contribute in a meaningful way to the study conduct, for example, by answering questions from institutions related to their role on the study. Study co-chairs are responsible for the section of the protocol specific to their modality or discipline, such as surgery, imaging, radiation, community involvement, etc. Identification as a study co-chair on the protocol face page does not assume authorship.

At least one member of the study leadership team in the role of chair or co-chair shall be a community oncologist (see section 13 of Alliance Bylaws).

6.3.2.1 Moving study co-chair to a non-Alliance institution

If the study co-chair moves to a non-Alliance institution, the study co-chair may continue to serve as study co-chair with the agreement of the appropriate committee chair and if no conflicts of interest have arisen because of the move of the study co-chair.

6.3.2.2 Replacing study co-chair

Study co-chairs will have their performance carefully evaluated and will be replaced if performance is not satisfactory. If a study co-chair is forced to relinquish responsibility for a study, the group chair (or designee) and committee chair will appoint a new study co-chair and re-assign authorship responsibility.

6.3.3 Committee chair

The committee chair is responsible for the scientific portfolio and priorities of his/her committee, including protocol development, conduct and analysis

and publication of results. As delegated by the Alliance Executive Committee, the committee chair approves concepts for further development and may select or assign study chairs or co-chairs. The committee chair is responsible for submitting study concepts that emerge from his/her committee to the SCRC. For more information see section 4.

6.3.4 Primary statistician

6.3.4.1 Primary statistician

The primary statistician has primary responsibility for all statistical aspects of the protocol, including description of the study design, calculation of the sample size necessary to meet the primary objective of the study, and description of the interim and final analyses that will be used to investigate the primary and secondary hypotheses of the study. The primary statistician oversees the development of case report forms and the forms schedule.

For studies monitored by the Data and Safety Monitoring Board (DSMB), the primary statistician is responsible for preparing the monitoring reports presented to the DSMB (see section 16). After the study is released from the DSMB, the primary statistician collaborates with the study chair to prepare the presentation of the results at scientific conferences and preparation of manuscripts. For non-DSMB monitored studies, the primary statistician performs the analysis after the primary endpoint data maturity (for example, after the required numbers of events have been entered in the database for a time to event endpoint; after all evaluable patients per protocol have data entered for the pre-specified time period for a binary endpoint) and collaborates with the study chair to prepare the presentation of the results at scientific conferences and preparation of manuscripts.

6.3.4.2 Secondary statistician

The secondary statistician assists the primary statistician in the design, conduct and monitoring of the trial. During the development of the protocol, the secondary statistician works in collaboration with data management staff, the primary statistician, and the study chair to review the protocol, develop case report forms, and assist with database testing.

6.3.5 Data managers

Data managers review protocols and case report forms, perform eligibility evaluations and facilitate case evaluations. The data managers are responsible for the data management of assigned protocols, working closely with the study chair and statistical team to identify data discrepancies requiring queries in Rave.

The data manager fields questions from sites about data submission and follow-up schedules. They also participate in database testing, review protocol updates and clarify data submission sections as needed.

6.3.6 Protocol coordinator

Protocol development occurs under the direction of the protocol coordinator. Protocol coordinators will establish timelines for protocol development, and work with study team members to draft, review and revise the protocol. They serve as the liaison for all protocol related correspondence with CTEP, DCP and CIRB, and are responsible for communicating official CTEP, DCP or CIRB communications to study team members.

Following study activation, the protocol coordinator fields questions from sites, coordinates answers from study team members to sites, and works with members of the study team or other functional areas to address study issues. The protocol coordinator is responsible for managing any protocol amendments, working with members of the study team or other functional areas as appropriate.

6.3.7 Executive officer

The executive officer monitors protocol development and assists the protocol coordinator with issues requiring physician input, for example reviewing SCRC meeting minutes or evaluating the appropriateness of eligibility criteria or dose modifications. The executive officer assists with reviews of serious adverse events (SAEs) and CTEP Adverse Event Reporting System (CTEP-AERS) reports, provides guidance on study-specific emergency actions, reviews correspondence with NCI, and responds to queries when the study chair is unavailable. The executive officer also participates in logistical activities of protocol development, for example assessing study budget needs or study feasibility. Additionally, the executive officer assists in the coordination of industry interactions.

6.4 Protocol development

6.4.1 Protocol numbering

A concept submitted for review by the Study Concept Review Committee (SCRC) or the Translational Research Program (TRP) Executive Committee, or concepts containing data-only requests, has a study number assigned by the Alliance database (table 6-1). The study number will be assigned prior to concept review.

The first character of the study number is an A, followed by two digits that indicate the committee associated with the protocol. The next two digits indicate the year the concept was introduced. The final two digits are assigned consecutively for that committee as concepts are submitted to the SCRC. For example, the Breast Committee is A01, so A012204 would refer to the fourth breast cancer concept submitted in 2022.

Table 6-1. Alliance protocol numbering system

Alliance Committee	**Committee Number**	**Sample Study Number**
Breast	A01	A011101
Gastrointestinal	A02	A021101
Genitourinary	A03	A031101
Leukemia	A04	A041101
Lymphoma	A05	A051101
Myeloma	A06	A061101
Neuro-Oncology	A07	A071101
Respiratory	A08	A081101
Alliance Scientific Discipline Committee	**Committee Number**	**Sample Standalone Study Number**
Experimental Therapeutics	A09	A091101
Imaging	A10	A101101
Leukemia Correlative Sciences	A11	A111101
Pathology	A12	A121101
Pharmacogenomics and Population Pharmacology	A13	A131101
Radiation Oncology	A14	A141101
Solid Tumor Correlative Sciences	A15	A151101
Transplant	A16	A161101
Alliance Cancer Control Program	**Committee Number**	**Sample Standalone Study Number**
Cancer in the Elderly	A17	A171101
Health Disparities	A19	A191101
Health Outcomes	A20	A201101
Prevention	A21	A211101
Symptom Intervention	A22	A221101
Cancer Care Delivery Research	A23	A231101

To more easily connect any embedded substudy with a treatment study, a two-letter and number extension is added (table 6-2). For example, "A021101-ST1" is a solid tumor correlative sciences embedded substudy study that appears in study A021101. If more than one type of embedded substudy is included in the treatment or intervention study for the same type of substudy, then sequential numbers are assigned (e.g., A021101-ST2, A021101-ST3, etc.).

Table 6-2. Alliance protocol numbering system - embedded studies

Committee	Embedded Study Suffix	Sample Study Number
Cancer in the Elderly	EL	A021101-EL1
Comparative Effectiveness Research *	ER *	A021101-ER1 *
Health Disparities	HD	A021101-HD1
Health Outcomes	HO	A021101-HO1
Prevention	PR	A021101-PR1
Symptom Intervention	SI	A021101-SI1
Imaging	IM	A021101-IM1
Leukemia Correlative Sciences	LC	A041101-LC1
Pathology	PA	A021101-PA1
Pharmacogenomics and Population Pharmacology	PP	A041101-PP1
Solid Tumor Correlative Sciences	ST	A021101-ST1
Cancer Care Delivery Research	CD	A021101-CD1

* not in use

6.4.2 Concept

6.4.2.1 Concepts other than translational research and data-only requests

Concepts are discussed at Alliance disease/modality/discipline committee meetings. If the concept includes various committee components, each relevant committee must approve the concept before it can be submitted for review.

The Alliance requires treatment studies to be submitted to the SCRC on an appropriate NCI/CTEP Letter of Intent (LOI) or Concept submission form. Cancer control studies (e.g., non-treatment studies) do not have an NCI-specific concept submission form, and are to be submitted to the Alliance SCRC in the same format as required for concept submission to NCI DCP. If applicable, concept submission should occur after NCI Task Force review. An Alliance Conflict of Interest Form (completed by the study chair online) and an Alliance Concept Submission Form must accompany the concept submission to the SCRC. Details

concerning the proposed funding must be included with the concept submission.

The committee chair must submit concepts to the SCRC. If the concept is submitted by a designate, the committee chair must indicate his/her approval of the concept in writing.

Concepts submitted by investigators external to the Alliance will be reviewed by the SCRC.

6.4.2.2 Concepts containing data-only requests

Studies that only require data that are already available in the Alliance Statistics and Data Management Center (SDMC) (data-only studies), and are not part of the original objectives of the parent Alliance study, will be considered for approval once the primary study analyses are published. If the proposed study requires data from a trial that is under active monitoring by the DSMB, the DSMB must review and approve the release of the data (see section 16).

The proposed data-only study may include data generated by a correlative study. Requests for use of biospecimens are covered by a separate review procedure, as noted in the translational research section (Chapter 11).

Requests for a data set fall under the Data Sharing policies (see sections 6.11 and 15).

6.4.3 Developing the protocol

6.4.3.1 Communications post-SCRC and NCI concept approval

Upon approval by the appropriate concept review body Alliance SCRC, all subsequent communications with NCI CTEP must occur through members of the Central Protocol Operations Program (CPOP). CPOP submits the approved NCI LOI or Concept Submission Form to CTEP for approval. The Alliance Cancer Control Program Manager submits concepts to DCP for approval.

Once CTEP or DCP approves the concept, the study team may begin developing the protocol. The protocol coordinator maintains the official, master version of the protocol document. Upon DCP

concept approval, all subsequent communications with NCI DCP must occur through CPOP.

6.4.3.2 Protocol authoring

Following concept approval by the SCRC, and then CTEP or DCP, the protocol coordinator seeds the Alliance Model Protocol template with information from the NCI approved concept/LOI. The study chair, study co-chair(s) and primary statistician(s) are responsible for authoring the first full draft of the protocol. The protocol coordinator edits the draft to Alliance standards and circulates it for initial review by the study chair, study co-chair(s), committee chair and vice chair, statisticians, reg office, the responsible executive officer, and the director of translational research.

Based on the comments received, a revised draft is constructed by the protocol coordinator and the study chair. This draft is then circulated for expanded review to the above reviewers, plus the following additional internal reviewers: director of protocol operations, group chair, , and other members of data operations as appropriate. External reviewers include liaisons from Pharmacy, CRP, Oncology Nursing, and Patient Advocates Committees, as well as representatives from IROC, and specimen repositories, as appropriate.

After internal reviews are completed, the protocol is submitted by the protocol coordinator to CTEP, DCP or other appropriate review agency. The Alliance will adhere to all NCI-mandated protocol development timelines.

6.4.3.3 Determining the trial participant eligibility criteria

In general, there should be as few eligibility requirements as possible, with the requirements only excluding those for whom the study is clearly inappropriate.

Alliance studies typically require trial participants to be at least 18 years old. In certain diseases, younger patient populations may be considered.

6.4.3.4 Inclusion of women and minorities

It is the policy of the National Institutes of Health (NIH) that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that explains why inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. The inclusion of women and minorities in Alliance protocols is a standard item of DCP and CTEP review. All protocols submitted to NCI include appropriate sections on women and minorities. The FDA issued guidance in 2022 on ensuring clinical trial diversity which will be required to be addressed in trials subject to review by the administration. The study team may include a Health Disparities Co-chair to provide input on recruiting minority participants to Alliance protocols.

6.4.3.5 Determining the trial participant follow-up period

Each protocol must explicitly state the required follow-up time, and the maximum time period for which data are required for each trial participant. The requirement is based on study objectives and statistical design considerations, including those of substudy studies. Disease committees may also specify disease-specific rules.

6.4.3.6 External protocol review

When ready, protocols are submitted to CTEP or DCP for review. Phase III, phase II, and select Phase I and select cancer control trials are also reviewed by an NCI Central Institutional Review Board (CIRB). Changes mandated by the NCI, CIRB or FDA do not need to be reviewed by the SCRC. In other cases, significant changes to the protocol, e.g., change in trial design or a significant change to sample size, must be re-reviewed by the SCRC.

Once all necessary external and internal approvals have been secured, the protocol is activated, generally in the next scheduled protocol posting.

6.4.4 Developing case report forms

The following policy describes the process of assembling the forms necessary to collect the scientific data required to meet the protocol objectives. The

policy covers scientific and supplemental data form development and revision. **Note: When the term "form" is used in this section, it refers to the data collection form and the form instructions, whether paper or electronic.** Scientific forms are defined as those forms that are used for study data collection. Supplemental forms are those forms providing reference information necessary for completion of scientific forms.

6.4.4.1 Determining data to be collected

Decisions about the amount and type of data collected are made jointly by the study chair, committee chair, primary statistician, and executive officer, if one is assigned to the study. As a general principle, Alliance studies attempt to collect the minimum amount of data required to meet the scientific objectives of the study.

6.4.4.2 Making use of standard Alliance forms

The Alliance Global Library of supplemental forms should be used for all studies. Whenever possible, the study chair and primary statistician should agree to make use of the Alliance's existing scientific forms.

6.4.4.3 Using Translated Patient-Reported Questionnaires

The most commonly used patient-reported questionnaires for Alliance protocols will be made available in the North American primary languages, i.e., English, and Spanish, if translated validated versions are already available. In studies with CCTG participation, the questionnaire will also need to be available in French. Questionnaires in additional languages may be made available if the instruments are available in those languages, etc. Mandarin, Russian, Korean, etc. If. If a translated questionnaire is not readily available, then the study chair must decide whether to: 1) pursue formal translation of the questionnaire working with the CCP Program Manager. Based on available funds, the costs of translation will be covered by the NCORP or NCTN grants. Ad hoc translation of patient reported questionnaires is not permissible**.**

The Alliance preference is to design all Alliance studies to allow accrual of patients with other non-English primary languages, at a minimum, Spanish.

However, if a formal translation is requested, the investigator or protocol coordinator must send an email request to the CCP Program Manager. The CCP Program Manager will work with Alliance grant administration personnel to ensure that there is adequate funding to cover the translation costs, and route requests to the external translation vendor as needed.

6.4.4.4 Using copyrighted forms

Any use of copyrighted forms should be coordinated through the Alliance. Copyright requests are made by the CCP program manager working with the Alliance contracts team which is responsible for reviewing and routing any licensing agreements for signatures. A copyrighted form is used as-is within the Alliance form shell. NO MODIFICATIONS MAY BE MADE TO THE FORM BY ANY ALLIANCE PARTICIPANTS. Only the copyright holder may make changes.

When the use of a copyrighted form requires a fee which cannot be waived, and there is no specific grant funding the use of the copyrighted form, approval to disburse any Alliance funds must be granted by the group chair or the principal investigator for the Cancer Control Program as appropriate.

6.4.4.5 Forms design

All Alliance forms contain basic identifying features and adhere to a common format. Appropriate IT staff ensure adherence to standard Alliance case report form formats.

6.4.4.6 Forms review and approval

All forms and instructions go through two review stages (initial and final review) before they can be used in a study or for administrative purposes.

The following individuals provide the final review of forms:

- Study Chair
- Statistician(s) and Statistical Programmer
- Data Manager
- Clinical Research Professional
- Protocol coordinator and executive officer (as applicable) (for information only)

- Modality/discipline co-chairs, as applicable

The Study Chair and primary statistician provide final approval of all forms. Other approvals may be obtained as deemed necessary by the development team. Upon receipt of all final approvals, further changes may not be made unless required by NCI review. The Alliance will not activate a study until all form approvals have been received.

6.4.4.7 Forms revision

When a form requires changes after study activation, the study developer will revise the form following either an expedited change pathway in the case of urgently needed changes or the bundled changes pathway. Changes will be bundled if the change request is not related to patient safety or primary endpoint analysis. Bundled changes will be pushed to production per a regular schedule.

All forms for most Alliance studies are available on the CTSU website.

6.4.5 Participation in studies led by other Lead Protocol Organizations

With few exceptions, all studies are to be available to all members of the NCTN. Exceptions may include certain DCP sponsored studies, pilot studies funded by Alliance or other grant mechanisms, and selected phase I or early phase II studies. CCDR studies are limited to NCORP sites only. Studies may have co-chairs from other groups who were involved in the study design added to the protocol. These individuals should be included in protocol development when possible and must be adequately informed about progress and problems with the protocols for which they are responsible. Substantive amendments, e.g., those changing the study design or requiring a significant change in sample size, should be discussed with representatives of the other groups.

6.5 Activating a study

After receiving final protocol approval from CTEP or DCP, the Alliance Protocol Office activates the study, in coordination with Alliance IT, registration, and data management staff. A notice indicating that a study is officially open for accrual is issued by the responsible protocol coordinator in the protocol posting on the CTSU website.

6.6 Waivers

6.6.1 Eligibility waivers

No eligibility waivers will be granted.

6.6.2 Other waivers

The Alliance adheres to CTEP's policy not to issue or approve any waivers for protocol deviations, including eligibility criteria, treatment schedules, dose modifications, toxicity assessment, response criteria, and statistical aspects.

6.7 Updating a study

6.7.1 Revisions and amendments

Protocol updates containing revisions and amendments may be generated in response to decisions by the study chair to change some aspect of the study design or conduct. All amendments that are not merely editorial in nature will be reviewed by the following: study chair, executive officer (if applicable), committee chair (if applicable), and primary statistician, the executive officer in charge of drug distribution (if applicable), the, director of translational research operations, and data management personnel.

Updates may also be generated in response to information or requests from external agencies, such as safety letters or action letters distributed by CTEP.

For any studies monitored by the DSMB, approval of substantive updates by the DSMB is required prior to submission to NCI. If the update includes changes in the trial design, these changes must first be discussed with NCI before submission to the DSMB, unless the DSMB has requested the change in trial design based on safety or outcome data available only to the DSMB. Major statistical redesign on Phase III trials requires an independent statistician involvement, assigned by the Alliance Group Statistician as outlined in the NCI policy.

6.8 Suspending a study

A suspension is a temporary cessation of accrual to a protocol, either planned or unplanned. Suspension may also result in a temporary cessation or modification of treatment of patients already registered to a study. An unplanned decision to suspend a study may be made by the study team based upon the recommendation of the NCI CTEP/DCP or industry partner, study chair, the primary statistician, relevant committee chair(s), or the DSMB.

6.9 Unblinding trial participants

The Alliance conducts clinical trials that mask, or blind, the identity of treatments given to trial participants and, sometimes, investigators. The DSMB, CTEP, or DCP may recommend that study accrual be stopped and treatment assignments be unblinded for all trial participants because of toxicity or safety concerns.

There are three scenarios, described below, where treatment assignments may be unblinded for individual trial participants.

Intentional unblinding of a treatment assignment, other than by the methods described below, is a serious breach of scientific ethics. The Alliance policies concerning scientific misconduct will be employed to investigate and report such incidents (see section 3.4).

6.9.1 Emergency unblinding

A trial participant's treatment assignment can be unblinded in emergent situations with approval of the appropriate Alliance executive officer (or designee) only if unblinding would influence management of the situation, e.g., if a child has swallowed a vial of pills. Study chairs, primary statisticians, and other Alliance staff are not permitted to approve emergency unblinding requests. Emergency unblinding requests should be directed to the executive officer on call, 24 hours a day, 365 days a year. If an Alliance executive officer determines unblinding is warranted, they can access the treatment assignment through the Alliance Registration Application. The executive officers and the Group Chair are the only personnel who can authorize the unblinding of a study patient.

6.9.2 Protocol Specific unblinding

The protocol may specify that a trial participant's treatment assignment can or should be unblinded based on certain criteria as specified in the protocol, such as for the purpose of crossover from placebo to active drug at disease progression. Protocol-specified unblinding may be performed by the Registration Office during regular business hours, with confirmation from the data manager that the protocol-specified criteria have been reached. No executive officer approval is required.

6.9.3 Elective unblinding

If allowed per-protocol, a trial participant, family member, or treating physician may request unblinding of the treatment assignment in non-emergent situations in order to inform subsequent disease management

decisions. Elective unblinding is only permitted if the trial participant has met the trial's primary endpoint. Elective unblinding will be performed by the Registration Office during regular business hours, with confirmation from the data manager that the appropriate criteria have been met. If the patient has not met the primary endpoint, or if the appropriate criteria have not been met, the Registration Office will refer the requestor to the appropriate executive officer for discussion. The protocol and Model Consent Form must specify whether elective unblinding will be permitted and, if permitted, that requestors should contact the Registration Office.

6.9.4 Unblinding for Regulatory Reporting

Regulatory unblinding is performed in accordance with non-North American regulations and does not involve provision of treatment assignment to investigators or patients. The protocol must specify whether regulatory unblinding will be permitted. If permitted, then requests will be made from the Alliance Pharmacovigilance team to the Registration Office. No executive officer approval is required.

6.10 Closing a study

Closing a study means that accrual to the study is permanently stopped. It is possible to close only a portion of a study.

6.10.1 Procedures for closing a study

The decision to close a study is made by the primary statistician, in consultation with the study chair and committee chair (and the DSMB for DSMB monitored studies). If unexpected adverse events occur, members of the study team may initiate the process. For DSMB monitored studies, the DSMB may recommend early closure of a study for reasons of patient safety or of differential treatment effectiveness, or slow accrual concerns.

For routine study closures, in order to allow sites to register patients who are already in the process of being worked up for the study, the Alliance routinely sets a future closing date, usually two weeks, once adequate accrual has been achieved. This may result in modest over-accrual to the study. Exceptions to this policy are phase 1 studies, for which over-accrual is not allowed, and certain phase 2 studies. These studies require tighter control of the number of patients registered and treated. More rapid study closures may be necessary for patient safety reasons.

6.10.2 Notifying patients about early closure of clinical trials

Disclosure to individual participants of study results often follows a recommendation that accrual be terminated early and/or that protocol specified treatment be discontinued or significantly modified. However, disclosure must not violate any state or federal laws regarding breaking the code on anonymized data.

The trial participant who provided the original consent to participate in the research is informed of the results of the clinical trial by his/her treating physician or designee. Participants are informed in a manner that will ensure that they receive the results with a minimum of disruption to the patient-physician relationship.

6.11 Release of data

6.11.1 Studies monitored by the DSMB

If a trial is being monitored by the DSMB (see section 16), requests for release of data to the study team must be submitted to the DSMB (see Section 16.1). If the request is approved, the data can be released to the study team and can only be used within the scope specified by the DSMB in their approval, see section 16.2.6.

For double blind trials, all data summaries and individual level listings while the trial is ongoing including requests for baseline, and adverse event data must adhere to the NCI policy for reporting for blinded studies.

6.11.2 Studies not monitored by the DSMB

For studies not monitored by the DSMB, see section 16.3 for monitoring and requests for data release. All approved requests for data release can only be shared with the individuals specified in the request, can only be used for the purpose stated in the request, and must be kept confidential.

6.11.2.1 Appeal process

If the request for early access to the study data or any information from an ongoing trial (open or closed to accrual and endpoint data is still maturing) is denied by the Alliance Group Statistician, the study team can appeal to the Director of Central Protocol Operations.

6.12 Completing a study

A study is declared completed by the study chair, the primary statistician and the relevant committee chair(s). Ordinarily, this occurs when the study has met all of its objectives, a definitive analysis has been performed, and an article has been published. Rarely, a study may be declared completed when the study chair and statistician agree that no analysis or publication of the study will be done. This latter category is considered "completed-administratively."

The classification of a study as "completed" has operational consequences, indicated below.

All requests for study summary reports or analyses should go to the study statistician.

6.12.1 Archiving paper records

CALGB, ACOSOG & NCCTG Legacy studies – As applicable, paper files of patient data are stored electronically at the Alliance SDMC in a document imaging system. Upon receipt of records they are scanned and stored electronically. The system is web-based and records can be viewed once authorization access has been approved. The stored electronic data are available for audit by requesting them from the Director of Data Management.

6.12.2 Archiving study database

The data for a completed study remains in the Alliance warehouse.

The Alliance SDMC maintains a warehouse of data used in monitoring reports, interim analyses and manuscripts.

The data sets used in monitoring reports, interim analyses and manuscripts are stored as SAS data sets or ASCII files with attached data dictionary. The statistician who prepares the reports or analyses is responsible for copying the necessary data files. The statistician uses naming conventions to index the data files by the study number, the type of report and the date the report was prepared. All data sets are archived on a designated archive server. At the discretion of the statistician, additional files may also be archived.

6.12.3 Access to data for completed studies

Statistical personnel are the only Alliance members who have access to study data, see Section 15 for data share requests.

6.13 Terminating a study

Studies may have all follow-up terminated for all trial participants either because all trial participants have been followed for the protocol-specified period or because it is decided that no further follow-up is needed. Upon termination, no further follow-up data, including new queries, are collected from participating sites. All studies are reviewed annually by the primary statisticians to determine if continued follow-up is required. A list of all studies with terminated follow-up is publicized on the Alliance website.

Study team members wishing to extend patient follow-up beyond the protocol-specified interval must obtain permission from the group statistician. A protocol amendment must also be generated.

6.14 Study Termination with the IRB of Record

In general a study termination occurs when a study is permanently closed to accrual, all participants have completed study intervention including follow-up and the primary study endpoint has been achieved. The Alliance will also stop collecting data at this point. A study may also be terminated by the Alliance due to poor accrual, study agent(s) no longer available, safety issues or futility based on an interim analysis.

The Alliance discourages site termination or permanent closure prior to the issuance of the official study termination memorandum. This is necessary to maintain the study's overall research objectives, data integrity and/or the need for the Alliance or regulatory authority to query a site for additional data.

If the Alliance has not issued the official study termination memorandum, the following criteria must be met prior to requesting a local termination of a study:

1. All patients at the institution have completed study related treatment and follow-up per the protocol, all study data has been collected and submitted, and the site has no outstanding data or queries.

   Or

2. All study patients at the institutions have died or been withdraw, and the site has no outstanding data or queries.

   Or

3. The institution did not consent, screen or enroll any patients.

Documentation confirming the site has no outstanding data or queries must be provided.

Sites must contact Alliance Regulatory staff to be given approval to terminate a study in the absence of a central study termination notice from the Alliance. The permission granted by Alliance regulatory staff must be documented by the site. An audit deficiency may be assigned at audit time for local study termination without prior Alliance approval.

There may be other scenarios where a study may be considered for termination. These site study terminations will be determined on a case-by-case basis.

6.15 Retrospective data collection from closed or completed studies

Generally, proposals that require the collection of additional material from Alliance sites will not be approved. Retrospective collection of data is expensive and time-consuming. These requests usually require IRB review at each participating site and may require obtaining additional patient consent and/or authorization. The Alliance may consider such requests in special circumstances provided adequate funding is available for both the Alliance Statistics and Data Center effort and for participating institutions. Studies that require the collection of additional material will be reviewed by the Alliance Program Operations Committee.

7 Patient registration

All Alliance institutions are allowed to register patients to Alliance and other trials, unless otherwise indicated (i.e., limited access studies), posted on the Cancer Trials Support Unit (CTSU) menu.

7.1 Authorization of institutions to register patients

Institutions intending to register patients must have IRB approval for the study. IRB approval documentation must be submitted to CTSU for entry into Regulatory Support System (RSS), prior to enrollment of the first patient. Submission instructions are available on the Regulatory page of the CTSU website.

Compassionate (expedited, emergency) approval, in which an institution wants immediate approval to put a patient on a treatment study not yet approved by its IRB, is not allowed. The IRB must give full-board approval before patients may be registered on a treatment study. Select non-treatment studies, such as laboratory or survey studies that present minimal risk to participants, may qualify for expedited review, which is noted at the time of protocol activation.

7.1.1 Limited access studies

Some studies may limit access to a subset of institutions, for quality assurance or other reasons (e.g., phase 1 studies). Participating sites in limited access studies will be identified in CTSU RSS.

7.2 Authorization of site personnel to register patients

All Alliance studies will use the Oncology Patient Enrollment Network (OPEN) online registration system (https://open.ctsu.org) maintained by the CTSU except where otherwise indicated in the protocol. Site personnel who register patients on NCTN trials must be registered with the Cancer Therapy Evaluation Program (CTEP) via the NCI Registration and Credential Repository (RCR) and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (username and password) used to access the member portion of the CTSU website (https://www.ctsu.org). Refer to the CTEP website for additional details on registration types and required documentation.

To perform patient registrations (including pre-registrations), site personnel must be assigned the 'Registrar' role in the CTSU RSS, found under the 'Regulatory' tab in the member portion of the CTSU website. The principal investigator (PI) of each main member must approve all personnel authorized to register patients.

7.3 Credentialing

If a protocol requires credentialing for the registering physician (e.g., to demonstrate proficiency in performing a particular type of surgery) or the registering institution (e.g., to administer radiation therapy), then the credentialing requirements listed in the protocol must be met.

7.4 Confirming patient eligibility

The institution confirms eligibility before registration or randomization by verifying the eligibility criteria listed in the protocol. Institutions should refer to all relevant protocol sections to ensure that all conditions for appropriate entry of a patient on study are met.

Exceptions to eligibility criteria or other protocol requirements will not be granted.

Treatment should begin no later than two weeks after registration, unless otherwise specified in the protocol.

As a general rule, sites should not register a patient to more than one interventional study when it is expected that one protocol's intervention might impact the other study's endpoints (e.g., registering a patient for two studies, where both protocols' treatments are expected to have an impact upon response, overall survival, etc.), although exceptions may be allowed by the study chair in collaboration with the executive officer. The study team should carefully consider the scientific and practical implications before allowing such exceptions.

7.5 Procedures to register patients to Alliance studies

Registration to Alliance studies is available 24 hours a day via OPEN. All participating sites (Alliance and non-Alliance sites) will use OPEN to enroll patients. OPEN can be accessed from the member portion of the CTSU website.

Study-specific OPEN Enrollment Form(s) are available for each study on the CTSU website. Information required at registration includes:

- Registering institution and investigator names and CTEP ID numbers
- Patient demographic information
- Pre-study and eligibility information
- Stratification and/or grouping factors if applicable
- Sub-study participation information if applicable

The OPEN system will provide the site with a printable confirmation of registration and treatment information.

7.5.1 Pre-registration

For select studies it is necessary to obtain a patient ID for study screening and eligibility using a pre-registration procedure. Patients will be pre-registered using OPEN.

7.5.2 Multiple-Step Registration

For select studies it is necessary to verify eligibility for additional treatment or treatment changes (i.e., safety run-in, cross-over, delayed or re-randomization). Patients will be registered for each step using OPEN.

7.6 Procedure to register patients to studies led by other Lead Protocol Organizations

For registration of patients to studies led by other Lead Protocol Organizations that are available on the CTSU menu, the Alliance institution must use OPEN. The institution must indicate its network group affiliation with the Alliance to receive enrollment credit for the Alliance.

8 Data management

8.1 Data submission

8.1.1 Completing forms

8.1.1.1 Alliance general instructions: all forms (electronic CRFs)

All data forms and supporting documentation as required by the study are submitted to the Alliance Statistics and Data Management Center (SDMC) typically using Medidata Rave. Access to Rave requires that the site has IRB approval of the study and that site staff have an iMedidata Rave account and have completed eLearning for their Rave role.

Use forms specified in the study data submission schedule and available on the Alliance website (http://www.allianceforclinicaltrialsinoncology.org), CTSU web site or in Rave. Do not store electronic copies of the forms on your computer; always download the most recent copy from the Alliance website or CTSU site. Forms for studies led by other Lead Protocol Organization are distributed by the coordinating group and may be obtained from the CTSU website (https://www.ctsu.org) or Rave. If you are unable to locate the form(s), contact the responsible Lead Protocol Organization.

When uploading supporting documents (path reports, lab results, etc.), remove all patient identifiers and write the Alliance study and patient number on each page.

8.1.1.2 Instructions for forms submitted during treatment/intervention and follow-up

Many Alliance forms are study- or disease-specific, but these general instructions may be used for all forms described below.

1. Each form must be supported by documentation as specified in the protocol for the same time period. Check the data submission schedule in the forms packet for required data and source documentation. The information recorded on each form should reflect only those events occurring during the time period covered.

2. The time period covered by each form is specified in the data submission schedule. The coding convention for the covered time period is as follows:

   If the data submission schedule states that forms are required for each phase/cycle of treatment/intervention, the time period covered by the forms should be from day one of each treatment/intervention phase/cycle up until the administration of the subsequent treatment/intervention. This allows for capture of responses and adverse events attributable to the entire phase/cycle but not fully assessed until the patient returns for the next treatment/intervention phase/cycle. For Example: all labs collected prior to the start of the next treatment/intervention phase/cycle should be added to the previous phase/cycle in order to have adequate source documentation.

Adverse event forms

General instructions for all adverse event forms are as follows:

- All studies use the NCI's Common Terminology Criteria for Adverse Events (CTCAE) that is available on the the Cancer Therapy Evaluation Program (CTEP) websites (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Use only these criteria to identify events and determine grade severity. The version of the CTCAE is specified within the protocol.

- The forms used with the CTCAE are study-specific. AE forms may provide a list of solicited events for which grade must be coded for each phase/cycle. Additional fields are provided for specifying other events that occur which are required per protocol.

- Code grade "5" if the event caused the death of the patient. Code only one grade 5 event for a patient. Code contributing events that are not the primary cause of death per CTCAE grade criteria.

- Note that for some events certain grades are not defined and are not allowed (e.g., grade 5 fatigue).

Adverse Event Expedited Reporting System (CTEP-AERS)

Expedited adverse events are reported using the NCI's Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP AERs, located at https://ctepcore.nci.nih.gov/ctepaers. Guidelines for CTEP-AERS reporting are included in each protocol.

Only file one CTEP-AERS report per course/cycle. Amend the previous report for the cycle if the adverse event data needs to be corrected, the adverse events worsen, or new adverse events occur that require expedited reporting.

- Don't assume that all hospitalizations require CTEP-AERS reporting— check the protocol.
- The "Surgical Intervention" section is to be used ONLY for the protocol related surgery.

For select trials (e.g., CTEP Held IND), Rave and CTEP-AERs are integrated. For these trials, CTEP-AERs reports are initiated through Rave data entry; therefore, the AE must be entered first in Rave before completed the expedited report in CTEP-AERs. More information can be found in the protocol for applicable trials.

8.1.2 Submission of data forms

The Alliance requires capture of data per protocol for all patients on Alliance studies. Data continue to be submitted per protocol until follow-up is completed or discontinued.

8.1.2.1 General data submission instructions

Data submission requirements are specified in the protocol.

Overdue data

The current expectations for form submission before being considered delinquent are: Baseline forms: within 15 days of target date, Treatment/Intervention forms: within 30 days of target date, Follow-up Forms: within 60 days of target date.

For studies using Rave, study-specific delinquency lists are available in real time via the Rave task summary. To assist with site performance, delinquent data reports are provided by the Alliance

SDMC and are available on the Alliance website to all Alliance rostered CRPs.

Information on study level data delinquency is also available on the CTSU website through a dynamic Data Quality Portal (DQP) across all NCTN led trials (including Alliance).

8.1.2.2 Registered patients who never receive treatment/intervention

Patient eligibility and willingness to participate in the protocol must be carefully assessed prior to registration to ensure the patient's ability to comply with protocol requirements. A patient may not be removed from an Alliance protocol after being registered.

In the event a patient never receives treatment/intervention, the institution must provide the SDMC with required data and supporting documentation per protocol and document the reason why treatment/intervention was never given.

8.1.2.3 Transfer of patient to another institution

A patient on an Alliance study may transfer their study-related care to another institution. It is the responsibility of the institution transferring the patient to ensure that all transfer procedures are followed. The institution accepting the patient transfer must have IRB approval for the protocol. A transferring patient must sign a new informed consent form with the accepting institution.

Prior to the transfer, the site clinical research professional (CRP) ensures that all data are up-to-date and all queries have been addressed and resolved. This will be confirmed by the Alliance Data Manager prior to the patient being officially transferred. Copies of all data required by the protocol and subject records must be submitted to the accepting institution.

The transferring institution is responsible for all patient data submitted up to the date of transfer. After the date of transfer, the accepting institution is responsible for submitting all subsequent data required by the protocol after the informed consent is signed.

The sites should follow the CTSU guidelines for patients registered via OPEN. Site staff will use the Transfer & Update Module (T&UM) within OPEN to request Site Transfers for completed subject enrollments that are maintained in OPEN. Each

request will undergo automatic regulatory validations and require manual approval by the Alliance Registration Office staff after confirmation from the Alliance Data Manager that patient data is up-to-date in Rave.

For patients registered via one of the Alliance legacy registration systems, both the treating investigator at the transferring institution and the treating investigator at the accepting institution must complete the CTSU's patient transfer form, which can be found on the CTSU website. The completed form must be sent to the CTSU Operations Center.

For all patient transfers, the Alliance database does not reflect the transfer until the transfer request has been approved in the OPEN T&UM or the completed CTSU Patient Transfer Form has been signed by both institutional treating investigators and has been received at the Alliance SDMC. The Alliance database retains documentation of the initial accrual to the institution that registered the patient.

8.1.2.4 Refusal for further protocol treatment/intervention

A patient who refuses further protocol treatment/intervention after therapy has begun is still considered to be part of the study and followed per protocol. The institution is required to submit all data required by the protocol.

8.1.2.5 Protocol non-compliance

A patient who is non-compliant with protocol defined requirements (i.e., QOL, specimen collection) is not considered a withdrawal of consent. Protocol non-compliance should be documented in the Case Report Forms.

A patient who refuses to follow the protocol test schedule and is still willing to be followed for data collection can opt out of Clinical Follow-up. This should be documented in the Case Report Forms.

8.1.2.6 Withdrawn consent for all future protocol data collection

A patient may, on rare occasions, withdraw consent for all future protocol data collection. This patient decision needs to be documented in the patient's research record; a source document will be submitted to the SDMC as documentation of consent withdrawal for all future protocol data collection. A patient's

refusal to comply with follow-up visits or requirements is not considered to be an implied withdrawal of consent.

All required study data up to and until the date consent withdrawal declared is expected to be submitted in Rave. Data generated after the date consent withdrawal declared should not be submitted. Patients that have withdrawn consent are removed from calculations of institutional performance related to timeliness. However, the percentage of patients that have withdrawn consent is included in the metrics for institutional performance related to data quality (see section 2.10).

A study patient may rescind their consent withdrawal, contact the Data Manager. Documentation needs to be provided in same fashion as for consent withdrawal designation.

8.1.2.7 Confirmation of lost to follow-up status

Institutions may confirm that a patient is lost to follow-up using specific procedures.

Patients who refuse aspects of participation or withdraw consent from all further data collection should not be designated as lost to follow-up.

8.1.2.7.1 Procedure for confirming a patient is lost to follow-up

Unless otherwise stated in the protocol, A patient can be deemed lost to follow-up after one year **and** 3 unsuccessful documented attempts to contact the patient. The one-year period starts on the expected date of the missed visit (when a patient is unable to be contacted).

All attempted patient contacts must be documented in the patient's research record.

For the patient to be confirmed lost, the institution must document the three attempted contacts in Rave as "no contact" and complete the applicable Case Report Form (for example: End of Study or Lost to Follow-up) after one year of no contact.

The institution is responsible for submitting protocol-required data (e.g., on-study, treatment/intervention, follow-up information) for the period from patient registration through the date the patient is deemed lost to follow-up. The site must record in Rave that no

contact occurred including the date of the attempt to contact the patient.

8.1.2.7.2 If a lost patient is found

If a patient is re-contacted or additional data are received that change the patient's survival or clinical status (from "lost to follow-up"), the institution must contact the data manager for the study.

8.1.3 Submission of samples, specimens, and modality materials

Specimens and modality materials (e.g., karyotypes, images) are to be submitted as specified in the Alliance protocol.

If a registered patient refuses further protocol treatment but agrees to be followed, samples should continue to be submitted as required by the protocol. If a registered patient withdraws consent for participation in the study or consent for follow-up, samples may not be submitted. At any point in the trial, study participants opt out of specimen collection; this will be documented in EDC system for that timepoint. Study participants may also change their permissions for future use of previously collected specimens. If samples have already been submitted but not distributed to investigators, when the patient withdraws consent, those samples will be withdrawn from the biorepository and will be disposed of appropriately – either destroyed or, in the case of paraffin blocks, returned to the submitting institution upon request. Attempts will be made by the repository staff to retrieve any samples that have been sent from the repository to investigators. However, processed samples and the research data generated from them will not be rescinded, and may be used in study analyses. See Chapter 11 for additional information.

If in the event a trial requires reconsent, patients cannot change their original answers. Instead, the outlined withdrawal of consent procedures must be followed.

8.1.4 Submission of samples for studies led by other Lead Protocol Organization

Samples, specimens, and modality materials are submitted per protocol-specific instructions.

8.2 Receipt and distribution of data forms by SDMC

Refer to the data submission section of the protocol for instructions and Data Submission Schedule on how to submit data to the Alliance Statistics and Data Management Center.

Data for studies coordinated by other Lead Protocol Organizations are submitted directly to the coordinating group via the instructions outlined in their data submission section of the protocol.

8.3 Quality assurance performed by Data Management Unit

Data submitted for Alliance coordinated studies are reviewed by the data manager responsible for the study. Quality assurance checks are performed to verify the completeness and accuracy of reporting. A careful review of the data is also conducted to evaluate protocol compliance, e.g., patient eligibility, stratification, safety reconciliation, treatment/intervention and endpoints. When discrepancies are found or data are missing, data management personnel query the institution.

8.3.1 Quality checks of on-study and eligibility data

Quality checks of on-study data include a detailed review of eligibility criteria and supporting documentation requested in the protocol. The first eligibility review is performed via the OPEN registration system. Upon receipt of the eligibility material and supporting documentation the data manager performs a second quality check.

If a patient is found to be ineligible or of questionable eligibility, the data manager will request review by the study chair. If the study chair and data manager do not agree on the eligibility of a patient, the study statistician attempts to adjudicate. If the statistician cannot adjudicate, the statistician will contact the executive officer. If the executive officer also cannot adjudicate, the group chair will make the final determination. The data manager will notify the institution of any patients deemed ineligible.

8.4 Alliance case evaluation process

Within a large clinical trials network, it is essential that patient information is collected and quantified in a standard manner across institutions and in particular that adverse events and outcome measures (response, relapse, etc.) are properly assessed. A case evaluation is a formal, centralized, review by the study chair on the accuracy and consistency of key adverse event and outcome data reported by the treating institution. The evaluation provides a centralized review of the data forms and other supporting documents by a medical expert, and ensures accurate data.

8.4.1 Objectives

The objectives of the case evaluation process are to provide an assessment by the study chair of the following:

- Treatment/Intervention compliance
- Study endpoint(s)
- Adverse events

8.4.2 Studies requiring case evaluation

Only studies that contain an intervention component, whether for cancer treatment or control, require case evaluation. Case evaluations may be performed on other studies upon request of the study team and joint approval of the group statistician and director of data management. Similarly, if a study team wishes to have their study excused from these requirements joint approval is necessary.

The study chair has the final responsibility for the case evaluation. While study chairs and other study team members are involved in ongoing monitoring and review of all patient data, a case evaluation is performed only once per patient unless approval is obtained by the group statistician and the director of data management. The study chair can perform the review in real time or in small batches. The case evaluation process for the study must be completed prior to the final statistical analysis to be used for manuscript publication. This policy does not apply to abstracts to professional society meetings.

For studies with fewer than 100 patients, all cases must be evaluated by the study chair. For large studies with 100 or more patients, the first 100 consecutive patients enrolled, and then 10 percent of the remaining target up to a maximum of 300 cases must be evaluated. Patients who were enrolled but never treated may be omitted. Additional cases may be evaluated as

deemed necessary by the study statistician and study chair. All exceptions must be approved by the directors of data management and statistics.

8.4.3 Case evaluation form

The study chair completes the case evaluation form to record his/her evaluation of the case. The case evaluation form solicits the study chair's opinion regarding adverse events, response, relapse or disease progression, and survival as recorded in the database. The study chair provides specific comments about treatment/intervention violations or inadequate reporting.

8.4.3.1 Patient summary report

The patient summary report is provided by the SDMC to summarize a patient's major clinical events. Reports will be based on a core set of items for all studies; additional items are determined by study phase and type (cancer/non-cancer treatment, QOL, etc.). Table 8-1 outlines the data elements included in the report.

Table 8-1. Data elements in the patient summary report

Treatment/Intervention **Compliance**	**Study Endpoint(s)**	**Study-Specific For Other Studies**	**Adverse Events (when applicable)**	**Additional Items**
• Date treatment or intervention started • Date treatment or intervention ended • Number of cycles or interventions given • Reason treatment or intervention ended • Dosing compliance (for treatment trials)	Required for all studies: • Primary and critical secondary endpoints • Examples: clinical tumor response, pathologic tumor response, disease recurrence or progression, death • Date(s) of endpoint(s)	• Examples: skeletal-related event, lymphedema, submission of final questionnaire • Date(s) of endpoint(s)	Phase 1 studies: • AEs of all grades Phase 2 studies: • Question: AEs of grade 2+ or AEs of grade 3+ Phase 3 studies: • AEs of grade 3+	• Determined by study team • Case by case basis

8.4.4 Data Access

Study chairs will have full access in Rave for phase 1 and 2 studies not monitored by the DSMB. Study chairs will not have access to completed case report forms in Rave for DSMB monitored studies (see section 16.1).

8.4.5 Study Chair Adherence to Policy

The study statistician and data manager will monitor study chair adherence to the case evaluation policy, including timeliness of reviews. Serious non-compliance, including delinquency, of the study chair will be reported to the committee chair, Director of Central Protocol Operations Program, and the Group Statistician. Possible consequences for serious non-compliance, including delinquency, are prevention from serving as continued services of study chair for this trial, ability to be a future study chair, and loss of authorship on the primary manuscript.

9 Information systems

The objective of Alliance Systems Management Unit and Information Systems Unit (SMU/ISU) policies is to ensure the confidentiality, integrity, and availability of Alliance systems and data. ISU staff is located at Mayo Clinic. SMU staff is located at Mayo Clinic. ISU and SMU personnel work collaboratively, maintaining controls at all levels to ensure that all necessary standards are met.

This policy and procedures document contains two parts. *Member Information* describes policies and procedures for Alliance members who require access to the ISU applications. *SMU/ISU Operations* shows policies and procedures used by the SMU/ISU staff to establish and maintain the applications, databases, and equipment for which they are responsible.

9.1 Member information

SMU/ISU develops and maintains the Alliance Information Systems (IS) that institutional and internal Alliance members use to enter and manage patient and study data. SMU/ISU also manages the Alliance website (http://www.allianceforclinicaltrialsinoncology.org), including the member site, and all Alliance databases. The website provides access to Alliance Web applications and other information useful to members and is updated regularly as additional Alliance applications and reports are made available. The databases are the repository for member, patient, and study data.

In general, users of Alliance information systems are registered members – persons who assist with Alliance studies or other Alliance mission-related tasks. A primary objective of SMU/ISU is to provide efficient and reliable systems that enable the members to perform their assigned tasks, while safeguarding Sensitive Electronic Information (SEI) and Protected Health Information (PHI), and meeting the requirements defined by regulatory bodies including Health Insurance Portability and Accountability Act (HIPAA) and Health Information Technology for Economic and Clinical Health (HITECH).

9.1.1 Member account request and setup

All Alliance members must have a Cancer Therapy Evaluation Program (CTEP) ID and a CTEP Identity and Access Management (IAM) account in order to log into the member portion of the Alliance website. Refer to the CTEP website (http://ctep.cancer.gov) or to the Cancer Trial Support Unit (CTSU) website (http://www.ctsu.org) for additional information.

Alliance member accounts give access to the Alliance member site (a restricted area of the Alliance website), and to Alliance IS Web applications. Prior to using the applications, Alliance members must be working with an

institution that has IRB approval for an Alliance-based clinical trial, be authorized (as appropriate) to work with a given study's clinical trial data, and receive required Web application training. Alliance Web applications are available to registered Alliance members only. However, users from other research groups may be given access to the Alliance website.

9.1.1.1 Individual institution members

To register a new member and request access to Alliance Web applications, an authorized institution representative must follow the application procedure specified on the Alliance website. During the application process, the prospective member's role assignment(s) is specified. When the application is approved, appropriate accounts are created in the Alliance Information Systems. The member's CTEP username and password is used to access the Alliance member site and SMU/ISU Web applications.

9.1.2 Institution registration

Alliance Institutional membership gives an institution the ability to participate in Alliance clinical trials. Institutional membership requirements and application instructions are available on the Alliance website under the 'Membership' heading.

9.1.3 Alliance application accounts

The Alliance uses Web-based and non Web-based applications for the capture, management, and reporting of clinical data for most Alliance-sponsored studies. Users (who meet the above requirements) from other research groups will have access to the Alliance website by being an active member of the NCTN.

9.1.4 User names and passwords

User names and passwords are managed by Cancer Therapy Evaluation Program (CTEP) through CTEP Identity and Access Management (IAM) using ID.me for two-factor authentication, as required by NCI.

9.1.5 Roles and permissions

During Alliance registration, members are assigned roles and permissions that determine the specific Alliance data they may access, and which tasks they may perform.

A member may hold one role or many roles. Roles are defined as group roles, institution roles, committee roles, or study roles. A member holding a role is granted all of the data access privileges defined for the role. When a member holds more than one role, any necessary operation must be defined for access with at least one of the roles held by the member.

Typically, institutional members may access data from their own institutions only. Members from main member institutions can access data from their own institutions and their affiliate institutions. Alliance staff members may access only data necessary to fulfill their job responsibilities.

Members are further granted permissions, which are actions (e.g., read, update) that may be performed on the data they access.

Beyond assigned privileges and permissions, any privilege may be granted, with proper approval, to a specific member. Institutional members who need access to additional data should contact the Alliance Help Desk and request the additional privilege. Help Desk staff will forward the information to Alliance management for approval. Refer to the Alliance website under the 'Contact' heading for Help Desk contact information.

9.1.6 System availability

All Alliance systems are available 24 hours a day, seven days a week, with exceptions for system maintenance. Whenever possible, system maintenance will occur in non-working business hours. Unscheduled maintenance may occur as needed to resolve critical security vulnerabilities or to resolve other critical systems issues. For extended unscheduled outages, a broad communication would be issued.

9.1.7 User support

Alliance members require information systems that support all activities related to the conduct of clinical trials. To help meet these requirements, the Alliance provides technical support by trained Alliance Service Center employees to assist users with system, database, Web application, Internet, or study-related problems. Alliance Service Center employees may also create trouble tickets to document user issues prior to assignment to appropriate technical staff.

9.1.7.1 Alliance Service Center

For systems support, the Alliance Service Center is available Monday through Friday from 9 AM to 5:30 PM Eastern Time (8

AM to 4:30 PM Central Time). Refer to the Alliance website under the 'Contact' heading for the Alliance Service Center contact information.

9.2 SMU/ISU operations

The remainder of this section contains policies the Alliance SMU/ISU uses to ensure the efficient and effective operation of its computing environment. The policies are divided into the following topics:

- Software development
- Documentation
- Technology selection and change management
- Usage of computing resources
- Security
- Backups and data retention
- Disaster recovery

Alliance IS staff adhere institutional IS policies of Mayo Clinic. In many cases SMU/ISU policies and procedures are more restrictive than institutional policies because of the national scope of the Alliance. However, all SMU/ISU policies and procedures serve the best interests of patients and members by providing the highest level of safety and security regarding data collection, maintenance, and reporting. Beyond safety and security criteria, the policies reflect the most efficient and effective means for meeting the goals of the Alliance and industry best practices.

SMU/ISU projects are overseen and prioritized by the SDMC Directors.

9.2.1 Software development

SMU/ISU develops software applications and interfaces that generate, collect, maintain, and transmit data for clinical trials conducted by the Alliance. The applications are developed using a variety of development tools, technologies, and databases.

ISU uses a tiered software development environment to ensure proper testing and migration from the development to production environments. Software is first deployed to a development environment for initial testing by the software development staff. Software is subsequently deployed to an integration environment for software quality assurance and user acceptance testing, prior to being released into the production environment. New software is deployed during scheduled downtimes unless they are deemed urgent or critical, in which case the software release is migrated as soon as possible.

Completed deployment plans are required prior to implementing upgrades or other software changes in the production environment. Each release is planned to allow thorough testing prior to its deployment to the production environment.

Software developers are required to use development tools that have been carefully reviewed and established as standard within the ISU. Developers use online software development tools to capture project notes, requirements, technical specifications, screenshots, and links to appropriate source code repositories. Developers check all new and modified code into a source code control system that supports team development on various projects, prevents accidental file loss, allows backtracking to previous versions, and manages releases.

Security and confidentiality of study data are maintained at all times. To protect sensitive and confidential information, applications incorporate sound security practices and comply with HIPAA guidelines. All Alliance applications safeguard protected health information (PHI) by requiring secure logins, limiting access to authorized users, and implementing encryption schemes for data transmission.

9.2.2 Documentation policies

Documentation may include but is not limited to user manuals, job aids, training manuals, development documentation, policies, and standard operating procedures. All SMU/ISU documentation – whether in-process or released – is housed in a common server location.

During documentation development, writers follow consistent documentation templates. Documents intended for external (non-SMU/ISU) audiences are reviewed by the applicable Alliance leadership through Program Operations before they are finalized for publication. The reviewer list is dependent upon the document content.

9.2.3 Technology selection and change management

As resources permit, the Alliance works to maintain a state-of-the-art computing environment. Alliance developers use open-source software customized to Alliance needs, or software developed in-house. In some cases, commercial software solutions are a better choice, and are used if the vendor places a high priority on integration capabilities. The Alliance does not use commercial systems provided by a single vendor that would create a closed environment.

9.2.4 Usage of computing resources for Alliance Staff

As part of its mission, the SMU/ISU acquires, develops, and maintains computers, databases, and networks. These computing resources are intended for Alliance-related purposes, including direct and indirect support of the Alliance mission.

Use of Alliance computing resources is not completely private. While the Alliance does not routinely monitor individual usage, normal operation and maintenance requires the backup of data and communications, the logging of activity, the monitoring of general usage patterns, and other activities necessary for the provision of service. Under prescribed circumstances, the Alliance may also specifically monitor the activity and accounts of individual Alliance computing resource users, including individual login sessions and the content of individual communications.

The Alliance does not permit use of its computing resources for personal, financial, or other gain.

9.2.5 Security

SMU/ISU uses industry best practices to protect information against unauthorized access, use, or destruction. Access is controlled in order to limit the exposure of sensitive patient data.

Four categories of access control are implemented:

- Facilities
- Network and servers
- Database
- Application (includes Alliance website(s) and Web applications)

For all users, the SMU/ISU completes an Alliance authorization and account creation process before physical or electronic access is granted.

When a user no longer requires access, and authorization to terminate an account is received, SMU/ISU Help Desk employees terminate the user's role(s) and disable accounts that provide access to the Alliance software applications.

9.2.5.1 Alliance SDMC Data Center facilities security

Permission to access to the Alliance SDMC Data Center facilities is determined by local institution guidelines.

The Alliance SDMC Data Center is a high security environmentally controlled and monitored computer room at Mayo Clinic. Access to Alliance SDMC Data Center facilities is controlled through use of an Access Identification Card provided to permanent staff or vendors who have management authorization to be at the Alliance SDMC Data Center and have received training. Vendors may be approved for temporary or long-term access. Visitors that require access to the Alliance SDMC Data Center must receive management pre-approval and must sign in at the wall-mounted computer near the entrance to the facilities. In addition, visitors must be escorted during their visit by a cardholder with Alliance SDMC Data Center access authorization.

The Alliance monitors for and protects its computer resources against environmental hazards. Systems are centrally monitored, kept in temperature-controlled conditions, and are protected against electrical power surges and short-term outages. Backup generators are available onsite to ensure the continuous operation of the Alliance SDMC Data Center in case of long-term utility power failures. To comply with local building and fire codes, computer resources are protected by automatic smoke detection and fire suppression equipment.

9.2.5.2 Network and server security

SMU/ISU passwords and network/server security upgrades must be managed to conform to local institution practice.

Alliance systems housed at the Alliance SDMC Data Center are protected by enterprise firewalls and network security, which provides continuous monitoring to identify and prevent malicious access.

Server login passwords are encrypted and stored in their encrypted form in protected files.

An administrative user account is a specific account type that allows access for system administration purposes, including setup of user accounts. Administrative users only are authorized to manage accounts and servers. An Alliance computing manager responsible for specific work units designates Alliance SMU/ISU staff administrative users and assigns them a unique user ID and password.

9.2.5.3 Database security

Because of the highly sensitive nature of data collected by the Alliance, and the right to privacy of patients entered on clinical trials, only authorized members with a need to know will be given access to data in the Alliance databases. SMU/ISU ensures the security and integrity of the databases through password controls, logging, monitoring, and auditing.

SMU/ISU implements database auditing for relevant features related to data definition, security administration, and logon failures. The SMU/ISU implements both database and application level auditing for relevant features related to data manipulation, security administration, and logon failures. A database audit trail is used to record date, time, and user for various levels of standard and suspicious activity. A correction history is available to record date, time, and user for all data manipulation activity.

SMU/ISU monitors each database product software lifecycle, and ensures that appropriate updates are applied. Each new release and version of the database software is identified, considered for installation, and installed after rigorous validation.

For database patches, SMU/ISU follows industry best practices. Database security patches are installed only after they are validated against the SMU/ISU computing environment. If validation is successful, installation will occur as soon as possible after the date of release.

Database user accounts are set up after authorization by the appropriate manager. Database passwords expire at preset intervals per institution standards and must be changed when required. SMU/ISU employees inactivate or remove user accounts immediately upon notification of termination of employment or Alliance membership.

9.2.5.4 Application security

SMU/ISU develops and/or supports software applications for use by Alliance members. These applications enable such functions as patient registration, specimen tracking, reporting, and data entry and review. ISU applications encrypt all data transmission to ensure security and confidentiality of data as it is entered and viewed.

Authentication and authorization services ensure consistent security for applications. Users are provided accounts and roles that determine their access, at a granular level, to data and functions. As roles are added or revised, appropriate access and permissions are analyzed by the SMU/ISU.

9.2.6 Backups and data retention

All system and database backup and recovery procedures adhere to industry best practices. Alliance data is safeguarded against loss via industry standard backup and retention schedules. Backups are performed on a daily basis. Using the backup scheduler and policy engine, data backups are targeted to a tape library located in a remote data center physically separated from the primary infrastructure hosting Alliance application and data services. Data are retained for a period not less than 30 days. Alliance employee workstations are managed by local desktop support and fall under the backup policies of the support environment.

9.2.6.1 System and database backups

Controlled and monitored backup rotations protect all servers, file storage devices, and server security information.

9.2.6.2 Servers

Servers are designated by institution policies as critical or non-critical. All servers receive a weekly full backup, and incremental backups. In the event of file loss, file corruption, or total equipment loss, SMU/ISU is able to recover from the previous full and incremental backups. Maximum file loss would be 24 hours.

9.2.6.3 Retention and storage

Backup tapes are retained for two months. Longer data retention is additionally determined by the study. Security access files for all machines supported by the SMU/ISU are backed up and retained as required by HIPAA. Backups are stored offsite from the main Alliance SDMC Data Center.

Statistical archives are stored in SAS data sets and housed on a separate server.

9.2.7 Disaster recovery

The Alliance has a formal disaster recovery plan to be used in the event of a significant failure of regular computing services. The plan identifies the primary and backup members of the disaster recovery assessment team and the functional systems area for which each person is responsible. If an event occurs that requires the attention of the team, all members assemble to begin an assessment of the situation for their respective area and prepare an estimate of the time and level of effort required to restore operations. Restoration efforts are directed by the ISU leadership. Recovery time will depend on the nature of the disaster.

10 Publications Committee charter and mission guidelines

"The Publications Committee shall review existing policies and best practices concerning authorship of scientific publications, and shall recommend to the Executive Committee for its approval a set of requirements for authorship of Alliance publications. These requirements shall be in the form of a guidance policy for Alliance publications and shall address rules governing authorship and disclosure of conflict of interest for Alliance publications. The chair and vice chair of the Publications Committee shall include one individual who is a scientific leader and one who is a community oncology leader. The Publication Committee shall include representatives from the Central Protocol Operations Program and the Statistics and Data Management Program, as well as other members as deemed appropriate. The Publications Committee shall meet at a frequency of not less than once yearly. The Publications Committee shall also adjudicate in a timely manner any issues related to publication of Alliance manuscripts, and make recommendations concerning these matters to be acted upon by the Executive Committee."

— Statement from the Alliance Constitutions and Bylaws

10.1 Data ownership

Data generated by Alliance Group activity, using Alliance resources, or associated with the Alliance belong to the Alliance. Therefore, the Alliance, through its publication policy, has oversight over the use and publication of any and all Group data. All planned abstracts or manuscripts reporting results of Alliance studies to a meeting or journal for publication are to undergo pre-submission review and approval, based on this Policy and Procedures document.

Publications resulting from external data-sharing agreements require only administrative review to check for basic elements (e.g., Alliance group name, grants) and do not require full Alliance review.

10.2 Committee members

Members of the Alliance Publications Committee are nominated by the committee chair/co-chairs to serve 3-year terms (renewable one time), and are expected to attend a minimum of 75 per cent of committee meetings.

Reviewer's Group Role	**Comments**
All co-authors of publication	
Chair/Co-Chairs Publications Committee*	
Vice Chair Publications Committee	
Committee Chair(s)	*Applicable studies only*
Director, Biospecimens and Correlative Science Operations*	*Translational studies only*
Director, Central Operations*	
Executive Officer	*Applicable studies only*
Group Administrator	
Group Chair*	
Group Statistician*	
Publications Project Manager	
Publications Consultant	
Project Manager, Pharmaceutical Collaborations	
NCI CTEP or DCP representative	
Industry representative, according to study agreement	*Applicable studies only†*
Executive Committee members	*Half of the EC membership (excluding those asterisked in this table) is selected to review publications in 2 5-month rotations; the entire EC reviews publications in December and January to provide sufficient coverage for ASCO abstracts.*

*Member of the Executive Committee who reviews publications in all rotations.
†Determined by Pharmaceutical Collaborations Project Manager

10.4 Abstract and manuscript preparation

10.4.1 General principles

The Alliance guidelines build on the publicly available *International Journal of Medical Journal Editors* (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org).

The study chair is responsible for providing leadership and writing manuscripts/abstracts for publications that describe an Alliance study. The document entitled "CHECKLIST – Recommended Content for Alliance Manuscripts and Meeting Abstracts" provides guidance related to title page, authorship, acknowledgements, scientific content for different sections, as well as template wording for support, monitoring, informed consent, locations of data collection and statistical analyses, randomization scheme, quality assurance, meta- or pooled analysis, and data lock. All authors are expected to review and follow this checklist.

The study chair sends the initial draft manuscript/abstract to all the co-authors for review, including the faculty and staff statisticians. All authors, including those assigned authorship based on accrual, are responsible for careful and meaningful review. The first author takes into account all comments and suggestions by co-authors and incorporates them into the revised draft, as appropriate. After initial co-author review, the study chair sends the revised draft to the publications coordinator (publications@AllianceNCTN.org) as an MS Word file; this way the Alliance files are properly up to date. This revised draft is sent for Group Review (see sections 10.5.3 and 10.5.4).

The author is responsible for submitting the final Alliance-approved version of the manuscript to a journal, and for advising the publications team (publications@alliancenctn.org) when this has been done (see section 10.6. Abstract or Manuscript Submission to Meeting or Journal). It is the responsibility of the corresponding author to collect and send to the journal all journal-specific conflict of interest forms prior to manuscript submission for publication.

It is required for all Alliance authors on publications addressing primary or secondary endpoints to be in compliance with Alliance Conflict of Interest (COI) policy. An investigator may be precluded from authorship due to the magnitude and nature of a financial COI. Under this circumstance, the investigator would likely have had prior notification of this determination. (see Conflict of Interest section 3.5). An updated COI form must be on file for authors at most 30 days prior to receipt of the publication. Any individual with a conflict of interest that is sufficient to render them ineligible for a study chair or co-chair role cannot serve as either first or senior (last) author of an Alliance publication (see Conflict of Interest table 3-1).

10.4.2 Cover page

It is important for the study number(s) to appear early in the manuscript/ abstract for ease of retrieval in literature searches. The title section of the cover page of the manuscript should indicate the Alliance or legacy study number(s) about which the manuscript is written. As example: "Phase III Alliance A1K study of drug A vs. drug B for treatment of X". For abstracts and manuscripts generated from the ACOSOG, CALGB, and NCCTG legacy groups, the recommendation is to add

"Alliance" after the study number. As example: "Phase III ACOSOG A1K (Alliance) study of drug A vs. drug B for treatment of X".

If it is not possible to include all study numbers in the title, the author should insert wording such as "A combined analysis of Alliance studies" in the title; include the study numbers within the abstract or introduction section.

The cover page of a manuscript also contains author affiliations and a paragraph indicating the supporting grant numbers for all authors listed; the National Institutes of Health (NIH) grant number for an author should reflect the main member institution with which the author was affiliated when the study was activated. Appropriate acknowledgment of other funding sources should be included as well (e.g., the Breast Cancer Research Foundation or company XYZ).

NIH requires that publication or oral presentation of NCI-supported work acknowledge that support. Publications and presentations as described here include abstracts, press releases, print-media articles/manuscripts, electronic media articles/presentations, and letters related to findings and results from NCI-sponsored studies. The Alliance publications team and the Alliance communications specialist insert grant support information into Alliance-related publications/presentations before Group Review. **Therefore, the corresponding author is responsible for ensuring that these grants appear in the final published version.**

The Alliance requires that industry support be acknowledged on all publications.

10.5 Authorship

Alliance authorship guidelines follow those of the publicly available *International Committee of Medical Journal Editors* (ICMJE) recommendations for authorship:

"The ICMJE recommends that authorship be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; **AND**
- Drafting the work or revising it critically for important intellectual content; **AND**
- Final approval of the version to be published; **AND**
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged. Committee-specific authorship issues will be addressed on an ongoing basis by the Alliance Publications team. Questions regarding committee-specific guidelines should be directed toward leadership of the committee.

If there are questions or discrepancies related to author order based on the study chair's decision and the publications guidelines, as seen below, arbitration is required by the Alliance Publications Committee chair/co-chairs/vice chair and the Alliance Group chair, with input from the other Group Review members.

A summary of required authorship by study endpoint can be found in Table 1.

10.5.1.1 Publication on the primary study endpoint

The listing and order of authorship for a manuscript/abstract for a primary study endpoint is determined by overall workload contribution, intellectual contribution, and participant accrual. Each author is responsible for obtaining any required clearances from his/her own institution (or network).

The first author of the manuscript/abstract is usually the study chair or co-chair. A study chair who moves to a non-Alliance institution may continue to serve in the full capacity of study chair with the agreement of the appropriate committee chair and if no conflicts of interest have arisen because of the move of the study chair. The original study chair therefore retains authorship rights by virtue of serving in the full capacity of the study chair role.

The first author is generally followed by the study's primary statistician. An exception occurs when two or more investigators contributed equally to the study. In this case, the statistician should be next author and an asterisk and footnote must explain the previous positions: "These authors contributed equally to the study." When the publications team receives an abstract or manuscript in which the statistician is not the second author, the publications coordinator contacts the statistician to confirm that the authorship order is appropriate.

Authorship should be granted to the responsible executive officer. The study community co-chair should be included as an author if appropriate by ICMJE recommendations stated above. If the modality co- chair participated in the design of the study and wrote the modality section of the protocol, they should be an author on primary endpoint publications. Pathologists, radiologists and other specialists who perform quality assurance (QA) for a study should be included in the authorship of any publications that result from the study, unless the publication is independent of QA results of their findings. The decision for inclusion of an Alliance study pharmacist, nurse liaison, clinical research professional, data manager and patient advocate should be included in the primary and/or secondary endpoint manuscript, as appropriate if meeting the ICMJE criteria. This policy does not apply to abstracts which limit the number of authors. Other individuals making significant contributions according to ICMJE recommendations may be listed.

Institutional authorship based on accrual is separate from (and in addition to) study chair, committee chair or other contributors. Institutional authorship representation on primary study publications is awarded to an institutional network, rather than an individual site, whose participant accrual contribution fulfills the following guidelines. Please note, Alliance network accrual data will differ from site accrual data available through CTSU; CTSU accrual is based on individual site and includes accruals by other NCTN groups.

Total number of participants in the study	**Number of participants at a network, based on total study accrual**
Fewer than 100 total study accrual	25% of the total or 8 participants, whichever is less
100 – 199 total study accrual	8% of the total or 12 participants, whichever is less
200 – 299 total study accrual	7% of the total or 17 participants, whichever is less
300 – 399 total study accrual	6% of the total or 21 participants, whichever is less
400 – 499 total study accrual	5% of the total or 22 participants, whichever is less
500 or greater total study accrual	Authorship is awarded to the three networks that accrue the most participants, not based by percentage or number of participants enrolled

The principal investigator of a network makes the assignment of authorship after being informed by the publications project manager, publications consultant, or publications coordinator of network merit. The network principal investigator is best suited to determine the assignment of authorship and may assign himself/herself, another physician in the same or another specialty, or an individual from the main member or an

affiliate. The author is discouraged from contacting the network principal investigator directly as this is done by the publications coordinator. In most cases, authorship is assigned to the highest accruing investigator in the institutional network. Institutional nurses or clinical research professionals making significant contributions should also be considered for authorship. Generally, the individual given the authorship assignment should be someone who was working at the institution during the period of accrual and who made substantive contributions to accrual at the institution. All authors should be included in manuscript preparation and approval.

For manuscripts/abstracts involving other National Clinical Trial Network (NCTN) group studies, it is not necessary to include all other NCTN group institutions, but it is expected that groups that enrolled >10% of patients should have at least one author included in the report of treatment studies. In primary endpoint publications, an NCTN group that contributes the requisite number of patients may be represented by both an accrual author and the NCTN group's champion.

All primary manuscripts (excluding those for multi-group studies) also acknowledge each network that enrolled participants on the study. The relevant local principal investigator, their network, and grant numbers are listed in that appendix.

When the study is a limited access pilot of fewer than 30 patients, involving only a few institutions, the study chair, primary statistician and committee chairs should discuss authorship. Ideally, all institutions participating will be represented.

10.5.1.2 Publication on a secondary (correlative) study

A secondary (correlative) study may include observations utilizing existing datasets or compilation of results from several studies. The secondary study may have been approved as a sub-study in an original protocol document, or may be a new study that was proposed by an Alliance or non-Alliance investigator. The work may involve biospecimens, quality of life, symptom analyses, and economic analyses, among others. The intention of the Alliance authorship policy is to be appropriately inclusive, consistent with authorship guidelines from major journals and the ICMJE.

Information related to the Alliance and its grant numbers should be in the cover page of secondary manuscripts.

1. **Authorship on publications of a secondary study <u>included in the original Alliance or legacy protocol</u>**

   All of the following are invited to participate in review of abstract/manuscript data, publication development and approval and should receive authorship if appropriate by ICMJE recommendations:
   - Study chair, study co-chair, executive officer, and community co-chair of the original study. Authorship by a modality co-chair on secondary endpoint publications should be a function of their involvement in the secondary analysis.
   - Study chairs and champions from other NCTN groups that accrued patients or samples to the secondary study
   - Correlative study statistician and primary statistician of the original study if different
   - Pathologists, radiologists and other specialists who perform quality assurance (QA) for the study, unless the publication is independent of QA results of their findings.
   - Pharmacists, Nurse Liaisons, and/or Patient Advocates whose contributions lead to creation of the publication as determined by the study chair.

- Accrual authors
  For accrual authors on CALGB and NCCTG publications, the principal investigator of the highest accruing network selects the network author based on investigator accrual or other study contribution. No minimum accrual threshold is required for the network or selected author.

  An NCTN group should be invited to add an accrual author if the group enrolled >10% of total patients.

2. **Authorship on publications of a secondary study <u>not in an original Alliance or legacy protocol</u>; study proposed by Alliance investigator**

   New secondary studies include observations utilizing existing datasets or specimens, or a compilation of results thereof from several studies that were not part of the original objectives of the primary study or studies.

   a. Intellectual authorship: When manuscripts/abstracts are prepared for new secondary (i.e., post hoc) studies, potential authorship should be extended to the following individuals. *However, authorship determination should be based on*

      ICMJE recommendations (*see section 10.4.3, first paragraph*)

      - Researchers performing the secondary study,
      - Study chair(s) of original Alliance study or studies,
      - Statistician of the new secondary study,
      - Primary statistician of original Alliance study or studies.
      - Co-chairs from other cooperative groups that accrued
      - any patients or specimens may be included if Alliance author or Alliance committee chair requests.
      - Pathologists, radiologists and other specialists who perform quality assurance (QA) for a study, unless the publication is independent of QA results of their findings.

      After primary study chair(s), primary statistician(s), QA specialists and researchers, other investigators who were

involved in the primary study or studies may not necessarily be included in secondary study publications; instead, authorship is determined by an individual's contribution specific to the secondary study and by ICMJE recommendations. Order of authorship should reflect the magnitude and effort contributed by each author to the secondary analyses, which may be independent of the primary studies' analyses or accrual.

b. Authorship based on accruals and new data: Authorship based solely on accrual is not a criterion for this category of abstract or manuscript. Alliance and other NCTN group accrual investigators are recognized in an acknowledgement section rather than with authorship, unless they are among the investigators conducting the secondary use study, in which case authorship depends upon contribution.

It is expected that all investigators who contributed new data to the secondary analyses will also

- be involved in interpretation of those data
- be given the opportunity to participate fully in preparation of resultant manuscripts/ abstracts
- be co-authors on those manuscripts/ abstracts.

This may also apply to non-tissue secondary abstracts/ manuscripts if the data collected by the investigators from the collaborative groups will be utilized.

c. Authorship in Alliance-led meta-analyses: When abstracts or manuscripts are based on Alliance-led analyses using data shared from multiple studies, authorship will include all members of the research teams involved in the current research. Alliance also encourages inclusion of the original study teams in publication authorship, with the understanding that ICMJE recommendations are followed. These policies apply to Alliance-led meta-analyses of data sets obtained from the Alliance, as well as to Alliance-led meta-analyses of Alliance data sets available through the NCTN Data Archive or Project Data Sphere

3. **Authorship on publications of a secondary study <u>not in an original Alliance or legacy protocol</u>; study proposed by <u>non-Alliance investigator</u>**

This category includes abstracts and manuscripts led by outside investigators who have been granted access to Alliance data or

biospecimens.

Authorship decisions regarding the non-Alliance study chair, statistician and researchers performing the secondary study are made by the non-Alliance investigator and team. NCI rules do not mandate that the Alliance investigators be considered for authorship. We suggest that outside investigators consider including the following Alliance leadership team in the preparation and formal approval of the manuscript:

- Alliance study chair(s), of original Alliance study or studies.
- Alliance primary statistician(s) of original Alliance study or studies
- Investigators who contributed annotated tumor specimens

For publications resulting from data sharing of multiple studies, including Alliance studies, Alliance encourages the inclusion of the original study teams in publication authorship, with the understanding that ICMJE recommendations are followed.

Table 1. Guidelines for Required Authorship by Endpoint Addressed in Publication

Author study role	Endpoint addressed in publication			
	Primary	**Secondary in original protocol**	**Secondary (post hoc) not in protocol; Alliance member**	**Secondary (post hoc) not in protocol; non-Alliance member***
Study chair, Alliance co-chairs of original study	X	X	X	X
Primary study statistician	X	X	X	X
Correlative statistician		X	X	
Other NCTN group co-chairs and NCTN group champions	X	From groups that contributed samples or patients	Not required. If first author or committee chair requests	
Community co-chair	X	X	Not required. If first author or committee chair requests	
Modality co-chair	If designed and wrote section of protocol	Function of involvement in secondary analysis.	Function of involvement in secondary analysis.	
Executive officer	X	X		
Other investigators performing primary study	Function of involvement in secondary analysis.			
Other investigators performing secondary study	If secondary study is included	Individual contribution and per ICMJE guidelines	Individual contribution and per ICMJE guidelines	
QA specialists (radiology, pathology)	Unless publication is independent of QA results	Unless publication is independent of QA results	Unless publication is independent of QA results	
Accrual authors --Alliance (network PI assigns)	Per Alliance accrual algorithm	Per Alliance accrual algorithm	Not applicable. Names may be added to acknowledgment.	Alliance investigators who contributed annotated specimens
Accrual authors --other NCTN groups (other group assigns)	If group enrolled >10% of patients	If group enrolled >10% of patients	Not applicable. Names may be added to acknowledgment.	
Pharmacists, Nurse Liaisons, and/or Patient Advocates	Individual contribution and per ICMJE guidelines	Individual contribution and per ICMJE guidelines	Not applicable. Names may be added to acknowledgment.	Not applicable. Names may be added to acknowledgment.

**NCI rules do not mandate that the Alliance investigators be considered for authorship. We encourage outside investigators to acknowledge the indicated members of the study team in the preparation and formal approval of the publication.

10.6 Abstract and manuscript timelines

10.6.1 Timelines for abstract and manuscript preparation

The process of abstract and manuscript generation for phase III studies begins promptly after the Alliance Data and Safety Monitoring Board (DSMB) has determined that the study results may be released and the study chair has completed case evaluations. In accordance with NCTN policy, the Alliance expects preliminary results of major phase III trials to be presented at a scientific meeting within 8 months of completion of the study analysis (if not sooner based on the relevance of the results). It is an NCTN requirement that a full manuscript on the primary study results be submitted for publication in the peer-reviewed literature (not as an abstract) within 1 year of the availability of the primary study results based on the completion date of the study recorded in the U.S. National Library of Medicine database, clinicaltrials.gov.

The Alliance Publications Committee monitors compliance with NCTN policy and communicates with authors, committee chairs, the Group chair, the Alliance Board of Directors, and the Alliance Executive Committee about delays. Action may be taken as indicated in the Delinquency in Manuscript Preparation section below.

For pilot studies, phase I-II studies, and nontreatment studies, the process begins when the study chair has received the study summary from the study's primary statistician. Of note, the statistician may need to conduct additional analyses in collaboration with the study team. Once the statistical analyses are completed, the statistician sends a copy of the analyses to the study chair and notifies the disease/modality chair

The first abstract/manuscript is expected to be based on the mature primary endpoint of the study. Submission of abstracts before data on the primary endpoint are completed is not generally endorsed, but may be considered on individual cases. Some examples are description of unexpected toxicities, enrollment procedures or data, and companion studies that are not dependent on the primary endpoint. This decision to submit an abstract before primary endpoint data are mature is made as a collaborative effort between the study chair, study primary statistician, committee chair, Group chair, and Publications Committee.

Almost all abstracts submitted to a meeting must be followed by a full manuscript (except in special situations that should be discussed with the Alliance Publications coordinator prior to the abstract submission); the manuscript should be sent to the Alliance publications coordinator (publications@AllianceNCTN.org) for Group Review no later than 6 months after the meeting. We suggest that the abstract author

create a draft manuscript by the time of meeting presentation using the statistical analysis that is prepared for the meeting abstract to optimize time and effort. This initial draft can be used as a guide from which to develop a final version that is sent to potential co-authors, etc., prior to submission to the Alliance publications coordinator.

For publications in which an abstract is not prepared prior to developing a draft manuscript, the draft manuscript should be sent to the publications coordinator within 2 months after completion of the statistical summary report.

10.6.2 Delinquency in manuscript preparation

A manuscript on the primary endpoint results of a phase III study must be submitted for publication in the peer-reviewed literature within 1 year of the availability of the primary study results. A manuscript on phase I-II, pilot, and nontreatment studies must be submitted to the Alliance publications coordinator for Group Review no later than 6 months after presentation at a medical meeting. As stated above, it is expected that a draft manuscript is completed at the time of data presentation at a meeting. When a study chair has not completed a draft manuscript according to this timeline, the disease or modality committee chair initiates a discussion with the study chair, as a warning (cc to publications@AllianceNCTN.org). After receiving a warning notice from the committee chair, the study chair has 30 days to submit a first draft of the manuscript to the protocol office.

If the study chair is unable to complete the manuscript in the expected time period, 2 actions by the disease and modality committee chairs may follow: (1) reassignment of first authorship and (2) prevention of the delinquent author from chairing a future Alliance concept or study for at least one year. The appropriate disease and modality committee chairs then request from the Group chair (and Publications Committee chair/co-chairs) permission to reassign the manuscript to an investigator responsible for a large percentage of accrual or with a substantial intellectual contribution to the study. The responsibility of reassignment of authorship rests with the appropriate disease or modality chairs, who should in turn notify both the new author and the study's executive officer of the reassignment. The disease or modality chair should clarify to the new author that the first draft of the manuscript should be ready within 30 days after re-assignment.

10.6.3 Timelines for review and revision of abstracts submitted to the Alliance publications coordinator

A meeting abstract must be submitted by the first or corresponding author to the publications coordinator (publications@AllianceNCTN.org) as a Word document at least 2 weeks prior to the meeting abstract submission deadline. The author receives scientific comments from Group reviewers, NCI, and industry partners typically

within 3 days after the publications coordinator sends the abstract for review. Comments concerning authorship may also be sent to the corresponding author. After revising the abstract based on Group Review, the first author must send the revised abstract to co-authors for their approval. When the abstract is accepted, the author must send the acceptance email and the final submitted abstract to all co-authors and to the publications coordinator within 1 week after acceptance.

10.6.4 Timelines for review and revision of manuscripts submitted to the Alliance publications coordinator

The publications coordinator (publications@AllianceNCTN.org) reviews authorship within 2 working days and submits the authorship to the study chair within those 2 working days. Barring any procedural delays or discrepancies/concerns between the study chair and publications coordinator's author list and order, the publications coordinator submits the manuscript for Group Review within 5 working days. The Alliance manuscript review (aka Group Review) members are described in the Group Review section above. Note that the publications team processes abstracts before manuscripts because of meeting deadlines, and this may affect a manuscript's timeline.

Reviewers are expected to provide written input to the publications coordinator within 7 working days. Comments from NCI and industry partners are expected back within 30 days. All abstracts and manuscripts (except those resulting from external data sharing) must be reviewed by an independent Alliance faculty statistician.

All comments from the Group Review should be sent to the manuscript's first author, the corresponding author, the co-chairs and vice chair of the Publications Committee, the publications project manager, and the publications consultant. The first author is expected to discuss suggestions with the study statistician, review comments, and complete a second version of the manuscript within 4 weeks. Inability to meet this timeline should be discussed with the modality/disease committee chair. Based on the situation, further discussion with the Publications Committee co-chairs and vice chair may be required, to better assist the author.

10.6.5 Approval of abstracts and manuscripts

All comments received from reviewers during Group Review are sent to the chair/co-chair/vice chair of the Alliance Publications Committee. The Publications Committee chair/co- chair/vice chair are responsible for approving abstracts and manuscripts, or requesting revisions followed by re-review.

10.7 Abstract or manuscript submission to meeting or journal

The study chair revises the manuscript/abstract based on internal and external reviews outlined above and sends the co-authors the revised publication for their approval. The study chair or corresponding author submits the approved manuscript/abstract to the journal or association for review, complying with all submission requirements. See section 10.10 for required author actions that pertain to the NIH Public Access Policy at time of manuscript submission.

The study chair also sends a copy of the submitted manuscript/abstract to the publications coordinator (publications@alliancenctn.org) for inclusion in the Alliance publication database within 1 week after submission.

10.8 Publication of abstract or manuscript

The study chair/corresponding author advises the publications coordinator (publications@AllianceNCTN.org) of the status of all abstracts and manuscripts submitted to a meeting or journal for publication. Letters of acceptance and a PDF file of the published abstract or printed manuscript must be sent by the study chair/corresponding author to the publications coordinator within 14 days after availability. This is necessary for the Alliance publication database to be accurate and complete (including the full citation). This material is reviewed on an ongoing basis by the Publications Committee. To facilitate access to Group study results, Alliance publication citations are posted in the publications bibliography and on the Alliance website.

10.9 Publicizing Research Information

All communication related to the dissemination of Alliance research to external audiences is handled by the Alliance communications specialist. This includes all written or recorded communication (i.e., press releases, news releases, press statements, video releases) directed to members of the news media, stakeholders, and the public, regarding the activation, progress, results and findings of Alliance research. This also relates to all communication generated by an institution or industry partner based on Alliance research. Such communication must be submitted the communication specialist (communications@AllianceNCTN.org) for review at least one week prior to its release. Also refer to Section 14.3, Dissemination of Information to the General Public.

10.10 Summary of study results for the public

The lead author must submit the completed plain language study results summary template to the publications coordinator (publications@AllianceNCTN.org) when the manuscript is sent for Alliance Group review. If a manuscript is not accompanied by a completed template, Group review will be delayed until its receipt.

For a phase III or randomized phase II study, a public study result summary of the trial design, goals and results is created by the Publications Committee, with input from the lead author of the manuscript, Patient Advocate Committee and Oncology Nursing Committee, using the plain language template for consistent and understandable information. The primary audience for public study result summaries includes study participants.

The Alliance web content administrator posts the public summary to the Alliance website at a time that coincides with publication of the manuscript.

10.11 NIH Public Access Policy (NIH PAP)

The NIH Public Access Policy implements Division G, Title II, Section 218 of PL 110- 161 (Consolidated Appropriations Act, 2008). The law states:
"SEC. 218. The Director of the National Institutes of Health shall require that all investigators funded by the NIH submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication: Provided, That the NIH shall implement the public access policy in a manner consistent with copyright law."

10.11.1 Overview of methods for manuscript submission to PubMed Central

There are four methods defined by the NIH to ensure the deposit of a manuscript into PMC in compliance with the NIH Public Access Policy: Methods **A, B, C,** and **D** (Table 1). A journal or publisher uses one of these four, or a combination. Some methods require more author involvement than do others. Methods A and B require an agreement between the publisher and NIH.

If a journal uses **Method A**, the publisher deposits the manuscript into PMC without author involvement. If the journal uses **Method B**, the author can choose to arrange with the journal to deposit the published article; this usually involves choosing the journal's fee-based open access option. If a journal uses or allows the author to use **Method C**, the author must take all steps to ensure the final accepted peer-reviewed manuscript is deposited into PMC. **Method D** publishers voluntarily deposit a final peer-reviewed manuscript to PMC if it falls under the NIH Public Access Policy.

Table 2. Overview of methods of compliance with NIH Public Access Policy

Question	Version of Manuscript Deposited; Associated Methods and Approvals	
	Version: Final Published Article	**Version: Final Accepted Peer-Reviewed Manuscript**
What is the difference between a final published article and a final accepted peer-reviewed manuscript?	This is the journal's authoritative copy of the paper, including all modifications from the publishing peer review process, copyediting and stylistic edits, and formatting changes.	This is the author's final manuscript version of a peer-reviewed paper accepted for journal publication, including all modifications from the journal's peer review process.
What are the NIH-defined methods of submission used by journals, publishers or authorsto deposit a version of the article?	• **Method A:** The publishers and journals automatically post an NIH-supported published paper directly to PMC if the author advises of NIH support. • **Method B:** Author must make special arrangements for these journals and publishers to post the published paper directly to PMC, since they do not automatically do so. *If an author does not make arrangements, then he/she must use Method C.*	• **Method C**: These publishers and journals do not submit manuscripts. *Author must submit final peer-reviewed manuscript to the NIHMS.* • **Method D:** These publishers and journals will submit final peer-reviewed manuscripts to the NIHMS if advised of NIH support. Author is responsible for ensuring manuscript is submitted to the NIHMS **upon acceptance for publication.**
Who approves the submission? (Initial approval)	Publisher	Author, via NIHMS. NIHMS sends email notifications to author.
Who approves the PMC web version? (Final approval)	Publisher	Author, via NIHMS. NIHMS sends email notifications to author.
Who is responsible for ensuring compliance?	Author	Author

10.11.2 Deadlines to ensure compliance with NIH PAP by journal method

According to the NIH PAP, **NIH-funded manuscripts must be publicly available in PubMed Central (PMC) no later than 12 months following their official publication date to be compliant.** NIH PAP compliance requires adherence to deadlines that are dependent on the publisher's method of manuscript deposition into PMC. The method-dependent deadlines are as follows:

1. **Method A**: The publisher or journal has an arrangement with NIH to deposit the final published manuscript directly into PMC and provide approvals. **The publisher must make the article publicly available (without embargo) in PMC no later than 12 months after the official publication date**. Although the author is not involved in the deposition or approval processes, the author must confirm that the publisher meets the 12-month deadline.

2. **Method B**: The author arranges with the publisher to have them post the published article to PMC (usually for a fee) and provide approvals. **The author ensures the publisher deposits the manuscript and that it becomes publicly available (without embargo) no later than 12 months after the official publication date.**

3. **Method C and Method D:** Immediately upon acceptance, the author or the publisher deposits the accepted peer-reviewed manuscript (not the published version) into PMC via the NIH Manuscript Submission (NIHMS) system. **The author must verify that all steps occur in a timely fashion in Method C and Method D.**

An NIHMSID is assigned. An NIHMSID is a preliminary and temporary identifier that applies only to manuscripts deposited into PMC via the NIHMS system, and must be replaced by a PMCID. The process for receiving a PMCID includes the following steps:

- **Author or publisher** deposits the accepted peer-reviewed manuscript into NIHMS. NIH PAP requires that this step occurs upon acceptance for publication.
- **Author** completes initial and final approval in NIHMS. A publisher does not provide approvals in Methods C or Method D.
- The **National Library of Medicin**e assigns a PMCID when the approved web version has a corresponding citation in PubMed.

Deadlines under Method C and Method D are as follows:

- The manuscript must receive a PMCID within 90 days of receiving an NIHMSID to be compliant.
- The manuscript must receive a PMCID within 90 days after the official date of publication to be compliant.
- The manuscript must become publicly available (without embargo) no later than 12 months after the official publication date.

10.11.3 Author responsibilities based on journal methods

At the time of manuscript submission**,** the author must determine the method used by the publisher or the journal and follow the steps required for that method. The instructions provided in this policy are designed to help the author identify journal method and understand author actions that lead to compliance.

Alliance authors are responsible for ensuring that Alliance NIH-funded manuscripts become publicly available (without embargo)**_in PMC no later than 12 months_ after the official publication date.** Additional author responsibilities depend upon the method used by the publisher or journal to deposit the manuscript into PMC and are described below and in section 10.11.2.

10.11.3.1 Method A publishers and journals

These publishers and journals make the *final published version* of all NIH-funded articles available in PubMed Central (PMC) no later than 12 months after publication without author involvement. This may be at an NIH agreement level that requires the author to alert the publisher to NIH funding. The author should inform the publisher of NIH funding, since that information may be required. The author is not required to submit the final peer-reviewed manuscript into NIHMS upon acceptance.

Author action:

At the time of manuscript submission, the author must advise the journal publisher that the manuscript is supported by NIH funding and that it therefore falls under the NIH public access policy. Once advised, the publisher will assist the author with public access policy compliance by depositing the final published version of the manuscript directly into into PMC.

10.11.3.2 Method B publishers and journals

These publishers and journals have a selective deposit agreement with NIH to post individual *final published articles* in PubMed Central (PMC) on a case- by-case basis. They do not automatically post every NIH-funded paper in PMC. The submitting author must arrange with the journal at the time of submission to post the specific article; this usually involves selecting the journal's fee-based open access option for publishing that article. The Alliance does not reimburse the author for the fee.

Many Method B journals also offer the alternative

Method D, which is a free deposit of the final accepted peer-reviewed manuscript into NIHMS (Method D; see below).

If a Method B journal does not offer Method D and the author does not make any arrangement with the journal or publisher (with or without a fee) at time of

submission, *the author must deposit the manuscript through the NIHMS using Method C (see below for required author actions for Method C journals).*

Author action: **At the time of manuscript submission**, the author must advise the Method B journal publisher that the manuscript is supported by NIH funding and arrange for the publisher to post the final published article in PMC (with or without a fee). If the author chooses to not use the Method B option, and the publisher also offers Method D, the author should ask the publisher to post the final accepted peer-reviewed manuscript into NIHMS. The author must take this action for the publisher to handle steps for public access policy compliance. *If the publisher does not offer the Method D option, the author must submit the manuscript through the NIHMS (see required author actions for Method C journals).*

10.11.3.3 Method C publishers and journals

Method C publishers and journals do not assist the author with public access compliance. The author must deposit the final peer-reviewed accepted version of the manuscript into NIHMS upon acceptance by a journal. The author should complete action steps below as soon as the journal accepts the manuscript in order to allow sufficient time for completion of all steps involved in moving it toward PMC. If the manuscript is not in PMC within 90 days after the official publication date, the NIH considers the manuscript to be noncompliant.

Author actions: All steps are necessary for compliance

1. **At the time of acceptance the author should**
   Submit the final peer-reviewed accepted manuscript to NIHMS. Method C submissions can be started from within NIH My Bibliography.
2. **After submitting the manuscript to NIHMS, the author should**
   a. Advise the Alliance publications coordinator (by sending email to publications@AllianceNCTN.org) of the NIHMSID assigned to the manuscript.
   b. Approve the initial submission for processing in the NIHMS system when notified by NIHMS.

c. Link the paper to all Alliance grant(s) that directly supported it (indicated in the support section of the Alliance-approved version of the manuscript).
d. Review and approve the PMC-ready web version for inclusion in PMC after the submitted files have been converted, when notified by NIHMS.

Note: The assigned author will receive an email notifying him/her when action is required in NIHMS. NIHMSIDs expire after 90 days.

10.11.3.4 Method D publishers and journals

These publishers and journals have volunteered to deposit the *final accepted peer- reviewed manuscript* into NIHMS when the author advises them that it falls under the NIH Public Access Policy. The publisher has no agreement with PMC. Authors are responsible for ensuring that the manuscript is deposited (by the publisher or, if necessary, by themselves using Method C) into the NIHMS upon acceptance for publication.

If the manuscript is not in PMC within 90 days after the official publication date, the NIH considers the manuscript noncompliant.

Author actions:

1. **At the time of manuscript submission**, the author must advise the journal publisher that the manuscript is supported by NIH funding and arrange for the journal to post the final accepted peer-reviewed manuscript into NIHMS. This step is necessary for the publisher to assist the author with public access policy compliance.
2. **At the time of acceptance,** the author should confirm with the publisher that the manuscript will be submitted to NIHMS.
3. **After the manuscript is submitted to NIHMS the author should**
   a. Approve the initial submission for processing in the NIHMS system, when notified by NIHMS.
   b. Link the paper to all Alliance grant(s) that

directly supported it (indicated in the support section of the Alliance-approved version of the manuscript).

c. Review and approve the PMC-ready web version for inclusion in PubMed Central after the submitted files have been converted, when notified by NIHMS.

Note: The assigned author will receive an email notifying him/her when action is required in NIHMS. NIHMSIDs expire after 90 days.

10.11.4 Resources for NIH Public Access Policy

For questions concerning Alliance compliance with NCI Public Access Policy, contact publications@alliancenctn.org. A description of the process can be found at the Alliance website, in the study chair training portion.

Authors may also contact the NIHMS or PubMed Central help desks using the following URLs or e-mail addresses: NIH Public Access:https://sharing.nih.gov/public-access-policy NIHMS: nihms-help@ncbi.nlm.nih.govPubMed Central: pubmedcentral@ncbi.nlm.nih.gov

Training on an author's responsibilities in complying with the NIH Public Access Policy can be found at http://publicaccess.nih.gov/communications.htm and at http://www.nihms.nih.gov/help/#slideshow.

Answers to frequently asked questions are available at NIHMS FAQ.

10.11.5 Alliance Monitoring of Compliance with NIH Public Access Policy

The Alliance publications team reminds authors about policy and submission methods; monitors compliance and alerts authors of delays; and communicates with the responsible committee chair and the Publications Committee about the possibility or presence of non-compliance.

The publications team requests to be informed of the journal of interest

when an author sends a manuscript for Alliance Group review. When the team sends an e-mail to the author communicating Alliance approval of a manuscript, that e-mail contains information about the NIH Public Access Policy and submission methods that apply to the journal of interest. Authors are asked to advise the publications team if they intend to submit to a different journal so that the team can send new instructions.

Authors are required to advise the Alliance publications team (publications@AllianceNCTN.org) within one week after manuscript submission and within two weeks after manuscript acceptance; at both time points, the team reminds the author to follow the steps outlined in section 10.11.2. The team may assist authors with completion of required steps and with contacting publishers, journals, NIHMS and eRA Commons. On an ongoing basis, the publications team checks the status of assignment of NIHMSIDs and PMCIDs.

The publications team communicates with the author, committee chair, and Publications Committee about noncompliance. The Publications Committee chair or co-chairs correspond with other committee chairs and the Group chair, when necessary, to suggest action (see section Delinquency in Manuscript Preparation).

The publications team maintains the group's NCBI MyBibliography for all NIH-funded Alliance manuscripts.

Policy Name: Quick view of Alliance deadlines for authors	**Policy Number:** 10.12
Section: Publications – 10.0	**Date Revised:** December 16, 2024

10.12 Quick view of Alliance deadlines for authors

Type of publication	**Timelines**		
	Initial Author Deadline	Group Review Period	**Subsequent Author Deadlines**
Meeting abstract	*Send to publications coordinator:* 2 weeks prior to meeting submission deadline or per online schedule	3 days for scientific review 7 days for operations review during high volume periods	*Send to publications coordinator:* 1. Copy of submitted abstract within 1 week after submission 2. Acceptance email and PDF of published abstract no later than 2 weeks after available
Manuscript with no prior meeting abstract	*Send to publications coordinator:* 2 months after completion of the statistical summary report	7 days for scientific review	*Send to publications coordinator:* 1. If not approved, next draft within 4 weeks 2. Notification of submission and submitted manuscript within 1 week after submission 3. If not accepted, send new prospective journal information to publications coordinator 4. Acceptance letter and PDF of published manuscript no later than 2 weeks after available
Manuscript that follows a meeting abstract	*Send to publications coordinator:* 6 months after presentation at meeting	7 days for scientific review	*Send to publications coordinator:* 1. If not approved, next draft within 4 weeks 2. Notification of submission and submitted manuscript within 1 week after submission 3. If not accepted, send new prospective journal information to publications coordinator 4. Acceptance letter and PDF of published manuscript no later than 2 weeks after available
Alliance-approved manuscript submitted to journal	*Submit to journal:* Determine the journal's NIH Public Access Policy method to assure compliance with government policy if manuscript is accepted		
Accepted manuscript	Manuscript acceptance: If journal uses NIH Public Access Method C, or if author has not made submission agreement in Method B, submit manuscript to NIHMS and follow instructions in section 10.10		If journal submission Method C or D was used, or if author has not made submission agreement in Method B, provide the following in NIHMS, per sect. 10.10: Approval of submitted or posted materials (initial NIHMS approval) Approval of PMC web version (final NIHMS approval)
External study communications, if applicable	*Send to publications coordinator and communications specialist:* 1 week prior to press release	1 week	

Policy Name: Quick view of Alliance deadlines for authors	**Policy Number:** 10.12
Section: Publications – 10.0	**Date Revised:** December 16, 2024

Contact information

Alliance publications coordinator: publications@AllianceNCTN.org Alliance communications specialist: communications@AllianceNCTN.org

PubMed Central: pubmedcentral@ncbi.nlm.nih.govNIHMS: nihms-help@ncbi.nlm.nih.gov

Policy Name: Functions of Biospecimen Repositories	**Policy Number:** 11.1
Section: Biospecimen Repositories and Translational Research – 11	**Date Revised:** January 1, 2018

11 Alliance Biorepositories and Biospecimen Resource (ABBR) and Translational Research

11.1 ABBR Infrastructure and Oversight

11.1.1 The Alliance **ABBR** is comprised of five federated biorepository facilities located at four academic medical centers.

11.1.1.1 **Alliance Biorepository at the Ohio State University (OSU)**. Formerly known as the "CALGB PCO", this facility stores primarily fixed tissue and biofluids from legacy, CALGB solid tumor and lymphoma studies, as well as solid tumor and biofluid biospecimens from newer Alliance studies.

11.1.1.2 **Alliance Hematological Malignancy Biorepository (HEME).** Formerly known as the "CALGB Leukemia Bank", this facility also resides at The Ohio State University and stores specimens from patients with acute or chronic leukemia, myelodysplastic syndrome, or multiple myeloma who are enrolled on an Alliance protocol. HEME primarily receives blood and bone marrow specimens, and, in some cases, buccal smears.

11.1.1.3 **Alliance Lung Cancer Tissue Bank (LCTB).** The Alliance Lung Cancer Tissue Bank (LCTB) is located at the Brigham and Women's Hospital in Boston, MA. The purpose of the LCTB is to collect, catalog and store frozen samples of lung carcinoma and when possible, portions of involved lymph nodes and adjacent uninvolved lung tissue obtained from previously untreated patients. In addition to tissue specimens, blood samples are also collected pre- and post-resection from the patients to provide a source of quality DNA, RNA and protein for molecular studies.

11.1.1.4 **Alliance Biorepository at Washington University in St. Louis** (**WUSTL**). Formerly known as the "ACOSOG Specimen Bank" this CAP-accredited facility collects and stores frozen and fixed tissue, and biofluids from breast, lung, GI, and other solid tumor Alliance trials.

11.1.1.5 **Alliance Biorepository at Mayo Clinic (MAYO).** Formerly known as the "NCCTG Biospecimen Resource", this second CAP-accredited facility processes and stores biospecimens associated with neuro-oncology studies, and is also the designated repository

for processing and storing biospecimens associated with Alliance NCORP studies.

11.1.2 Biospecimen tracking, reporting, and inventory management is integrated across all biorepository sites and centrally coordinated at the WUSTL biorepository, through the use of the Alliance BioMS biospecimen management tool.

11.1.3 Although each biorepository site maintains its own local set of policies and standard operating procedures to comply with institutional requirements, those individual site policies specifically pertaining to Alliance trial biospecimen integrity and management are harmonious and meet the minimal standards set forth in this document.

11.1.4 The ABBR is supported by a National Cancer Institute (NCI) U24 funding mechanism. Each of the Alliance biorepository leaders at the four academic institutions serve as a co-Principal Investigator (PI) on the U24 grant, with the WUSTL bank director currently serving as contact PI.

11.1.5 One or more of the ABBR U24 grant PIs also serves on the Alliance Translational Research Program (TRP) Executive Committee and the Alliance Executive Committee. These appointees are charged with ensuring that the ABBR serves the needs of the NCTN Alliance network.

11.1.6 Three of the ABBR U24 grant PIs (or their designees) also serve on the NCTN Group Banking Steering Committee (GBC). The GBC is charged with developing and adopting harmonized policies and practices across all NCTN biospecimen resources.

11.1.7 The TRP Executive Committee is primarily responsible for oversight of compliance of the Alliance repositories with Alliance and NCI policies regarding specimen collection and distribution. In addition, this committee is responsible for ensuring that the repositories follow the NCI guidance document "Best Practices for Biospecimen Resources" that was published and updated in 2011. Each Alliance biorepository site will undergo periodic audits to ensure compliance with the NCI Best Practices (http://biospecimens.cancer.gov/practices) and oversight for the audits will be a function of the TRP Executive Committee.

11.1.8 The Alliance Translational Research Program (TRP), the TRP biorepository sub-committee, study chairs and correlative science co-chairs, individual disease/modality/discipline committees (usually the vice-chair of the

disease/modality/discipline in charge of translational research) are jointly responsible for: (1) determining biospecimens that should be collected on each Alliance trial and the appropriate methods for collection and processing of those biospecimens and (2) ensuring that the ABBR sites have the appropriate quality control and quality assurance procedures in place for biospecimen handling, processing, storage and distribution.

11.1.9 As the Alliance steward of biospecimens, each biorepository director agrees to procure, store, process and distribute the specimens according to Alliance and NCI policy. In addition, if the biorepository does not comply with Alliance policy, the Alliance can move the biospecimens to another approved Alliance location.

11.2 Biorepository Functions

The ABBR serves a number of important functions in the context of NCTN Alliance clinical trials. These roles include, but are not limited to:

11.2.1 Biospecimen Collection. The ABBR may design, construct, and distribute supplies and 'kits' to facilitate biospecimen collection from remote sites. It is the responsibility of the ABBR to ensure that the design of such materials maintain biospecimen integrity during collection and transport while minimizing cost and logistical complications at the clinical site. The ABBR is also responsible for prospectively tracking and reporting on biospecimen collection activities for all Alliance clinical trials and when necessary, work with other Alliance team members to resolve systematic hindrances with biospecimen collection.

11.2.2 Storage. The ABBR is responsible for storing all biospecimens collected on NCTN and NCORP Alliance trials using methods that optimally preserve biological integrity and ensure biospecimen security.

11.2.3 Processing. The ABBR may be responsible for initial processing of tissue and biofluid specimens to a stable state for long-term storage. This may include centrifugation and/or separation of blood components and processing or embedding of tissue samples. At the discretion of each ABBR biorepository PI, the trial-associated biorepository site may develop and validate specialized processing methods to support specific trial procedures. An ABBR site may also perform secondary processing procedures, such as nucleic acid extraction, tissue sectioning, or tissue microarray (TMA) construction in order to create 'assay ready' materials that may be distributed for correlative science studies.

11.2.4 Quality Assurance. The ABBR is responsible for conducting or facilitating the conduct of quality assurance procedures for all collected biospecimens. This includes documenting physical quality of all specimens received, ensuring that proper biospecimen identification is preserved, facilitating histopathology review of tissue specimens when necessary, and ensuring that all material leaving the biorepository is fit for purpose and of suitable quality for all studies planned with those biospecimens.

11.2.5 Regulatory Compliance. The ABBR is the custodian and 'honest broker' of all biospecimens collected from patients enrolled on Alliance clinical trials. The ABBR ensures that biospecimens are appropriately de-identified and utilized for scientific studies that are commensurate with the corresponding patient informed consent.

11.2.6 Distribution. The ABBR works with other components of the Alliance to facilitate the review and distribution of biospecimens for correlative science studies.

11.2.7 Direct submission. For all Alliance trials, the ABBR should be the primary resource for all biospecimen collection, processing, and storage activities. In some cases, however, it may not be desirable or feasible to have biospecimens sent or processed by the ABBR. In these cases, with permission from the Director of Translational Research Operations and/or the Principal Investigator of the Alliance Translational Research Program, biospecimens may be sent directly to an investigator or commercial laboratory. However, even in such cases the investigator or commercial laboratory must follow all policies and procedures related to Alliance biospecimen tracking and handling (as outlined in this document). Furthermore, all biospecimens still remain under the custodianship of the ABBR and any remnant specimens must be returned to the ABBR at the completion of the assay. Examples include:

11.2.7.1 Assay requires rapid processing of fresh biospecimens using a technology or platform that is not available at the ABBR.

11.2.7.2 Assay is consumptive of the entire biospecimen and no material would remain for banking or future use anyway.

11.2.7.3 Assay is an integral biomarker assay that must be performed in a clinically accredited clinical laboratory and/or with rapid turnaround time, following clinical standards of biospecimen identity management and chain of custody.

11.2.8 Depending upon the specific trial design, the ABBR may support biospecimen activities for three different study types as defined by the NCI, the NCTN, and the Alliance. Each activity may be supported by a different funding mechanism, as explained below.

11.2.8.1 Integral Biomarker Studies. Studies in which biospecimens are mandatory and collected to perform an assay (or pathology review) in 'real-time' for the purposes of determining patient eligibility, arm assignment, or stratification. As noted above, biospecimens collected for integral biomarker studies may be sent directly to the relevant assay lab. However, once the biomarker assay is complete, unused biospecimens must be sent to the ABBR for other embedded or secondary use studies, unless determined otherwise by the ABBR director.

11.2.8.2 Integrated (Embedded) Correlative Studies. Studies in which biospecimens are collected to perform a well described, pre-defined correlative biomarker study that may be a secondary or tertiary end point of the trial itself. Collection may or may not be mandatory. With appropriate consent, remnant biospecimens from integrated correlative studies may be stored and used for stand-alone secondary correlative science studies.

11.2.8.3 Biobanking for Stand-alone Secondary Correlative Studies. Collection of biospecimens in the absence of a specific study that is described in the trial protocol itself, but that may be stored and made available for future studies proposed by investigators within or outside of the Alliance or the NCTN groups.

11.2.9 In addition to facilitating biospecimen collection for Alliance clinical trials, the ABBR may serve as a biorepository site for any NCTN intergroup trial, even if the Alliance is not the 'lead group' for that trial. As described below, support for intergroup trial biobanking activities must be pre-arranged prior to trial activation.

11.3 Biospecimen Collection Funding

A number of different funding mechanisms support ABBR activities. Funding is dependent upon the trial and the nature of the activity.

11.3.1 NCI U24 Biorepository Funding. The Alliance U24 biorepository grant is designed to support the staff and resources necessary for basic biorepository operations that include routine biospecimen processing, biospecimen storage, biospecimen information management, and administrative functions. Activities that are NOT supported by U24 funding include:

11.3.1.1 Design, manufacturing, and shipping of specialized biospecimen procurement kits.

11.3.1.2 Procedures related to biospecimen procurement at the site.

11.3.1.3 Biospecimen shipping.

11.3.1.4 Specialized biospecimen processing.

11.3.1.5 Pathologist time for central pathology review to confirm diagnosis.

11.3.1.6 Extraction of nucleic acids, or other secondary biospecimen processing.

11.3.2 Clinical Trial Budget. For some trials where biospecimen collection, processing, or pathology review is integral to the trial itself, these expenses may be primarily part of the trial budget and supplemented by U24 biorepository funding where appropriate. Otherwise, funding may be obtained from other sources noted below.

11.3.3 BIQSFP. The NCI BIQSFP mechanism may be used to support the conduct of integral and/or integrated biomarker studies as well as the expense of biospecimen procurement, shipping, and processing to conduct those studies. This funding mechanism will not support collection of biospecimens for other correlative studies or biobanking purposes.

11.3.4 Non-NCI Funding. Funding from other non-NCI sources (e.g. Komen Foundation, DOD, Breast Cancer Research Foundation), if obtained, may be used to support the construction and distribution of specialized biospecimen collection kits, reimbursement for research biospecimen procurement procedures, and specialized processing at the ABBR, when needed.

11.3.5 Research Grants (Federal and Non-federal). Investigators requesting biospecimens for either embedded / integrated correlative science studies or secondary use studies should anticipate that there will be nominal costs associated with the preparation (i.e. TMA slides, nucleic acid extraction, tissue quality assurance review) and distribution of biospecimens for funded research projects. These should be supported by research grant budgets, with expenses returned to the appropriate ABBR site to help support operations.

11.3.5.1 Costs for secondary processing of biospecimens for research studies will be charged by each ABBR site. Charges will be dictated by individual ABBR site policies.

11.3.5.2 Additionally, for secondary use studies, a standardized 'application' and/or 'processing fee' may be charged, in keeping with NCI NCTN policies.

11.3.6 Prior to any trial activation, an appropriate and sufficient funding source(s) should be identified to support all aspects of required biospecimen-related activities, from procurement to distribution. Funding resource(s) for integral biomarker must be secured prior to study activation.

11.4 Correlative Science and Biospecimen Collection Protocol Development

11.4.1 Proposals to utilize the specimens collected in a prospective trial ideally should be included in the clinical trial protocol concept at the time it is submitted to the Alliance Study Concept Review Committee. An appropriately powered, foreseeably funded, biospecimen-based correlative science study with a strong biological and/or clinical rationale may be included as a secondary end-point of the trial itself and will not need further review or approval once it has been approved in the context of the trial itself.

11.4.2 Once an NCI-approved trial concept moves to protocol development phase, stakeholders from the TRP Pathology Committee and/or TRP Biorepository Committee should begin immediate work with the Alliance Offices, disease/modality/discipline committee, Alliance Statistics and Data Center, Trial study chair(s), and Correlative Science co-chair(s) to develop the integral /integrated / biobanking study plan and biospecimen collection logistics.

11.4.3 Investigators performing laboratory studies may serve as study chairs of Alliance correlative science companion trials.

11.4.4 All embedded correlative science (CS) research requires review and approval by the disease/modality/discipline committee and TRP prior to submission of the main study to the NCI for final protocol approval. Subsequent review of the embedded CS research may be also required by the Alliance biorepository and disease/modality/discipline committee CS vice chairs during the protocol development process. Additional review of other relevant Translational Research Program sub-committees, such as Pathology Committee, Imaging Committee, Pharmacogenomics and Population Pharmacology Committee, Sequencing Committee may also be required for some studies.

11.4.5 Collection time points and biospecimens to be collected at each time point will be defined in a biospecimen collection calendar. Considerations in developing the correlative science and biospecimen collection plan include:

11.4.5.1 Biospecimens that are required for planned integral / integrated biomarker studies.

11.4.5.2 Low cost, minimally invasive collection opportunities (ideally synchronized with collections required for integral / integrated biomarker studies or standard of care) that can be leveraged to create a trial-based biospecimen resource for future correlative science studies.

11.4.5.3 Biospecimens, collection methods, and collection time points that minimize cost and simplify the logistics of collection, shipping, and processing.

11.4.6 Protocols that include a "research use only" biopsy must specify eligible biopsy location(s), methods and number of cores must be defined, along with other protocol specific requirements. Source(s) of funding for research tissue collection must be identified (see section 11.3).

11.4.7 Protocols that require extensive specimen sampling or processing, non-standard specimen collection time point, or the use of "kits" must be reviewed and approved by the TRP Operation Director and the ABBR director. Source of funding for any "kits" or special collection materials must be identified (see section 11.3).

11.4.8 Protocols that require central pathology review require approval by the TRP Operation Director and Pathology Committee. Source(s) of funding for real time central pathology review must be identified (see section 11.3).

11.4.9 Protocols that require central imaging review require approval by the TRP Operation Director, Imaging Committee and Imaging and Radiation Oncology Core lab (IROC). Source(s) of funding for real time central pathology review must be identified (see section 11.3).

11.4.10 Protocols that require international specimen shipping must be reviewed and approved by the TRP Operation Director and the ABBR director. Sources of funding for international specimen delivery must be identified (see section 11.3).

11.4.11 Although not required, it is strongly recommended that the study chair contact the TRP Operation Director, TRP Executive Officer, the ABBR director, and the appropriate disease committee CS co-chairs, the disease pathology cadre leaders, the disease Imaging Committee liaison, or other relevant TRP subcommittees, if applicable, prior to study concept submission to the SCRC.

11.4.12 Amendments to the main study wherein the embedded CS research is modified require review and approval by the main Study Chair, Correlative Science Study co-Chair, study statistician, and TRP Operation Director. If these changes involve modification to the standard protocols for biospecimen collection, processing, or shipping, then review and approval is also needed from the ABBR director. If these changes involve modification to the standard protocols

for imaging collection or processing, then review and approval is needed from the Alliance Imaging Committee and/or IROC.

11.4.13 Once a biospecimen collection schedule is created and approved by all stakeholders, a budget will be created. Based upon the cost and the parameters discussed in section 11.3 Biospecimen Collection Funding, appropriate funding must be identified.

11.4.14 The ABBR site that will support biospecimen collection for a trial will be determined by the ABBR director, with approval from the corresponding ABBR site director. Considerations for choosing the ABBR site include:

11.4.14.1 Existing site capacity and resources to manage a new collection.

11.4.14.2 Need for central pathology review or other correlative science support. To minimize shipping costs and logistical complications, trials where pathology support or correlative study assays will be provided by an institution that is also an ABBR site should also use that site for biobanking.

11.4.14.3 Biospecimens from neuro-oncology and Alliance cancer control program trials will be preferentially banked at the MAYO site.

11.4.14.4 Biospecimens from hematological malignancy trials will be preferentially banked at the HEME site.

11.4.15 Sites with logistical inability (e.g., sites outside the continental U.S.) to collect, process and ship specimens according to the protocol must apply for a waiver for exemption with the Alliance Protocol Operations Office, the Alliance TRP, the Alliance Statistics and Data Center (SDC), the study chair and the disease/modality/discipline committees. An administrative memorandum stating the shipping issue(s) and any protocol violation(s) from the site must be approved and filed with Protocol Operations through the assigned Protocol Coordinator prior to study activation. Collection, processing and shipping instructions for these sites will be provided on a study-by-study basis by the assigned biorepository.

11.5 Biospecimen Collection Policies

11.5.1 Each trial protocol document or associated Correlative Science Manual (CSM) must specify how to collect, prepare and ship specimens to the appropriate ABBR site. Questions regarding the collection and/or shipment of the materials should be directed to the assigned biorepository site where the specimen is being sent.

11.5.2 Each trial protocol or CSM document will follow a standard set of protocols (SOPs) for biospecimen collection, shipping, and processing.

11.5.3 All sites are required to send protocol-mandated biospecimens to the appropriate ABBR site, providing that appropriate patient consent is obtained and it is physically possible to send such biospecimens.

11.5.4 In cases where institutional policy prohibits the release of clinical pathology tissue blocks, an enrolling site may receive permission to submit a tissue block alternative (such as unstained slides or a tissue punch from the block) provided that permission is granted by the TRP Operations Director and trial study chair(s) and study co-chair(s). Note that for some protocols, submission of a tissue block may be absolutely required for participant enrollment.

11.5.5 ABBR biorepository sites themselves are not clinically-accredited medical laboratories. Therefore, any biospecimen processing that must be performed by a clinically accredited analytical laboratory (e.g. for integral biomarker testing or return of individual patient results) should not be performed by the Alliance biorepository. The Alliance biorepository is allowed to receive and store slides for retrospective histopathology review. All local diagnostic slides submitted for histopathology review can be returned to submitting sites upon request.

11.5.6 All specimens shipped to Alliance repositories must have patient consent and be accompanied by the appropriate paperwork as outlined in the protocol (e.g. forms, pathology report, etc.).

11.6 Biospecimen Processing and Storage Policies

11.6.1 For diagnostic clinical pathology tissue specimens that have been submitted to any Alliance repository, the appropriate representative sections and/or cores will be prepared and the block will remain on file and will be available to the submitting institution for any medical-legal need.

11.7 Biospecimen Reporting and Tracking

11.7.1 All biospecimens submitted by sites are tracked by a database system (the Biospecimen Management System—BIOMS). Any exception must be granted by the ABBR director.

11.7.2 Each specimen submitted must be accompanied by the appropriate paperwork, as required by the protocol. Local records are kept in addition to the database. Local records will be secured in a locked cabinet/office at all times and database security will follow that recommended by the Alliance Statistics and Data Center (SDC).

11.8 Patient Consent, Confidentiality, and Regulatory Compliance

11.8.1 Patient consent for studies must be obtained prospectively. Consent forms must include adequate information to assess risks.

11.8.2 For trials that involve integral biomarker assessment to determine eligibility or treatment stratification, biospecimen submission for the integral biomarker assay is mandatory from all sites and all patients. All non-integral embedded correlative science requiring specimen submission must be offered to all patients enrolled on the study, although patients may opt not to participate. Therefore, specimen submission for non-integral correlatives, in general, is optional for the patient but not optional for the site. Exceptions to site participation in specific embedded correlative science studies may be granted by the study chair(s), in consultation with the corresponding correlative sciences co-chair(s) and the Translational Research Program Principle Investigator, in circumstances when the requisite resources or other infrastructure are not available at that site. In some rare instances, non-integral specimens can be mandatory for patients to participate after the group chair and/or the principal investigator of the Translational Research Program grant permission.

11.8.3 In the case of future (secondary use) studies that will use biospecimens collected for an Alliance clinical trial, including germ line susceptibility studies (studies of heritable genes), participants are asked to grant broad permission (i.e., it is unknown exactly what tests might be appropriate or performed in the future at the time the specimen is banked). Participants will NOT be re-contacted for each individual study.

11.8.4 Previously banked material that was not originally intended for extensive DNA studies (e.g., whole genome sequencing, whole exome sequencing, and genome-wide association studies) and for which informed consent was not originally obtained may be used for such research, but in these cases whether a re-consent must be obtained from the participant at the institutional level or not will be determined by the Alliance Ethics committee. For deceased patients, where re-consent is not practicable, whether a waiver of consent must be obtained at the institutional level or not will also be determined by the Alliance Ethics committee.

11.8.5 A unique Alliance biospecimen identification number will be assigned to each biospecimen submitted to Alliance Biorepositories. At the Alliance biorepositories, biospecimens must be stored and distributed with this number only. Investigators may not receive any patient identifiers, only the unique

biorepository specimen number. However, this may not apply to biospecimens sent directly to an investigator or commercial laboratory (see section 11.2.7).

11.8.6 Only authorized biorepository personnel may have access to match the unique sample ID with the Alliance patient ID number and only authorized Alliance statisticians may have the ability to link the unique specimen ID number, patient information, and clinical outcome. Exceptions must be approved by the principal investigator of the Translational Research Program and the group statistician for the Alliance.

11.8.7 If a registered patient withdraws consent from treatment but agrees to be followed on protocol, biospecimens may be submitted as required by the protocol.

11.8.8 If a registered patient withdraws consent for participation in the study or consent for follow-up, biospecimens may not be submitted.

11.8.9 If biospecimens have already been submitted but not distributed to investigators at the time when the patient withdraws consent, those biospecimens will be withdrawn from the repository and will be disposed of appropriately – either destroyed or, in the case of tissues, returned to the submitting institution upon request. Attempts will be made to retrieve any specimens that have been sent from the repository to investigators. However, processed specimens and the research data generated from them will not be rescinded, and may be used in study analyses.

11.8.10 Biospecimens are not released from the repository to investigators until the Alliance statistician assigned to the study or designee confirms the record of patient consent in the Alliance database. If a specimen is present in the repository but is later found to not have the appropriate patient consent, the specimen will be withdrawn from the repository and will be disposed of appropriately – either destroyed or, in the case of a diagnostic clinical pathology tissue blocks, returned to the submitting institution.

11.8.11 It is the Alliance policy that the Alliance biorepository shall not release clinical, pathology reports submitted by sites to correlative science investigators. Requests for data elements collected from local pathology reports should be submitted to the Alliance Data Center. This rule does not apply to study pathologists performing retrospective central reviews.

11.8.12 Disagreement between investigators and statisticians with respect to consent language for specific analyses will be adjudicated and decided by Alliance ethics leadership, statisticians, and the translational research program.

11.8.13 Reports (including manuscripts, abstracts, and progress reports) may never list any patient by name or initials. If needed, only unique identification codes may be used.

11.8.14 Unless indicated in the protocol and performed in a CLIA-certified laboratory, results from correlative science studies may not be provided to the patient or physician. Upon request, information may be made available as aggregate data in the form of abstracts or manuscripts.

11.8.15 The Alliance maintains Certificates of Confidentiality for each of its repositories from the US Department of Health and Human Services (HHS), which protects against the involuntary release of information collected during the course of the study. The researchers involved in a project may not be forced to identify a patient in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state, or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the HSS, or for purposes of program review or audit.

11.8.16 For biospecimens sent directly to an investigator or commercial laboratory, certain Protected Health Information (PHI), such as patient initials and collection dates, may be sent to the investigator/commercial laboratory along with the biospecimens. In those cases, the trial protocol and informed patient consent form will inform sites and patients of any potential regulatory considerations.

11.9 Biospecimen Pathology Review

11.9.1 In no cases will the Alliance or an Alliance study pathologist render a clinical diagnosis. It is assumed that the submitting institution and the appropriate institutional pathologist will have rendered a clinical diagnosis in a way that is most appropriate for standard of care for the patient, prior to submission. In particular, fresh, 'research only' biopsy specimens will not receive a clinical diagnosis from an Alliance pathologist. If it is deemed necessary to make a histopathologic diagnosis of a biospecimen collected from a patient with an uncertain diagnosis (e.g., a metastatic lesion of a presumptive but unconfirmed primary origin), then it is incumbent upon the institution to perform any necessary diagnostic evaluation prior to submitting the biospecimen to the Alliance, even if the trial will perform a central pathology review.

11.9.2 In any case involving an apparent significant discrepancy between an observation made by an Alliance study pathologist and a diagnosis rendered at the submitting institution, the Alliance pathologist takes the following steps to determine the nature of the problem:

11.9.2.1 The study pathologist will verify the case identifiers. If the case was submitted to the Alliance biorepository for retrospective central diagnosis confirmation, the study pathologist will notify the biospecimen repository regarding the potential diagnostic discrepancy in the case. If the problem is clerical (e.g., incorrect specimen submitted to or distributed from the biorepository), the study pathologist and/or repository rectifies the problem directly with the submitting institution through Alliance institutional personnel (e.g., the institutional clinical research professional).

11.9.2.2 If it is determined that all case identifiers are correct, the Alliance study pathologist will contact the institutional clinical research professional (CRP) and, if necessary, will arrange to contact the submitting pathologist. The Alliance study pathologist will discuss the case with the submitting pathologist and detail the findings and the need for a re-review by the submitting institution. The Alliance study pathologist will discuss with the responsible institutional CRP and/or submitting pathologist whether other/additional pathologic materials from that case exist that might explain a discrepancy. Any problems related to case identification, specimen selection, or additional diagnostic information or materials will be discussed and resolved, if possible, by this direct communication,

and the nature of the resolution will be communicated to the repository by the study pathologist.

11.9.2.3 If an apparent discrepancy still exists, the appropriate Pathology Committee leader and at least one other committee member will review the case to confirm the diagnostic discrepancy. It is highly recommended that the study pathologist, the pathology committee leader and the submitting pathologist discuss the case directly before the final confirmation of discrepancy.

11.9.2.4 If the discrepancy is confirmed, the study pathologist or the chair of the Pathology Committee will immediately report the correct diagnosis to the responsible data coordinator. The data coordinator will report the correct diagnosis to the clinical research professional at the submitting institution. It is the responsibility of the clinical research professional to notify the submitting pathologist and the physician who registered the patient that there is a difference in diagnosis. The Alliance SDC will consider the discrepancy in the final analysis of the study.

11.10 Accessing Banked Biospecimens Overview

11.10.1 An Alliance membership is not required to request Alliance specimens.

11.10.2 Samples are furnished to the investigator by the appropriate Alliance specimen repository for the purpose of the project as approved. Research must be limited to that described in the approved protocol. Investigators may not share any portion of specimen or derivative specimen with another investigator or lab without permission of the NCI and the Alliance.

11.10.3 Investigators must discuss return of all unused specimens to the Alliance specimen repository prior to the completion of their correlative study. This includes RNA, DNA, urine, plasma, serum, tissue, slides, unstained sections, etc.

11.10.4 When investigators request specimens for nucleic-acid based (RNA / DNA) studies, it is the policy of the ABBR that whenever possible, only nucleic acid derivatives aliquots prepared by the ABBR will be distributed to the investigators. Exceptions can only be made with approval from the ABBR director.

11.10.5 No diagnostic, clinical pathology tissue blocks shall be released to research investigators. In general, no research blocks shall be released to research investigators either. However, exceptions for research block release may be granted by the ABBR director.

11.10.6 Once the project is approved, the investigator will be responsible for ensuring that his/her research is conducted under regulatory policies (human subjects, intellectual property, material transfer) governing their individual institution, as well as those set forth by the Alliance/NCI.

11.10.7 Correlative science investigators are required to have funding for their projects prior to receiving specimens.

11.10.7.1 In order to facilitate the successful application for funding, the Alliance will review concepts without established funding. For this review, investigators must provide the information requested for a preliminary concept review. In order to receive a letter of support from the Alliance, interested investigators must provide a preliminary concept at least six weeks prior to the grant deadline. Exceptions to this rule have to be approved by the principal investigator of the Translational Research Program.

11.10.7.2 Approved preliminary concepts, must include a description of the collaboration with the Alliance in their proposal submission and they must comply with the Alliance guidelines, which have been written to ensure scientific integrity, patient confidentiality, specimen protection, and support of the Alliance infrastructure resources.

11.10.7.3 Any collaboration with the Alliance that impacts Alliance resources, including protocol development, data management, statistical analysis, and specimen banking may require additional funding support. In addition to funds to support laboratory science (supplies, equipment, personnel, etc.), investigators may also be required to establish contracts and agreements with the Alliance, and/or subcontracts with the different resource offices of the Alliance being used, including the following:

11.10.7.3.1 Alliance Group Chair's Office

11.10.7.3.2 Statistics and Data Center (for data management and statistical support)

11.10.7.3.3 Any relevant biorepository (for sample preparation and distribution, etc.)

11.10.8 Subcontract arrangements must be performed in accordance with Alliance policy and submitted in advance to ensure appropriate time is given for review and sign-off. A final copy of the grant must be submitted to and approved by the Alliance before submission to the granting agency.

11.11 Stand-alone Secondary Biospecimen Use Studies

11.11.1 Any proposal to utilize biospecimens from an Alliance NCTN study will be reviewed by the NCI NCTN Core Correlative Science Committee (CCSC) through a process managed by NCI. NCI NCTN-CCSC is charged with scientific review & prioritization of proposals requesting use of banked, non-reserved biospecimens collected from NCTN trials for use in correlative science studies. NCTN-CCSC prioritization ensures optimal use of these irreplaceable clinical trial biospecimens.

11.11.2 All correlative science investigators must agree to use the specimens for only the NCI NCTN-CCSC-approved research project and to follow Alliance and NCI policies and procedures. Investigators will be charged for all services that the biorepository provides (see 11.3)

11.11.3 Submission to the Alliance Translational Research Program for approval is strongly encouraged, but not required to obtain specimens from Alliance NCTN studies. A letter of support will be provided for the proposals endorsed by the Alliance.

11.11.4 A correlative science proposal should be based on an innovative idea, built around a strong biologic hypothesis including preliminary data supporting the hypotheses and/or feasibility, be scientifically valid and have significant clinical relevance. The investigator must demonstrate expertise, both technical and scientific, relevant to the work proposed. Therefore, previous publications in the area and/or preliminary data are required. Preliminary data are also required to evaluate the scientific rationale and logistics of the concept, the performance characteristics of the assay(s) to be employed (including accuracy compared to a gold standard, reproducibility, variability, and/or other available analytic validation), and to demonstrate clinical relevance.

11.12 Data Generation, Ownership, and Publications

11.12.1 Data from all laboratory tests performed on samples from any Alliance repository will be submitted to the Alliance SDC, usually via electronic means. The analysis of the data will be conducted by the responsible Alliance statistician or designee with the necessary expertise. The designee must be approved by the principal investigator of the TRP and the group statistician. The group statistician must approve any exception to this rule.

11.12.2 All publications must be reviewed and approved by the Alliance, following guidelines in the Alliance Policies and Procedures. The grant support of the appropriate Alliance repository will be acknowledged in publications.

Policy Name: Agent Accountability and Procurement	**Policy Number:** 12.1
Section: Investigational Agents – 12	**Date Revised:** December 16, 2024

12 Investigational Products

In Alliance studies, any product that is provided to institutions is considered "investigational" for purposes of this policy. For investigational products used under an IND or IDE, the IND/IDE holder is either the NCI or Alliance. Investigational products may be provided by NCI/CTEP or directly by the industry partner. Investigational products may be distributed to the institutions by NCI, industry, or a third-party distributor. The Alliance generally follows PMB policies (https://ctep.cancer.gov/branches/pmb/default.htm) and CTEP investigator guidelines (https://ctep.cancer.gov/investigatorresources/investigators_handbook.htm) for all IND/IDE investigational products, irrespective of the IND/IDE holder.

12.1 Investigational Agent Accountability and Procurement

12.1.1 National Cancer Institute (NCI) Investigational Agents

Investigators must have current investigator registration documents (FDA Form 1572, Financial Disclosure Form, HSP/GCP training, biosketches, Agent Shipment Form, and CV on file with the NCI in order to receive investigational agents. These registrations must be renewed annually. Registration must be completed via the NCI Registration and Credential Repository (RCR). Additional information regarding registration types and required documentation is available at the Cancer Therapy Evaluation Program (CTEP) website (https://ctep.cancer.gov/investigatorresources/).

Investigational agents provided or distributed by the NCI are ordered through the Pharmaceutical Management Branch (PMB) Online Agent Order Processing (OAOP)-AURORA application. Access to the OAOP system requires a CTEP Identity and Access Management (IAM) account and the maintenance of an active account status and a current password. Users must complete the ID.me authentication and link the ID.me credential to their CTEP-IAM accounts.

NCI distributes investigational agents for which it holds the IND and may also distribute investigational agents, either Alliance-held IND or IND exempt, provided by industry.

12.1.2 Investigational Agents distributed by the Alliance

Instructions for ordering agents distributed by the Alliance or third-party distributors vary from study to study, and can be found in the Drug Information section of the protocol. The specific order form required to ship drug to an institution is described in the protocol.

12.1.3 Shipment of investigational agents

Multiple pharmacy addresses may be listed on the Agent Shipment Form. By providing accurate shipping information this will assure that the FDA regulations are being followed, along with decreasing investigational agent shipping delays and expense and ensures accountability.

Investigational agent(s) will only be shipped to the designated pharmacies of the investigator who is ordering the agent. Alternatively, investigators at affiliate institutions may order agents directly from PMB and not through their main member institution.

PMB policy allows centralized pharmacies to receive investigational agents for re-distribution to local satellite institutions and affiliated investigators who are registered with PMB and have designated a "central pharmacy" as their shipping address. If investigational agent is ordered through the main member institution, then the agent can be couriered to the satellite location if necessary. When agents are transported between control and satellite locations, care must be taken to ensure all appropriate storage conditions are maintained.

In the instance of investigators who staff more than 1 location, investigational agent(s) should be ordered to the central pharmacy where the patient will be receiving the investigational agent.

PMB policy also forbids secondary distribution of investigational agents to physicians who are not listed on the Delegation of Tasks Log (DTL) or transfer of investigational agents between institutions or other sites. Shipment of agents directly to patients is allowed as described by the CTEP Oral IND Agent Shipment Guideline/Alliance Oral IND Agent Shipment Guideline.

12.1.4 Use of Investigational Agents

Investigational agents must be used only in accordance with the protocol and only for patients registered on the study. Investigators must not charge for or seek reimbursement for investigational agents.

Commercial agents may not be substituted for an investigational agent nor can an investigational agent be used to "pay back" or "replace" commercial supplies.

The Alliance audits the pharmacy according to the NCI Guidelines for Auditing Clinical Trials (CTMB Guidelines) section 5.3 (https://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring.htm).

Compliance with investigational drug use and accountability procedures is reviewed at the time of Alliance audits and will result in the pharmacy audit being rated as critical non-compliant, non-compliant, compliant or not reviewed. A rating of critical non-compliant will automatically result in an Unacceptable audit rating for Drug Accountability and Pharmacy. Any Unacceptable rating will require a re-audit within 12 months.

Auditors review investigational agents provided by industry partners according to the same procedures used for agents provided by NCI.

12.1.5 Storage and Accountability of Investigational Agents

A pharmacist or designated individual is responsible for investigational drug ordering, storage, dispensing and accountability. All study site personnel responsible for investigational agent(s) accountability must be listed on the Delegation of Tasks Log (DTL). The appropriate NCI Drug Accountability Record Form (DARF) should be used to record the receipt and disposition of all drugs supplied (by the NCI or pharmaceutical companies) for Alliance protocols. Specific procedures for completing DARFs and policies for storage and accountability are available on the PMB website. Guidelines are also available in the CTEP Investigator's Handbook.

12.1.6 Deviation from Study Protocol

The appropriate Alliance protocol resource must be contacted if the handling or dispensing of the investigational agent(s) deviate from the protocol instructions. The deviation must be reported to the CIRB or IRB of record, documented in a note-to-file, and retained in the records of the site.

12.2 Investigational Devices Accountability and Procurement

12.2.1 Investigational Devices Distributed by the Alliance

Instructions for ordering devices distributed by the Alliance or third-party distributors vary from study to study, and can be found in section 10.0 of the protocol. The specific order form required to ship device to an institution is described in the protocol.

12.2.2 Shipment of Investigational Devices

Investigational device(s) will only be shipped to the designated shipping addresses on the Agent Shipment Form of the investigator who is ordering the device.

Investigational device may be ordered through the main member institution, then couriered to the satellite location if necessary. When devices are transported between control and satellite locations, care must be taken to ensure all appropriate storage conditions are maintained.

In the instance of investigators who staff more than 1 location, investigational devices(s) should be ordered to the facility where the patient will be receiving the investigational device.

12.2.3 Use of Investigational Devices

Investigational devices must be used only in accordance with the protocol and only for patients registered on the study. Investigators must not charge for or seek reimbursement for investigational devices.

Commercial devices may not be substituted for an investigational device nor can an investigational device be used to “pay back” or “replace” commercial supplies.

The Alliance audits the pharmacy or designated facility according to the NCI Guidelines for Auditing Clinical Trials (CTMB Guidelines) section 5.3 (https://ctep.cancer.gov/branches/ctmb/clinicalTrials/monitoring.htm). Any Unacceptable rating will require a re-audit within 12 months.

12.2.4 Storage and Accountability of Investigational Devices

A pharmacist or designated individual is responsible for investigational device ordering, storage, dispensing and accountability. All study site personnel responsible for investigational device(s) accountability must be listed on the Delegation of Tasks Log (DTL). The appropriate Product Accountability Record Form should be used to record the receipt and disposition of all devices supplied for Alliance protocols. Specific procedures for completing forms and policies for storage and accountability are available in the protocol.

12.2.5 Deviation from Study Protocol

The appropriate Alliance protocol resource must be contacted if the handling or dispensing of the investigational device(s) deviate from the protocol instructions. The deviation must be reported to the CIRB or IRB of record, documented in a note-to-file, and retained in the records of the site.

12.3 Investigational New Drug Applications

Alliance reviews each study in development to determine if an IND/IDE application is required for a trial**.**

12.3.1 Investigational New Drug (IND)

12.3.1.1 IND Required

IND applications for Alliance-held INDs are submitted to the FDA by the Alliance Office. The Alliance group chair is the Responsible Investigator on all Alliance IND applications. The FDA will provide documentation of IND approval.

12.3.1.2 IND Exemption

If the FDA determines that an IND is not required, the FDA will provide documentation of IND exempt status.

12.3.2 Investigational Device Exemption (IDE)

Alliance studies may include the use of investigational devices. As in the case of INDs, the Alliance will submit an application for Investigational Device Exemption. The Alliance will also submit an IDE application or request for risk determination of investigational device, if required, for trials in which NCI holds the IND. A Center for Medicare and Medicaid Services (CMS) application will be submitted for the IDE, after study receives CIRB approval. If a study includes an investigational device, the protocol provides instructions on how to obtain the device as well as information regarding any special handling requirements that must be followed.

12.3.3 FDA Reporting

For Alliance-held INDs/IDEs, annual reports, correspondence, amendments, and all other reporting requirements are submitted by the Alliance Office. All serious adverse events (SAE) whose causality may be both related and unexpected (SUSAR) are reported to the FDA by the Alliance within the required reporting timelines.

13 Industry Relations

Either Alliance or the National Cancer Institute (NCI) serve as the regulatory sponsor for Alliance studies, depending on who files the Investigational New Drug (IND) or Investigational Device Exemption (IDE) to research the agent. Regardless, the NCI serves as Alliance's governing entity, providing necessary trial infrastructure and research grants to support these studies. Regardless of industry collaboration status, Alliance member institutions participating on NCORP/NCTN trials follow the Alliance Policies and Procedures per their membership.

Alliance trials may involve working with pharmaceutical, biotech or other health-related industry companies (hereinafter, Industry). These partnerships allow access to investigational agents or devices that are relevant to Alliance research interests and provide financial support for trial components that are unfunded or under-funded. Financial support may be sought by Alliance to offset costs associated with non-standard elements of Alliance trials such as procedures associated with study development, trial activation and implementation, trial management, data management, study monitoring, research-specific medical tests, subsidiary laboratory studies, statistical analyses and other related activities.

Negotiations with Industry are managed through the Alliance Central Protocol Operations Program. Study chairs and committee chairs are not authorized to negotiate or sign agreements on behalf of Alliance.

The Federal principles governing study contributions from Industry in oncology trials are well-established and described in the "NCI –Network Group – Industry Relationship Guidelines" that can be accessed via the following:

http://ctep.cancer.gov/IndustryCollaborations2/guidelines.htm

The "NCI – Network Group – Industry Relationship Guidelines" includes information on NCI and Industry's collaboration to co-develop an agent. The co-development collaboration is formalized via a Cooperative Research and Development Agreement (CRADA) or sometimes a Clinical Trials Agreement (CTAs). The CRADA is a statutorily based mechanism created under the Federal Technology Transfer Act of 1986 for the purpose of facilitating Government-Industry collaboration and technology transfer. The CTA is an NCI-initiated mechanism for the clinical co-development of an agent.

If the NCI were to distribute drugs for an Alliance trial, independent of a CRADA or CTA, the basic tenets of these agreements still apply to Alliance/Industry collaborations.

13.1 Industry Documents

Alliance for Clinical Trials in Oncology Foundation (Foundation) is a tax-exempt, nonprofit organization dedicated to supporting the research and educational initiatives of the Alliance.

For studies supported by Industry, a legal agreement is required before funds (or agent/device) can be provided to the Foundation.

Additional documentation, such as a memorandum of understanding with Alliance regarding drug, device or services may be required for certain studies. Examples of documents and associated information are provided below.

13.1.1 Letter of Support

For a trial needing Industry support, Alliance requires a Letter of Support from the industry collaborator. The Letter of Support is not considered a legally binding document. However, the Letter of Support is a formal document that must be accepted by the Central Protocol Operations Program. A Letter of Support or an acceptable alternative may be provided as part of concept submission to NCI.

An acceptable Letter of Support should entail accurate information pertaining to the device/agent and associated funding components that the industry partner will support. Without an accepted Letter of Support, Alliance may not be able to allocate appropriate resources or be able to obtain concept approval from NCI which are needed to proceed with trial development.

13.1.2 Protocol Document

When a study agent is provided by NCI – including agent provision per CRADA or CTA between the NCI and Industry – standard language is included in the protocol document. The template for the standard language is in the "NCI Standard Protocol Language for Collaborative Agreements" document which can be accessed via the following:

https://ctep.cancer.gov/ProtocolDevelopment

The language in the protocol document may be modified when the study agent's distribution and management is the responsibility of Alliance.

13.1.3 Legal Agreement for Provision of Financial Support

The agreement details the terms of the financial support (or in-kind support of the provision of the agent). These terms include funding amount, description associated with the funding, milestone payment schedule, safety/FDA reporting requirements, data sharing (if applicable), study and agreement termination conditions, scope/statement of work and the responsibilities of each party. The agreement is between Industry and the Foundation and is legally binding.

13.1.4 Memorandum of Understanding Regarding Drug, Device or Services Provision

When appropriate, Alliance may utilize a Memorandum of Understanding to enter into with one or more parties. The Memorandum of Understanding is used to provide a general outline of the intent and general terms of a collaboration amongst various parties prior to further collaboration for development of a trial or negotiation of the main research agreement. This may be used to supplement a legally binding agreement, such as with international, non-member collaborators. This document may entail information regarding the following:

- The structure and function of Alliance
- The drug, device or service that will be utilized/implemented
- The specific study for which the drug, device or service is utilized for
- Reference to the Alliance Policies and Procedures, as appropriate

13.2 Confidential and Proprietary Information

Prior to discussions with Industry or provision of the study concept/protocol documents for review by Industry, the Alliance requires Industry to enter into a confidentiality or nondisclosure agreement with Alliance.

At the institutional level, for all studies involving collaboration with Industry, it is the responsibility of all site staff to maintain confidentiality of proprietary, trade secret, or other private information. Confidential and proprietary industry information is strongly discouraged from inclusion in study protocol documents. Should it be absolutely necessary for study activities, Industry is asked that any confidential information be indicated as such with appropriate watermarks or other acceptable reference to its confidentiality.

Similarly, Alliance study personnel must maintain confidentiality of Industry information, as applicable. Study chairs must abide by Alliance Group policy which requires strict confidentiality of study information (see Section 6). The Alliance statistician conducts all interim analyses, if applicable for a study, in a confidential manner. No one other than those explicitly authorized to be part of the monitoring process has access to the results.

All authorized personnel are required to maintain strict confidentiality throughout their deliberations. Results are released only after authorization has been granted. Any violation of these confidentiality obligations is considered a serious offense.

13.3 Data Ownership and Release in the Context of Industry Collaboration

Data sharing requirements and agreements related to Alliance studies (including translational research studies) are governed by Alliance and NCI data sharing policies (see Section 15). Pursuant to NCI policy, Alliance retains ownership of data resulting from Alliance trials and complies with federal requirements to release study results data to the NCTN/NCORP Data Archive and www.ClinicalTrials.gov, after data have been released by the Data and Safety Monitoring Board (DSMB) and the primary endpoint data have been published, as applicable.

The manuscript of primary study results is usually published within 12 months of DSMB release (see Section 10). Datasets corresponding to the primary endpoint manuscript for Phase III trials can be requested directly from the NCTN/NCORP Data Archive, which may be accessed via the following:

https://nctn-data-archive.nci.nih.gov/

For trial data that are not available in the NCTN/NCORP Data Archive, datasets corresponding to the primary endpoint manuscript may be requested from Alliance by Industry. These primary endpoint data are available after the primary endpoint manuscript publication. All other data sharing is dependent on the protocol and the trial-specific statistical analysis and publication plans.

Industry data requests or transfers require a written request to the Alliance Data Sharing Committee and a feasibility review with the Alliance Statistics and Data Management Center. Further review by NCI may be needed too. Data sharing may require supplemental funding, involving an agreement, for the staff effort and development of associated materials for these data-related activities.

13.4 Standard Reporting to Industry Collaborators

Alliance may routinely provide accrual summary reports to Industry on a quarterly basis, as documented in an executed agreement with Industry. Accrual reporting entails cumulative enrollment of the overall study. Depending on the circumstance, Alliance may consider requests to provide Industry with other accrual information or alternative frequency.

Safety reporting, such as for serious adverse events (SAEs), may also be provided to Industry. Requests from Industry on specifications of safety reporting should be discussed and final determination documented, such as in an agreement.

In addition, Alliance may provide the Annual Study Summary Report to Industry, which is generated by the Alliance Statistics and Data Management Center, at a timeframe preliminarily established by Alliance – typically in quarter 4 of the year. The Annual Study Summary Report entails study-specific information consistent with the IND Annual Report to FDA.

Other reporting requests from Industry must entail valid justification. Alliance will consider trial confidentiality, DSMB requirements, and NCI policy adherence for such requests. Any additional reports that Alliance is amenable to providing must be documented, such as in an executed agreement.

13.5 Indemnification

Alliance and the Foundation will not assume responsibility or be liable for any acts or omissions of Industry with respect to the conduct of Alliance studies. The Alliance and the Foundation will not assume responsibility or be liable or offer indemnification to Industry on behalf of Alliance members or overarching NCTN Participating Institutions for any Participating Site activities at their facilities.

Industry is responsible for providing Alliance with appropriate representations and warranties under any agreements with the Foundation that the Study agent is appropriately manufactured. Industry is required to ensure handling according to Good Clinical Practice/Good Manufacturing Practice guidelines and any applicable regulatory requirements and laws related to the appropriate manufacturing, design, and handling of the agents.

Alliance requests that Industry indemnify all investigators against loss related to the agent provided by Industry. This includes Industry assuming responsibility for drug information in the Investigator's Brochure as well as for product liability issues, should there be a manufacturing or design defect or issue with the provided agent.

13.6 Intellectual Property and Patent Rights

An invention resulting from work performed by an Alliance investigator generally is the property of either the investigator or the Alliance institution with which they are affiliated. Alliance requires investigators to disclose any inventions or discoveries resulting from Alliance studies (aka "Intellectual Property") to the Alliance group chair, regardless of whether it is patentable or not. The disclosure should be submitted in writing within ninety (90) calendar days of the discovery thereof.

Once notified, the Alliance group chair and investigator(s) will confer to establish next steps. The planning of next steps includes determining the most appropriate institutional personnel to meet with regarding matters of recognition and remuneration related to the patenting, licensing, exploitation or commercialization of the Intellectual Property. Alliance and Alliance member institutions are required to follow their terms of award, as applicable, for NCTN and NCORP requirements of all NCI/NCORP supported studies and are required to adhere to the Alliance Policies & Procedures, including those related to Intellectual Property.

The NCI's Cancer Therapy Evaluation Program "Intellectual Property Option to Collaborators" ("CTEP IP Option")" is required for all Industry partnerships and collaborations on government-supported studies and is reflected in legally binding agreements. More information regarding the CTEP IP Option can be found at the following:

https://ctep.cancer.gov/branches/rab/intellectual_property_option_to_collaborators.htm

13.7 Publication of Study Results

Alliance requires that its investigators have the absolute right to publish all study results which is consistent with the traditional principle of academic freedom; the right of the public to know about government-funded trial results; and the policy of major medical journals.

A copy of the draft manuscript is provided to Industry at least thirty (30) calendar days prior to the planned publication submission for advisory review and so that Industry can review for the disclosure of Industry proprietary information.

Abstracts are also provided to Industry for courtesy review at least three (3) business days prior to presenting or publishing.

During this review, Industry has the right to request that publication be delayed for at least thirty (30) calendar days in order to ensure that Industry's intellectual property rights are protected (i.e., if patent-related action is necessary).

NCI's summary of publication obligations and guidelines for industry collaborators that Alliance must adhere to can be found at the following:

https://ctep.cancer.gov/industryCollaborations2/guidelines.htm

13.8 Use of Agent/Devices Provided by Industry Collaborator (Industry)

Participating institutions, its investigators and study teams may not use any agent/device for any other purpose outside the scope of the protocol. Participating institutions, its investigators and study teams cannot submit claims for reimbursement to any governmental healthcare plan, third-party, commercial healthcare insurers or the patient enrolled for any item or service supplied at no charge for study-specific activities.

Policy Name: Authorized Group Representation	**Policy Number:** 14.1
Section: Public Relations – 14	**Date Revised:** December 16, 2024

14 Public relations

14.1 Authorized group representation

No one other than the group chair, or the authorized representative of the chair, may represent the Alliance in any manner.

14.2 Public service

The Alliance receives major support from the National Cancer Institute (NCI), Division of Cancer Treatment and Diagnosis (DCTD), Cancer Therapy Evaluation Program (CTEP). The goal of this national program is to seek improved methods of cancer therapy, a goal shared by the Alliance. The Alliance represents a bridge between the NCI and cancer patients throughout the country who receive new methods of treatment devised by Alliance investigators and approved by the NCI. In addition, the Alliance depends upon the scientific and financial resources provided by academic medical institutions and community sites throughout the country. The group is committed to conduct its science in a spirit of open inquiry, to critically evaluate promising new ideas and technology, and to take measures to minimize the risks of these new treatments to study participants. The institutions that participate in Alliance studies must agree to furnish study-related data concerning participants who have consented to be enrolled in Alliance studies, regardless of the level of institutional funding, and to undergo audits that evaluate and help to ensure the integrity of the data collected. In turn, the Alliance provides these medical centers with the opportunity to see their ideas evaluated in definitive national trials and to provide novel therapies to their patients.

The Alliance also receives support from the NCI's Division of Cancer Prevention (DCP) and Division of Cancer Control and Population Sciences (DCCPS). Using these resources, the Alliance pursues studies to reduce the incidence and prevalence of clinically significant cancers, to alleviate the symptoms of cancer and the toxicities of cancer treatment, and to improve the delivery of cancer care in community and academic practices, with special emphasis on issues affecting minority, underserved, and older patient groups.

Thus, the Alliance serves three constituencies:

1. The public whose taxes support Alliance, in part

2. The research participants who agree to take part in Alliance-sponsored clinical and cancer control research

3. The academic institutions and community sites that support many scientists of the Alliance, physicians, and staff

14.3 Dissemination of information to the general public

It is the responsibility of the Alliance Operations Center and each member of the Alliance to furnish accurate information concerning the Alliance and its research programs to the general public.

Questions from the public fall into various categories and are answered according to category.

- **Questions about new treatments:** These questions are usually referred to an executive officer or a protocol coordinator. If the Alliance has a relevant protocol that is open to accrual, it is appropriate to describe it and refer patients to an appropriate Alliance institution. If the question comes from a geographic location not served by Alliance, it should be indicated that there are other network groups that may also have studies that are appropriate, and that information concerning all NCI-sponsored clinical trials in cancer may be obtained from the Clinicaltrials.gov website (https://clinicaltrials.gov) and also under the "Resources" tab on the Alliance website (http://www.allianceforclinicaltrialsinoncology.org).

- **Questions of a medical nature about a specific patient:** Alliance personnel do not furnish medical advice. For answers to questions of this nature, individuals are referred to the patient's physician.

- **Requests from patients or physicians for copies of Alliance protocols and forms:** Alliance protocols are considered confidential documents and are generally not provided to the public. A non-Alliance physician may receive a copy of an Alliance protocol upon request and after approval by the principal investigator of the Alliance Central Protocol Operations Program (CPOP) or the group chair. The request must be made in writing and the intended use of the protocol must be clearly stated.

- **Inquiries concerning gifts to support cancer research:** These questions should be referred to the Alliance for Clinical Trials in Oncology Foundation.

- **Questions about the Alliance history, structure, and membership:** Refer to the Alliance communications specialist, chief operating officer (COO), or refer to the About Us section of the Alliance website.

- **Questions about Alliance research results:** The Alliance works closely with the NCI, industry partners, member institutions, and patient advocacy groups to disseminate information regarding the activation, progress, results, and findings of its research. All requests should be referred to the Alliance communications specialist.

- **Requests for access to the Alliance website:** The Alliance website contains sections available to the general public as well as sections that are accessible only to Alliance members or others who have been granted access. The Alliance periodically receives requests for access to the password-protected section of the website. Such requests should be submitted in writing to the COO and should explain the purpose of the request in detail. The COO authorizes access if the request is deemed appropriate. In most cases, access is time-limited.

- **All other questions:** Refer to the Alliance communications specialist.

14.4 Confidentiality of patient information

The Alliance has instituted procedures designed to protect the privacy of its clinical trial participants. Although there are some limits to non-disclosure of information to federal regulatory agencies, the Alliance intends to protect the privacy of its clinical trial participants, to the limit allowed by the law. The Alliance consent form describes the steps taken in this regard. Alliance information systems are HIPAA compliant and Alliance is covered by a Certificate of Confidentiality from the NIH to protect information about specimens or data obtained from participants in Alliance studies.

Information about Alliance clinical trials may also be provided to companies, foundations and others that support the work of the group. In all instances the Alliance takes steps to protect the privacy of the clinical trial participant. Patient identifiers (including but not limited to patient name, social security number, address and phone number) are not released. Alliance reports and publications do not present information that would allow the identification of its trial participants.

15 Data sharing

Each Alliance study has a formal protocol document, which includes a statement of the objectives of the study. Patient consent and authorization are obtained to collect the individual patient data required for addressing the study objectives. These data are transmitted from the treating or enrolling institution to the Alliance Statistics and Data Management Center (SDMC), where these data are reviewed, processed and stored in the Alliance database. Not all information submitted becomes part of the electronic database; for example, only some information on supporting documents such as operative and pathology reports may be entered into the database. The electronic database is used as the basis for analyses of Alliance studies, with the analyses performed by the staff at the Alliance SDMC.

The procedures described here do not cover requests – from the National Cancer Institute (NCI), the Food and Drug Administration (FDA), or other federal agencies – for information required by federal regulations or by the terms of the grant awards from federal agencies (e.g., Cancer Therapy Evaluation Program (CTEP), Division of Cancer Prevention (DCP) and Division of Cancer Control and Population Sciences (DCCPS), NCI, and National Institutes of Health (NIH) to the Alliance. Such requests will be honored as expeditiously as possible.

For Data and Safety Monitoring Board (DSMB) monitored studies, see section 16 for more information on restrictions for data release.

This policy covers requests for existing data, not requests for collection of additional data. Requests for individual-level genomic or other large-scale genomic data not used in the primary publication (see section 15.2) may be subject to other NCI and NIH regulations.

Data requested by an investigator can include images and/or data generated from Alliance laboratory correlative studies. However, requests for use of biospecimens are covered by a separate evaluation and review procedure described in section 11.

The sharing of data with industry is further described in section 13. However, in cases where industry requests data from studies in which it has not participated, it would follow the procedure indicated in this section.

15.1 Clinical Trial datasets

15.1.1 Clinical dataset definition

A clinical data set refers to individual-level de-identified data sets that would be sufficient to reproduce results provided in a publication (i.e., published manuscript) containing the primary study analysis.

15.1.2 Guidelines for availability of data sets

For phase II/III and III studies primary publications published on or after January 1, 2015, it is anticipated that clinical data sets will be available via the NCTN/NCORP Data Archive. It is anticipated that data sets containing patient-level entry data of all variables summarized in the primary publication(s) will be available within 6 months after the earliest publication date of the primary analysis. In addition, all data from secondary publications of these phase II/III and phase III trials that contain updated survival data published on or after April 01, 2018 will be available within 6 months of the earliest publication date. Clinical data from secondary publications of phase II/III and phase III trials that include large-scale genomic data consisting of 50 or more variables on 50 or more patients (e.g., DNA or RNA sequencing, gene expression microarray, proteomics, methylomics, etc.) may be requested by NCI for submission to the NCTN/NCORP Data Archive. Data from all other publications (e.g., quality-of-life, economic, toxicity data, biomarker data or meta-analyses, phase II primary, etc.) may be submitted to the Archive on a voluntary basis.

The NCTN/NCORP Data Archive has its own requesting procedures: https://nctn-data-archive.nci.nih.gov. Some data may also be available via Project Data Sphere: https://www.projectdatasphere.org/projectdatasphere/html/home. If the desired data are not contained within the NCTN Data Archive or Project Data Sphere, these data will be available to individuals via the requesting procedures described in section 15.3 (subject to restrictions in sections 15.4 and 15.5). This process could take several months depending on workload and prioritization within the SDMC.

For non-phase III studies, clinical data sets containing the variables analyzed in the primary results paper will be available upon request (subject to restrictions in sections 15.4 and 15.5). This process could take several months, based on the type of request and workload amount/priorities of the SDMC. The release of data may also be constrained in cases where the sample sizes are too small to reliably de-identify data

Release of data collected in a clinical trial conducted under a binding collaborative agreement between CTEP and a pharmaceutical/biotechnology company must be in compliance with the terms of the binding collaborative agreement and must be approved by CTEP and the company. Release of data is also subject to the terms of any contracts between the Alliance and other entities, which cover any of the requested data. These two considerations could, in some instances, delay the release of data to requesting investigators.

15.2 Large-scale genomic data sharing

15.2.1 Large-scale genomic data definition

Large-scale genomic data refers to a dataset where the number of features on the assay is far greater than the number of samples tested in the study. Further details can be found in the NIH definition of large-scale genomic data (https://osp.od.nih.gov/wp-content/uploads/Supplemental_Info_GDS_Policy.pdf).

15.2.2 Guidelines for availability of data sets

Generally, large-scale genomic data will be available publically within 6 months of publication. Refer to chapter 11 for more details

15.2.3 NIH data sharing policies

Assay types used most often include microarrays and next generation sequencing. In accordance with NIH data sharing policies, large-scale genomic data generated from Alliance studies are deposited into the database on Genotypes and Phenotypes (dbGaP) or other appropriate public data repository. The study team statisticians and bioinformaticists, commonly but not always within the Alliance SDMC Computational Genomics and Bioinformatics (CGB) Unit, are responsible for this process. It is expected that the corresponding large-scale genomic data sharing policies will, of necessity, evolve as NIH policies regarding large-scale data evolve.

15.2.4 Alliance large-scale genomic studies

Alliance large-scale genomic studies are typically conducted as substudies to Alliance clinical trials including large-scale genomic data and phenotype data (clinical patient data, i.e., demographics, outcome(s), adverse events).

Phenotype data prepared by SDMC and the study team associated with analyses of large-scale genomic data will determine when the standard quality control processes have been completed and prepare data for applicable submission(s).

De-identified (coded) high throughput genotype data and other large-scale genomic data (which may include primary analysis files and/or intermediate files) will be made available to public repositories (such as dbGaP) according to NIH policies.

The study analysis team is responsible for data deposits/sharing; the Alliance SDMC CGB Unit is not responsible for data deposits/sharing in situations in which they are not members of the study analysis team.

If the desired data are not contained within a public repository, large-scale genomic data will be available to individuals via the requesting procedures described in section 15.3 (subject to restrictions in sections 15.4 and 15.5). This process could take several months depending on workload and prioritization within the SDMC and/or Translational Research Program (Alliance Standardized Translational Omics Resource, A-STOR), which houses Alliance large-scale genomic data for sharing 11.12).

15.3 Request procedures

The Alliance makes research data available to investigators, as required by NIH policies. Any investigator who wishes to use individual patient data from one or more of the Alliance studies that are not available through NCTN/NCORP Data Archive, Project Data Sphere, or large-scale genomic repositories (i.e., dbGAP) must make a formal request to the Alliance Data Sharing Committee.

The Alliance requires the investigator to fill out a formal request form, available on the Alliance website. The Alliance also requires the investigator to sign a data use agreement or a formal data release form specifying who will have access to the individual patient data and specifying that it will not be shared with others outside this specified set of individuals unless first approved by the Alliance.

There will be no scientific review of requests for data; principles regarding requests for data housed in the Alliance TRP A-STOR large scale genomic data repository are in Chapter 11. If the Alliance is unable to fulfill a request, the Alliance will inform the investigator(s) of the reason the request cannot be fulfilled. In most cases it is likely the investigator(s) will be able to amend the request to comply with the procedures. If the Alliance believes the request will not be amendable, the Alliance will inform the investigator of the appeals process outlined in section 15.6, and also notify the lead chief of the Clinical Investigations Branch (CIB) of CTEP in the Division of Cancer Treatment and Diagnosis (DCTD) at the NCI, the lead NCTN program director, and the DCP or NCORP Director, as appropriate. Release of data is subject to the disclaimer in section 15.5.

15.4 Regulatory considerations

All research use of data collected on human subjects from network group studies led by the Alliance Central Protocol Operations Program and Alliance SDMC is subject to applicable Office of Human Research Protections (OHRP) regulations and to applicable regulations of the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). Generally, patients consent to have their data stored and possibly shared for the purpose of future research, with protections for privacy. The standard policy is to provide data that have been rendered fully anonymous, de-identified, or coded. IRB approval from an investigator's institution may be required to fulfill requests for non-de-identified data.

Guidance on these matters can be found in the OHRP document "Guidance on Research Involving Coded Private Information or Biological Specimens" located at http://www.hhs.gov/ohrp/policy/cdebiol.html. Information is also available on the NIH website (http://privacyruleandresearch.nih.gov/clin_research.asp) for Clinical Research and the HIPAA Privacy Rule. The criteria for de-identification of data under HIPAA are given in the Code of Federal Regulations, Part 46, Section 164.514. It is possible to conduct most projects using coded data (as described in the OHRP Guidance) that meet the criteria for a limited data set that can be released under a data use agreement (as described in Part 46 of the CFR, Section 164.512 and in the NIH HIPAA guidance documents), without obtaining additional patient consent or authorization.

15.5 Release conditions and disclaimer

A data use agreement or a formal data release form specifying who will have access to the individual patient data (and specifying that it will not be shared with others outside this specified set of individuals), as well as covering the release conditions described below and the regulatory considerations described in sections 15.3 and 15.4 above, is required.

It is anticipated that most data requests can be provided as non-complex data sets in electronic form.

In releasing data, the Alliance makes no representations and extends no warranties of any kind, either expressed or implied. There are no expressed or implied warranties of merchantability or fitness for a particular purpose, or that the use of data will not infringe any patent, copyright, trademark, or other proprietary rights. No indemnification for any loss, claim, damage, or liability is intended or provided.

Data ownership and authorship guidelines are contained in sections 10.1 and 10.5.1.2

When abstracts or manuscripts are based on Alliance-led analyses using data shared from multiple studies, authorship will include all members of the research team involved in the current research. The Alliance encourages the inclusion of the original study teams in assignment of abstract or manuscript authorship. This applies to Alliance-led meta-analyses of data sets obtained from the Alliance, as well as to meta-analyses of Alliance data sets available through the NCTN Data Archive or Project Data Sphere. Full authorship guidelines and further publications guidelines are contained in section 10.5.1.2.

15.6 Appeals process

If a request for data is denied, the applicant may appeal the decision. The appeal is reviewed by the Alliance Group Chair, the lead NCTN or NCORP Program Director (as applicable), CTEP or DCP Associate Director or his/her designee (as applicable), and an outside statistician (i.e., a statistician who is not a member of the Alliance). The outside statistician is named jointly by the Alliance Group Chair and the lead NCTN or NCORP Program Director.

15.7 Fees

In alignment with NCI policies, data is routinely shared within public domains when required (i.e., dbGaP, NCTN/NCORP Data Archive). When the requested data are not publicly available through these established mechanisms, the Alliance may require funding for support to compile the data set in an electronic format. Such funding will include, but not be limited to, the actual time, effort, and materials required for preparing and documenting the data set requested.

Sometimes the data requested will not all be coded in the Alliance database but will be available from supplementary material that was submitted as part of the trial. In this case, data would need to be abstracted from the supplementary material. Data abstractions can only be performed if adequate funding to support the abstraction is available. Even if funding is available, the Alliance may not have staff available to perform the abstraction. In this situation, Alliance may consider inviting the investigator(s) to the Alliance SDMC to perform the abstraction. Some funding for clerical support may still be required.

For large-scale genomic data requests, sometimes data requested will not have been generated during completion of the original work and thus would require additional bioinformatic analyses to generate the requested data. In this case, raw files would be shared so that the requestor can generate the needed data at their expense. A fee may be required for sharing large files and/or additional analysis.

16 Study monitoring and interim analyses

The primary purpose of monitoring a clinical trial is to ensure the safety and well-being of the specific participants entered on the trial. All interventional protocols must include a formal monitoring plan. All randomized phase 2 all phase 3 trials, and some specially-designated trials are formally monitored by a standing Alliance Data and Safety Monitoring Board (DSMB). The monitoring functions for other trials (e.g., phase 1 and non-randomized phase 2), including accrual monitoring, are carried out by the study chair, the primary statistician, and the executive officer along with other members of the study team and Alliance staff.

16.1 Study monitoring by the DSMB

16.1.1 Studies requiring DSMB monitoring

All Alliance-led phase 3 and randomized phase 2 NCTN or NCORP sponsored trials are monitored by the Alliance DSMB. Non-interventional (i.e., Screening) trials do not usually require formal monitoring procedures, however other studies may be monitored by the DSMB if deemed appropriate by the NCTN/NCORP group chair and DSMB chair.

16.1.2 Function of the DSMB

The responsibilities of the DSMB are as follows:

1. The primary responsibility of the DSMB is to review adverse event data in conjunction with protocol-specified interim and final analyses of outcome efficacy data (prepared by the study statistician) and to recommend whether the study needs to continue per protocol or be changed or terminated based on these analyses. For phase 3, phase 2/3, and randomized phase 2 trials, the committee also determines whether and to whom outcome results should be released prior to the public reporting of study results at the time specified in the protocol.

2. The DSMB reviews reports of related studies performed by the network groups or other organizations to determine, considering information and recommendations supplied by the study team, whether the Alliance led study needs to be changed or terminated.

3. The DSMB oversees the safety and accrual data; however it is also the responsibility of the study team (including medical monitoring, as applicable) to review the safety and accrual information on a regular basis. The study chair also oversees safety through processes defined in Sections 8.3 and 8.4.

4. All patient level clinical trial data release requests, including baseline data, or patient level or aggregate outcome data, including projections of analysis milestones outside of the NCI policy, on DSMB monitored studies have to be submitted to the DSMB for review and approval. Per NCI policy, the timing of the final analysis (6 months or less in advance) will be given to NCI (and company partners as applicable).

5. The DSMB reviews major modifications to the study proposed by the study team (e.g., termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, other major design changes).

16.2 Overview of DSMB procedures

Each study to be monitored requires periodic (at least every 6 months) confidential reports to be prepared by the primary statistician. These reports are submitted to the DSMB, a single standing committee established for the purpose of reviewing all of the individual reports. No individuals other than members of the DSMB receive a copy; specifically, the study chair does not receive a copy.

16.2.1 Confidentiality

All interim and final analyses are carried out in a confidential manner. No one other than those explicitly authorized to be part of the monitoring process have access to the results. All such persons must keep all aspects of their deliberations in strict confidence. Any violation of confidentiality is considered a serious offense.

All members of the DSMB pledge to maintain confidentiality. The Alliance SDMC maintains confidential files of all reports and in conjunction with the Alliance Operations Center retains the meeting minutes and record of actions taken on each study. No communication of the deliberations of the committee, either written or oral, may be made except as provided for in these DSMB policies and procedures. Any violation of confidentiality must be reported to the Alliance group chair.

16.2.2 Membership

The DSMB chair is nominated for a five-year term by the Alliance group chair and confirmed by NCI. The group statistician is a non-voting member of the DSMB. All other members are appointed by the Alliance group chair for three year terms, and include individuals primarily from outside of the Alliance. The majority of the voting DSMB members cannot be affiliated with the Alliance, and voting quorums for a DSMB meeting require that the majority of voting members not belong to the Alliance. Individuals are selected based on their breadth of experience, reputation for objectivity, absence of the actual conflicts of interest or the appearance of conflicts of interest, and knowledge of good clinical trial methodology. There is at least one lay member and a voting statistician from outside the group. One or more NCI physician(s) and a NCI statistician, selected by NCI, are nonvoting *ex officio* members. Members of the DSMB who chair or co-chair studies being monitored by the committee excuse themselves from all DSMB discussions concerning that study and do not receive DSMB reports concerning that study. Members of the DSMB who are leaders (chair or vice chair) of disease or modality committees excuse themselves from all DSMB discussions concerning

studies being conducted by their committee and do not receive DSMB reports concerning those studies.

16.2.3 Meetings

The DSMB meets at least twice yearly, ordinarily in conjunction with scheduled group meetings (see section 5). Additional DSMB meetings may be held at any time or in any form as decided by the DSMB chair.

The DSMB meeting itself consists of open (optional, per discretion of DSMB chair) and closed (required) sessions for each study under consideration. During the open session, the study chair, primary statistician, and committee chair are available to answer questions posed by DSMB members. During the closed session, the DSMB decides what action, if any, is required. The study chair, primary statistician, and committee chair must absent themselves from the closed session even if they are members of the DSMB.

16.2.4 Recommendations

The results of each DSMB meeting are summarized in a formal report by the group statistician and sent to the Alliance group chair within two weeks of the meeting (urgent matters are addressed immediately). The DSMB report contains recommendations on whether to modify or close each study reviewed, whether to release and report the results, and whether to continue study per protocol. A primary recommendation (e.g., continue with no change; recommended or required modification; release study results and stop further DSMB monitoring) must be included in the document. Upon approval from the Alliance group chair, the recommendations are sent to NCI for review approval before any action is taken.

The Alliance group chair, or designee, is responsible for notifying the study chair, primary statistician, and committee chair before the recommendations of the DSMB are carried out. An edited version of the recommendations is distributed to Alliance membership. The Alliance Operations Center keeps an archive of DSMB recommendations; the SDMC keeps an archive of the DSMB meeting minutes.

16.2.4.1 Study change for patient safety reasons

In the event that the DSMB recommends a study change for patient safety reasons (including early stopping for inferior therapy), the Alliance group chair will act to implement the change as expeditiously as possible. For studies that are being closed based on a DSMB recommendation, although NCI pre-approval is not

required, the Alliance group chair (or his/her designee) must inform and discuss the closure of the study with the NCI leadership before disclosing the study closure to anyone. If the DSMB recommends closure of a study, the NCI physician member of the DSMB will provide the current 24/7 contact information for NCI leadership.

16.2.4.2 Study closure due to slow accrual

In the event that the DSMB recommends a study be closed early due to slow accrual, then the recommendation of the DSMB would be processed as described in 16.2.4.1 above. Note: NCI may have additional closure policies that apply to studies with slow accrual that have not yet had formal interim efficacy analyses presented to the DSMB.

16.2.4.3 Study change for non patient safety reasons

In the event that the DSMB recommends a change in a study for reasons other than either patient safety or study closure due to slow accrual such as extend accrual because of an event rate lower than expected, the DSMB will provide to the Alliance group chair an adequate rationale. In the absence of disagreement, the Alliance group chair (working with the study chair) will be responsible for having an amendment prepared and submitted to the appropriate NCI Protocol and Information Office reflecting the recommendations of the DSMB and providing the rationale for the changes. (This is required even if NCI approval has been obtained prior to the amendment being presented to the DSMB.) NCI approval of the amendment will be required prior to implementation of the change, although it is anticipated that a decision to override the recommendation of the DSMB will be made only in the most exceptional circumstances. In the event that the Alliance group chair disagrees with the DSMB recommendation, the recommendation would be processed as described in 16.2.4.4.

16.2.4.4 Disagreement with Alliance DSMB Recommendations

In the unlikely situation that there is a disagreement with the Alliance DSMB recommendations, the Alliance and NCI leadership will work together with the Alliance DSMB chair and group statistician for a mutual resolution.

Confidentiality will be maintained during these discussions, but relevant data will be shared with the Alliance and NCI leadership, and other parties whom they wish to involve in reaching a decision.

In the exceptional circumstance that a mutually acceptable decision cannot be reached, final responsibility for a decision will rest with the applicable NCI division director.

16.2.5 Study modifications

Major modifications to the study design by the study team not motivated by confidential outcome data or patient safety/toxicity data (e.g., increasing the sample size because of more rapid than expected accrual) must be discussed with NCI before being presented to the DSMB for consideration. If NCI is willing to approve the modifications, the network group informs the DSMB at the next scheduled DSMB meeting.

In an event that the study team wishes to request permission not to follow the protocol pre-specified decision rule and/or a major redesign, such a request must first be discussed with the NCI, and the DSMB notified. This request (change in the design of the trial) needs to be approved by the NCI, including assignment of an independent statistician as appropriate following the NCI policy for major redesign. The study team works with the group statistician and the independent statistician on the redesign proposal, with consultation from NCI. Upon receiving NCI approval, the DSMB is notified of the redesign and an official amendment is submitted to the appropriate NCI Protocol and Information Office.

16.2.6 Release of data & results

For phase 3, phase 2/3, randomized phase 2 trials, and any other trial monitored by the DSMB, ***any*** release of outcome data (either internal to the network group, to NCI personnel not members of the DSMB, or external [e.g., a paper presented at professional society meetings, seminars, papers, etc.]) prior to the final approval of general dissemination of results must be reviewed and recommended for approval by the DSMB to the Alliance group chair. In general, outcome data from phase 3, phase 2/3, and randomized phase 2 trials would not be routinely made available to individuals outside of the DSMB until accrual has ceased and all patients have concluded their randomized treatment and completed study follow-up and/or reached a protocol-specified endpoint. After this time point, the DSMB may recommend the release of outcome data on a confidential basis to the study chair for planning the preparation of manuscripts, and/or to a small group of individuals for purposes of planning future trials. The DSMB will consider

special requests for information from the disease committee chair prior to that time point. The DSMB should be made aware of any communication of analysis results from phase 3, phase 2/3, and randomized phase 2 trials outside of the SDMC at any time. The Alliance group chair may not be able to accept the recommendation of the DSMB to release data for a specific trial if the Alliance and/or NCI has a binding agreement with a company collaborator (or other entity) that specifies data exclusivity for the trial without discussing the release with NCI (for Alliance trials with a NCI binding agreement) and/or the company or other collaborator (for Alliance studies that are under other binding agreements).

16.2.7 Presentation of results by intervention group

The DSMB assesses relative efficacy according to the protocol specified interim and final analyses; therefore, results by intervention are presented and discussed. No intervention-specific results, coded or not, are released to anyone not on the DSMB.

16.2.8 Phase 2/3 trials

With respect to implementation of phase 2 decision rules in phase 2/3 designs of clinical trials, any protocol-specified phase 2 decision-rule analysis must be performed timely when the required number of events are observed and reported in the database, and report submitted to the DSMB. If the trial follows the decision rule (i.e., continues or stops depending on whether the continuation threshold is met), then the DSMB review and decision of the status of the trial (i.e., continuing or stopping) based on the protocol-specified phase 2 decision rule is communicated to Alliance and NCI leadership. Any deviations from the protocol specified design specifications follows the NCI policy for a major redesign, see 16.2.5 above.

16.2.9 Industry-supported studies

Studies supported by industry are also covered by these policies and procedures. Industry representatives may not serve on the Alliance DSMB.

16.2.10 Conflict of interest

Individuals invited to serve on the DSMB are subject to the Alliance Conflict of Interest policy (see section 3.5).

16.3 Monitoring phase 1 and 2 studies

16.3.1 Phase 1 studies

Phase 1 studies are ordinarily limited access studies. Routine monitoring is carried out via conference call among representatives of each participating institution, the primary statistician, the study chair and members of the study team. A representative from each institution must participate whenever the institution has any participants currently receiving protocol therapy. Institutions that fail to submit adverse event data as required or that do not participate in the conference calls will be prohibited from continuing to enroll participants on the study.

16.3.2 Phase 2 studies

Non-randomized phase 2 studies are routinely monitored by the study team (study chair, primary statistician, executive officer, protocol coordinator, data management personnel) following the protocol specified plans for efficacy and adverse event monitoring, as well as other Operations Center staff (e.g. director of regulatory affairs), as applicable.

All patient level clinical trial data release requests, including baseline data, or patient level or aggregate outcome data, including projections of analysis milestones cannot be shared outside of the statistical team. Requests for this data would have to be submitted to the study statistician who will consult with group statistician and Alliance leadership for review and approval. The timing of the final analysis (6 months or less in advance) can be given to the study chair (and company partners as applicable), NCI may be notified.

17 Quality Management

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

17.1 Quality Management and Assurance Department

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

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

17.2 Alliance Quality Monitoring and Management Committee (QMMC)

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

17.2.1 Studies requiring QMMC oversight

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

17.2.2 Function of the QMMC

The responsibilities of the QMMC are as follows:

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

17.2.3 Overview of the QMMC procedure

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

17.2.4 Membership

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

17.2.5 Review Process

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

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

17.2.6 Recommendations/escalation process

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

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

Recommendations may include, but are not limited to:

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

17.3 Regulatory Authority Inspection Readiness Activities

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

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

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

17.4 Monitoring

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

17.4.1 Central Data Monitoring

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

17.4.2 On-site/remote Monitoring

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

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

17.5 Institutional audits

17.5.1 History

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

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

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

17.5.2 Quality assurance

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

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

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

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

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

17.5.3 NCI audit participation

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

CTMB staff reviews all audit schedules and all reports of audit findings. To assure consistency of auditing across the group/cancer center research bases, a CTMB representative may attend on-site audits. Staff from the CTMB may

make specific recommendations for action if they do not believe the action taken by the network group or site has been adequate.

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

17.5.4 Overview of Alliance auditing policies and procedures

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

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

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

17.5.5 Scheduling of audits

17.5.5.1 Selection of main member and affiliate member institutions for audit

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

institutions, it may be appropriate to audit these institutions on a more frequent interval given the high number of cases for review.

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

17.5.5.2 Scheduling audits for NCORPs and NCORP components

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

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

17.5.5.3 Case/protocol selection

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

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

(1) 10% Group/NCORP cases

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

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

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

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

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

17.5.5.4 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 is sent to the institution four to six weeks prior to the audit to allow adequate time to prepare.

17.5.5.5 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 the required CTMB Auditor and Monitor Training Course via the CLASS (Compliance, Learning, and SOP Solutions) training system 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 NCORP principal investigator is responsible for recommending physicians who are able to serve as physician auditors.

17.5.6 Audit preparation by the institution

Principal investigators and institutional clinical research professionals are responsible for preparing for an audit and ensuring that all relevant materials are available for review. An institution may be audited off-site at the Network Main Member, NCORP, or LAPs main member.

The following records must be available for auditor review:

17.5.6.1 IRB approvals, continuing reviews, amendment approvals, and safety reports, copies of the locally utilized informed consent documents, Delegation of Tasks Logs (DTLs) and other regulatory documentation, if applicable.

17.5.6.2 Current versions of requested protocols.

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

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

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

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

3. Complete medical records.

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

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

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

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

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

17.5.7 Conduct of an Alliance audit

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

17.5.7.1 Regulatory requirements

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

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

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

17.5.7.1.1 Critical, Major and lesser deficiencies

Deficiencies are categorized as either “critical”, "major" or "lesser"; examples are provided in the

appropriate sections. An exhaustive list of examples is not given, but the examples are intended to guide the reviewers in their assessment and categorization of specific deficiencies. Deficiencies too trivial to warrant comment are not included in the report.

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

Major deficiency: a variance from protocol-specified procedures or practice that makes the resulting data questionable.

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

17.5.7.2 Review of IRB documentation and informed consent content

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

17.5.7.2.1 IRB documentation

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

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

Documentation of full-board initial IRB approvals with the IRB chair's signature and date, full-board annual re-approvals (expedited review under

appropriate exceptions) for each audited protocol and approval for amendments should be available at the site visit for review by the audit team. The same is true for IRB review of safety reports. If an institution being audited is covered by another institution's IRB, the written agreement should be available for review.

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

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

Critical IRB deficiency:

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

Major IRB deficiencies may include but are not limited to:

- Initial approval by expedited review for protocols requiring full board review per OHRP guidelines.
- Expedited re-approval for situations other than approved exceptions.
- Registration and/or treatment of patient prior to full IRB approval.
- Re-approval delayed more than thirty days, but less than one year.
- Registration of patient on protocol during a period of delayed re-approval or during a temporary suspension (i.e., Request for Rapid Amendment).
- Missing re-approval.
- Expired re-approval.
- Internal reportable adverse events reported late or not reported to the IRB.

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

Lesser IRB deficiencies may include but are not limited to:

- Protocol annual re-approval delayed less than 30 days.
- Delayed re-approval for protocol closed to accrual for which all patients/study participants have completed therapy.
- Copy of CIRB approval letter/study worksheet is not available or accessible at the time of the review.

17.5.7.2.2 Informed consent content (ICC)

The audit team verifies that the most recent IRB-approved local informed consent document for at least four protocols (if the number of protocols allows) contains the elements required by federal regulations. In addition, each of the four 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.

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

If the site identifies a **significant** error in risk (e.g. missing risks, or risks erroneously attributed to the drug), the responsible investigator must send an email to the protocol coordinator listed on the study cover page and the Alliance regulatory group providing written justification for correction of the identified

error. The Alliance will determine if a protocol amendment is required to address the issue.

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

Critical ICC Deficiency:

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

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

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

Lesser ICC Deficiencies:

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

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

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

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

Critical DTL Deficiency:

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

Major DTL Deficiency:

- Performing tasks not assigned to individual
- Failure to keep DTL current
- Individual not listed on DTL
- Individual performing study-related activities with DTL unapproved greater than 30 calendar days

Lesser DTL Deficiencies:

- Individual performing study-related activities with DTL unapproved 30 calendar days or less

17.5.7.2.4 Assessing the IRB, ICC and DTL

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

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

Acceptable	• No deficiencies identified. • Few lesser deficiencies identified. • Any major deficiencies identified during the audit that were addressed and/or corrected **prior to** the audit for which a written and dated CAPA plan exists, and no further action is required by the Alliance, or NCORP, the institution, or the principal investigator because no similar deficiency has occurred since the CAPA plan was implemented. However, this approach may not be applicable if a deficiency is associated with a safety concern and determined that further action is necessary. In any case, the Alliance will provide the CTMB with a copy of the CAPA plan at the time the final audit report is submitted or by the date follow up is due.
Acceptable Needs Follow-up	• Multiple lesser deficiencies identified. • Major deficiencies identified during the audit but not corrected and/or addressed **prior to** the audit.
Unacceptable	• A single critical deficiency identified. • Multiple major deficiencies identified. • Excessive number of lesser deficiencies identified.

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

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

17.5.7.3 Review of accountability of investigational agents and pharmacy operations

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

Agent accountability and storage procedures described in this section are required under federal regulations and NCI policy for NCI-supplied study agents (by PMB/CTEP or designated

company/Group for DCP and imaging agents). See NCI/CTEP policies under the Agent Management section of the NCI Division of Cancer Treatment & Diagnosis website.

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

A waiver statement allowing use of electronic DARFs (eDARFs) has not been issued by the NCI and the NCI does not endorse any eDARF pharmacy package. Institutions that choose to use an electronic accountability system must ensure the database is capable of producing a paper printout that is identical to the NCI DARF. Electronic accountability system database limitations are not valid reasons for improper accountability documentation according to NCI policy. NCI launched the electronic accountability module in AURORA, known as the eDARF on December 27, 2024.

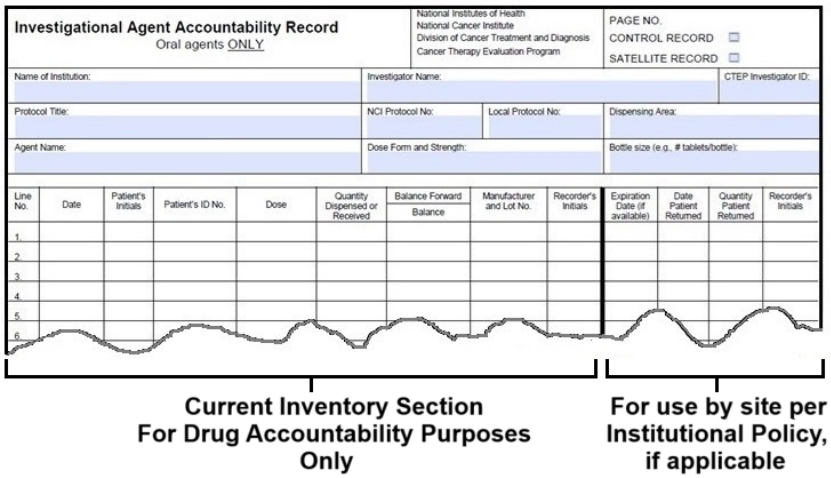
All protocols that use investigational drugs, or commercially available drugs for an investigational purpose when designated by the protocol, must have a specific drug supply for use with that protocol only. This means there may be several supplies of the same drug, each designated for use for only one 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.

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

For NCI Oral DARFs, study participant returns are considered waste pharmaceuticals and not part of agent accountability. The

study participant return section of the DARF is for the convenience of the site (if required by site SOP) and is not part of study agent accountability for protocol auditing purposes.

Example of NCI Oral DARF


Investigational Agent Accountability Record
Oral agents ONLY

National Institutes of Health
National Cancer Institute
Division of Cancer Treatment and Diagnosis
Cancer Therapy Evaluation Program

PAGE NO.
CONTROL RECORD ☐
SATELLITE RECORD ☐

Name of Institution:	Investigator Name:		CTEP Investigator ID:
Protocol Title:	NCI Protocol No:	Local Protocol No:	Dispensing Area:
Agent Name:	Dose Form and Strength:		Bottle size (e.g., # tablets/bottle):

Line No.	Date	Patient's Initials	Patient's ID No.	Dose	Quantity Dispensed or Received	Balance Forward / Balance	Manufacturer and Lot No.	Recorder's Initials	Expiration Date (if available)	Date Patient Returned	Quantity Patient Returned	Recorder's Initials
1.												
2.												
3.												
4.												
5.												
6.												

Current Inventory Section
For Drug Accountability Purposes
Only

For use by site per
Institutional Policy,
if applicable

Auditors are required to inspect the drug logs and tour the area where the investigational drugs are stored (on-site audits). The pharmacy (if one participates in the handling of protocol drugs) must also be visited to evaluate storage and security compliance. Arrangements should be made with the staff pharmacist for the audit team to visit the pharmacy area. If no pharmacy is used, drug-handling procedures in the clinic/office must be audited.

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

17.5.7.3.1 Guidelines for conducting the review

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

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

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

Compliant	Non-Compliant
• NCI DARF/Oral DARF/eDARF maintained and maintained completely, accurately and in real-time basis • Paper and/or electronic DARFs (eDARFs) contains all required information; paper printout of eDARF is identical to NCI DARF • Corrections are lined out, initialed and dated on paper DARF Corrections are appropriately documented on eDARF in electronic inventory system • Study-supplied Agent was dispensed to a registered study participant is recorded on the appropriate DARF • Multiple dose vials appropriately used for more than one study participant with doses documented correctly on separate lines of the DARF • Study-supplied agent is appropriately dispensed to a registered study participant • Handling of study participant returns of oral study-supplied agents are documented in the study participant return section of the oral DARF if applicable per institutional policy • Study participant returns of non-oral study agents are not documented on the NCI DARF • Study agent final disposition of undispensed inventory is documented on DARF • NCI DARF maintained to verify cancer control/imaging study-supplied agent is administered to study participant	• NCI DARF/Oral DARF/eDARF not maintained or not maintained completely, accurately or in real-time basis • Paper and/or eDARF are not completed as required; paper printout of eDARF is not identical to NCI DARF • Erasures or whiteout used on paper DARF • Corrections are not lined out, initialed, and dated on paper DARF • Corrections are not appropriately documented on eDARF in electronic inventory system • Study-supplied agent dispensed to a registered study participant is not recorded on the appropriate DARF • Multiple dose vials not used for more than one study participant and/or doses not documented correctly on separate lines of the DARF • Study-supplied agent dispensed to a non-registered study participant recorded on the DARF • Study participant return of oral agents are documented as part of 'current inventory' section on DARF • Study participant returns of non-oral study agent are documented on NCI DARF • Study agent final disposition of undispensed inventory is not documented on DARF • NCI DARF not maintained to verify cancer control/imaging study-supplied agents is administered to study participant

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

Compliant	Non-Compliant
• Study agent is appropriately dispensed and administered to study participant when study agent is supplied per protocol • Separate DARF is maintained by protocol, study agent, strength, formulation and by ordering investigator • Maintain separate DARF for each study participant on a patient-specific supply studies, as directed by the protocol • Study-supplied agent is only used for pre-clinical or laboratory studies with written approval from NCI	• Non-study drug is dispensed and/or administered to study participant when NCI study agent is supplied by protocol • DARF maintained by lot #, when multiple lots have been received • Separate DARF not maintained by protocol, study agent, strength, formulation and ordering investigator when agent is supplied by protocol • Separate DARF not maintained for each study participant on participant-specific supply studies as dictated by protocol • Study-supplied agent used for pre-clinical or laboratory studies without written approval by NCI

Table 17-4. Assessing compliance for satellite records

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

Table 17-5. Assessing compliance for agent inventory and accountability documentation

Compliant	Non-Compliant
• Study-supplied agent order receipts/ documentation (paper or electronic) are retained and available for review • Documentation on Control DARF of study- supplied agent transactions including local destruction of undispensed inventory • Balance on DARF matches physical inventory • [For NCI-sponsored Study] NCI oral study agent shipped to study participant per NCI oral agent shipment policy	• Study-supplied agent order receipts/documentation (paper or electronic) are not retained or not available for review • Lack of documentation on Control DARF of study-supplied agent transactions including local destruction of undispensed inventory • Quantities not accounted for in physical inventory; quantity does not match DARF [For NCI-sponsored Study] NCI oral study agent shipment policy is not followed when shipping directly to study participant

Table 17-6. Assessing compliance for return of undispensed study agent (NCI sponsored study)

Compliant	Non-Compliant
• Return of Study agent is transferred to another site, authorized investigator, or protocol with NCI written approval • Undispensed study-provided agent not returned to NCI when supplied by another source • Return Form or documentation of local destruction authorization for undispensed inventory is maintained • Undispensed NCI-supplied study agent is returned, transferred or locally destroyed within 90 calendar days when requested by the NCI • Undispensed NCI-supplied study agent is returned to NCI within 90 days of when all study participants transition to follow-up or study is closed to enrollment and NCI-supplied study agent is not being administered	• Study agent is transferred to another site, investigator or protocol without NCI written approval • Undispensed study-provided agent returned to NCI when supplied by another source • Return Form or documentation of local destruction for undispensed inventory is not maintained • Undispensed NCI-supplied study agent not returned, transferred or locally destroyed within 90 calendar days when requested by the NCI • Undispensed NCI-supplied study agent remains on inventory greater than 90 days after all study participants are in follow-up, or study is closed to enrollment and no NCI-supplied study agent is being administered

Table 17-7. Assessing compliance for agent storage

Compliant	Non-Compliant
• Study-supplied agent is stored separately by protocol, agent, strength, formulation, and by ordering investigator • Study-supplied agent is stored under proper conditions (i.e., refrigeration, freezer or room temperature) with appropriate documentation and maintenance of temperature monitoring	• Study-supplied agent is not stored separately by protocol, agent, strength, formulation, and by ordering investigator • Study-supplied agent not stored under proper temperature conditions; temperature monitoring documentation not maintained

Table 17-8. Assessing compliance for adequate security

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

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

Compliant	Non-Compliant
• [For NCI sponsored Study] Prescribing investigator (IVR) or non-physician investigator (NPIVR) writing orders for study-supplied agent has an active registration status in the CTEP Registration and Credential Repository (RCR) • [For NCI sponsored Study] Prescribing investigator (IVR) or non-physician investigator (NPIVR) is an authorized, study-eligible person, and is qualified to write orders per institutional policy, their local, state laws and regulations, and follow applicable international requirements • Pharmacy has procedures in place to ensure the person prescribing and writing orders for study-supplied agent is an authorized person	• [For NCI sponsored Study] Prescribing investigator (IVR) or non-physician investigator (NPIVR) writing orders for study-supplied agent does not have an active registration status in the CTEP Registration and Credential Repository (RCR) • [For NCI sponsored Study] Prescribing investigator (IVR) or non-physician investigator (NPIVR) writing orders is not an authorized, study-eligible person, or is not qualified to write orders per institutional policy, their local, state laws and regulations, or follow applicable international requirements • Pharmacy does not have procedures in place to ensure person prescribing or cosigning prescriptions for study-supplied agent is an authorized prescriber

17.5.7.3.2 Assessing the accountability of investigational agents and pharmacy operations

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

Table 17-10. Pharmacy audit assessment categories

Acceptable	• Compliance found for all categories. • Any non-compliant item identified during the audit that was addressed and/or corrected prior to audit for which a written and dated Corrective and Preventive Action (CAPA) plan exists and no further action is required by the Network Group, NCORP Research Base, CTSU, the institution, or the principal investigator. No further action is necessary because no similar non-compliance issues have occurred since the CAPA was implemented. However, this approach may not be applicable if the non-compliance is associated with a safety concern and determined that further action is necessary.
Acceptable Needs Follow-up	• Category found non-compliant during the audit, which was not corrected and/or addressed prior to the conduct of the on-site audit.

Unacceptable	• A single Critical Non-compliance finding • Multiple non-compliant categories identified. • Inability to track the disposition of NCI-supplied study drug

No Assessment Required	• No IND or NCI-supplied study drug is in stock or in use during the audit period.
	• This designation applies under the following two conditions:
	  • The review of the pharmacy consists of only security, storage and review of pharmacy procedures to ensure investigator has an active PMB registration.
	  • Review of security, storage and pharmacy procedures were found to be compliant.

Limited Review Needs Follow-up	• Non-compliance identified under Pharmacy and audit was limited to review of storage, security and/or pharmacy procedures; and CAPA plan or follow-up response is requested.

17.5.7.4 Review of patient case records

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

Assessment of patient cases should include:

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

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

Auditing Patient Cases for Studies in Medidata RAVE

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

Source documents should be independently verifiable. Copies of Group study forms generally are not considered to be primary source documents. The use of flow sheets as primary source documentation is strongly discouraged, except for flow sheets that are signed, dated and accepted as part of the official institutional medical record. Primary laboratory reports, progress notes, etc., are considered adequate. Documentation of oral drug administration should be included in the patient's primary record independent of the flow sheet (e.g., notation in progress notes or photocopy of prescription, as well as documentation in the NCI Drug Accountability Record Form where appropriate).

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

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

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

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

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

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

A **lesser deficiency** is a deficiency that is judged to not have a significant impact on the outcome or interpretation of the study and is not described above as a major deficiency. **An unacceptable frequency/quantity of lesser deficiencies should be treated as a major deficiency in determining the final assessment of a component.**

17.5.7.4.1 Examples of critical, major and lesser deficiencies

Informed Consent-Critical Deficiencies

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

Informed Consent-Major Deficiencies

- Failure to document the informed consent process with the study participant; electronic/remote consent process not followed
- Study participant signs consent form document containing changes not approved by the IRB of record

- Consent form document missing
- Translated consent, short form or other form of translation not available or signed/dated by a non-English speaking study participant
- Consent form document not signed/dated by study participant prior to study registration/enrollment
- Consent form document does not contain all required signatures
- Consent form document signed was not the most current IRB-approved version at the time of participant registration
- Consent form document does not include updates or information required by IRB
- Study participant not re-consented or notified as required
- Consent form document for ancillary/advanced imaging studies not executed properly

Eligibility – Critical Deficiency

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

Eligibility – Major Deficiencies

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

Treatment – Critical Deficiencies

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

Treatment – Major Deficiencies

- Additional agent/treatment/intervention used which is not permitted by protocol
- Dose deviations or incorrect calculations (error greater than +/- 10%)
- Dose modification/treatment/intervention not per protocol; incorrectly calculated
- Treatment/intervention incorrect, or not administered correctly Timing and sequencing of treatment/intervention not per protocol
- Unjustified delays in treatment/intervention
- Treatment/intervention not documented in source documentation; or not documented correctly[1]
- Treatment/intervention not reported; or not reported correctly on Case Report Forms[2]

Note regarding Treatment category: Review of documentation for how and when treatment is administered should focus on the study/IND agents under investigation (i.e., start/stop times), unless otherwise specified in the protocol. Documentation of standard of care drug(s) should include total dose and start/stop dates for prolonged IV infusions ≥ 24 hours.

[1] Assigning a major or lesser is based on the extent of treatment data not documented; or not documented correctly.
[2] Assigning a major or lesser is based on the extent of not reporting treatment data; or not reporting correctly.

Disease Outcome/Response – Critical Deficiency

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

Disease Outcome/Response – Major Deficiencies

- Inaccurate documentation of initial sites of involvement
- Tumor measurements/evaluation of 'status of disease' not performed
- Tumor measurements/evaluation of 'status of disease' not documented in source documentation; or not documented correctly[3]
- Tumor measurements/evaluation of 'status of disease' not reported; or not reported correctly on Case Report Forms[4]
- Protocol-directed response criteria not followed
- Claimed response (i.e., partial response, complete response, stable) cannot be verified
- Failure to identify cancer progression or failure to detect cancer in adjuvant or prevention study

Adverse Events – Critical Deficiency

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

[3] Assigning a major or lesser is based on the extent of disease outcome/response data not documented; or not documented correctly.
[4] Assigning a major or lesser is based on the extent of not reporting disease outcome/response data; or not reporting correctly.

Adverse Events – Major Deficiencies

- Failure to report or delayed reporting of an adverse event that would require filing an expedited Adverse Event (AE) report or reporting to the Group
- Adverse events not assessed by the investigator in a timely manner (per protocol)
- Grades, types, or dates/duration of serious adverse events inaccurately recorded
- Serious adverse events reported on Case Report Forms but cannot be substantiated in source documentation
- Routine adverse events not documented in source documentation; or not documented correctly[5]
- Adverse events not reported; or not reported correctly on Case Report Forms[6]
- Follow-up studies necessary to assess adverse events not performed
- Recurrent under- or over-reporting of adverse events

[5] Assigning a major or lesser is based on the extent of adverse event data not documented; or not documented correctly.
[6] Assigning a major or lesser is based on the extent of adverse event data not reported; or not reporting correctly.

Correlative Studies, Tests, and Procedures – Major Deficiencies

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

General Data Management Quality – Critical Deficiency

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

General Data Management Quality – Major Deficiencies

- Recurrent missing documentation in the patient/study participant records
- Frequent data inaccuracies in primary source documentation[7]; unredacted data[8]
- Significant number of errors in submitted data[7]; data cannot be verified
- Delinquent data submission[9]

[7] Assigning a major or lesser deficiency is dependent on the number of instances or extent of inaccurate data or errors in submitted data.
[8] Assigning a major or lesser deficiency is dependent on the number of instances and type of unredacted data (e.g., security number, study participant name, etc.).
[9] Assigning a major or lesser deficiency is based on the following: extent of the delay, percentage or number of delinquent forms, type of form (baseline, treatment, follow-up, etc.), phase of the trial, and study participant on active treatment versus follow-up. Network Group/NCORP policies and decisions from the Data Quality Working Group should be taken into consideration.

17.5.7.4.2 Assessing the findings from patient case records

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

Table 17-11. Patient case records audit assessment categories

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

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

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

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

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

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

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

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

17.5.7.5 Exit interview

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

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

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

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

17.5.8 Re-audits

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

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

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

17.5.9 Audit review

17.5.9.1 Audit evidence of scientific misconduct

The audit team leader must notify the Audit Program Director, or the Director, Group Operations in his/her absence another designated person within the Operations Center, immediately if the audit team uncovers any evidence of systematic or apparently deliberate submission or intent to submit false data to the Alliance.

The Audit Program Director immediately notifies the Director, Group Operations, the Chief Operations Officer, 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 take steps to preserve the evidence of false data submission and undertake expansion of the audit to gather additional information. A re-audit with an augmented team which may include NCI, Office of Research Integrity (ORI), and FDA representatives will be scheduled by Alliance in cooperation with the appropriate federal agencies.

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

17.5.9.2 Action taken based on audit results

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

- The PI and institution's staff is advised of the problems encountered during the audit and advised of ways to improve performance.
- If the Alliance is not satisfied that the problems are correctable, it may choose to terminate the membership or affiliate status of the institution.

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

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

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

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

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

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

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

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

17.5.9.3 Report submission to CTMB

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

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

17.5.9.4 Changes to the Alliance database subsequent to audit

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

17.6 Institutional Network Performance Evaluation

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

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

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

17.6.1 Institutional Network Performance Evaluation Scoring System

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

Table 17-13. IPEC scoring for quality

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

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

Table 17-14. IPEC scoring for timeliness

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

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

Table 17-15. IPEC scoring for group participation

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

17.7 Institutional probation

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

17.7.1 Probation based on institutional network performance evaluation

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

17.7.1.1 Criteria for warnings of substandard institutional network performance

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

17.7.1.2 Criteria for IPEC recommendation of probation of main member networks

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

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

17.7.2 Recommendation of probation for an affiliate member

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

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

17.7.3 Probationary process

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

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

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

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

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

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

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

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

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

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

17.7.3.1 Implications of probationary status

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

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

Immediate

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

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

Year 1 Anniversary

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

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

Year 2 Anniversary

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

17.7.4 Probation based on unacceptable audits

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

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

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

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

Appendix Name: Summary of Changes	**Appendix:** A
Section: Appendices	**Date Revised:** November 7, 2025

Chapter 1 Introduction

Section 1.2 Overview of program structure
Table 1-1 Alliance program structure - Addition of new Data Sharing Committee, editorial changes

Section 1.2.2 Statistics and Data Management Program
Minor editorial changes

Chapter 3 Participants

Section 3.5.1.5 Training
Updated link to Chapter 3

Chapter 10 Publications

Section 10.5.1.1 Publications on the primary study endpoint
In the second paragraph, updated titles eligible for authorship in primary and/or secondary endpoint manuscripts

"Authorship should be granted to the responsible executive officer. The study community co-chair should be included as an author if appropriate by ICMJE recommendations stated above. If the modality co- chair participated in the design of the study and wrote the modality section of the protocol, they should be an author on primary endpoint publications. Pathologists, radiologists and other specialists who perform quality assurance (QA) for a study should be included in the authorship of any publications that result from the study, unless the publication is independent of QA results of their findings. The decision for inclusion of an Alliance **study pharmacist, nurse liaison, clinical research professional, data manager and patient advocate should be included in the primary and/or secondary endpoint manuscript, as appropriate if meeting the ICMJE criteria. This policy does not apply to abstracts which limit the number of authors."**

Section 10.5.1.2 Publication on a secondary (correlative) study
New bullet added to *1. Authorship on publications of a secondary study included in the original Alliance or legacy protocol*

- **Pharmacists, Nurse Liaisons, and/or Patient Advocates whose contributions lead to creation of the publication as determined by the study chair.**

Table 1 Guidelines for Required Authorship by Endpoint Addressed in Publication

- Addition of new roles and guidelines for authorship

Chapter 13 Industry Relations

Section 13.3 Data Ownership and Release in the Context of Industry
Updated "Alliance Data Sharing Working Group" to "Alliance Data Sharing **Committee**" in the fourth paragraph.

Chapter 15 Data Sharing

Section 15.3 Request procedures
Alliance Data Sharing Working Group updated to Alliance Data Sharing **Committee**

Minor editorial changes

Section 15.5 Release conditions and disclaimer

Language in first paragraph updated as follows (new text bold):

A **data use agreement or a** ~~simple~~ formal data release form specifying who will have access to the individual patient data (and specifying that it will not be shared with others outside this specified set of individuals), as well as covering the release conditions described below and the regulatory considerations described in sections 15.3 and 15.4 above, is required.

Minor editorial changes

Section 15.7 Fees

First paraph deleted and replaced with the following:

In alignment with NCI policies, data is routinely shared within public domains when required (i.e., dbGaP, NCTN/NCORP Data Archive). When the requested data are not publicly available through these established mechanisms, the Alliance may require funding for support to compile the data set in an electronic format. Such funding will include, but not be limited to, the actual time, effort, and materials required for preparing and documenting the data set requested.

Fourth paragraph deleted

Chapter 17 Quality Management and Audit

Section 17.5.3 NCI audit participation
Minor editorial change; updated CTMB Audit guidelines webpage link

Section 17.5.5.1 Selection of main member and affiliate member institutions
Deleted the 2nd, 3rd, and 4th paragraph

Section 17.5.5.2 Scheduling audits for NCORPs and NCORP components
Deleted the following text from the first paragraph "Alternatively, the NCORP may be audited as a separate entity."

Deleted the following sections:

- 17.5.5.3 Scheduling audits for inactive sites
- 17.5.5.4 Single-Site Audit Initiative (Multi-Group Audits [MGA])

Section 17.5.5.4 Notification of audit (*previously section 17.5.5.6*)
Modification in the time between selection of cases and notification of site. New text **bold**

"A list of cases selected is sent to the institution **four to six weeks** ~~14-28 days~~ prior to audit to allow adequate time to prepare."

Section 17.5.5.5 Audit team (*previously section 17.5.5.7*)
Required training language updated. New text in bold
All auditors must complete **the required CTMB Auditor and Monitor Training Course via the CLASS (Compliance, Learning, and SOP Solutions) training system** ~~Alliance auditor training~~ prior to their first audit and must maintain a signed confidentiality agreement on file at the Chicago office of the Alliance.

Second paragraph deleted

Section 17.5.6 Audit preparation by the institution
Extensive changes made throughout section to reflect the new CTMB Audit Guidelines. New text in bold

Principal investigators and institutional clinical research professionals are responsible for preparing for an audit **and ensuring that all relevant materials are available for review. An institution may be audited off-site at the Network Main Member, NCORP, or LAPs main member.**

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

The following records must be available for auditor review:

Section 17.5.6.1
IRB approvals, continuing reviews, amendment approvals, and safety reports, **copies of the locally utilized informed consent documents, Delegation of Tasks Logs (DTLs) and other regulatory documentation, if applicable**.

Section 17.5.7.1.1 Critical, Major and lesser deficiencies
Minor editorial changes

Section 17.5.7.2.1 IRB documentation
Minor editorial changes

New third bullet under 'Lesser IRB deficiencies may include but are not limited to:'

- Protocol annual re-approval delayed less than 30 days.
- Delayed re-approval for protocol closed to accrual for which all patients/study participants have completed therapy.
- **Copy of CIRB approval letter/study worksheet is not available or accessible at the time of the review.**

Section 17.5.7.2.2 Informed consent content (ICC)
Minor editorial changes

New third bullet under 'Lesser ICC Deficiencies'

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

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

New fourth bullet under 'Major DTL Deficiency'

- Performing tasks not assigned to individual
- Failure to keep DTL current
- Individual not listed on DTL
- **Individual performing study-related activities with DTL unapproved greater than 30 calendar days**

New section Added:
Lesser DTL Deficiencies:

- **Individual performing study-related activities with DTL unapproved 30 calendar days or less**

Section 17.5.7.2.4 Assessing the IRB, ICC and DTL

Minor editorial changes

Section 17.5.7.3 Review of accountability of investigational agents and pharmacy operations

Minor editorial changes

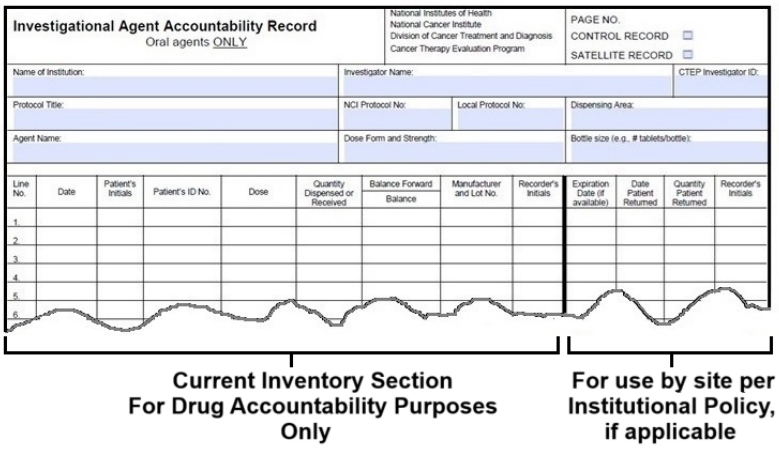
New text added to the fourth paragraph

A waiver statement allowing use of electronic DARFs (eDARFs) has not been issued by the NCI and the NCI does not endorse any eDARF pharmacy package. Institutions that choose to use an electronic accountability system must ensure the database is capable of producing a paper printout that is identical to the NCI DARF. Electronic accountability system database limitations are not valid reasons for improper accountability documentation according to NCI policy. **NCI launched the electronic accountability module in AURORA, known as the eDARF on December 27, 2024.**
New 6th and 7th paragraph added

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

For NCI Oral DARFs, study participant returns are considered waste pharmaceuticals and not part of agent accountability. The study participant return section of the DARF is for the convenience of the site (if required by site SOP) and is not part of study agent accountability for protocol auditing purposes.

Example of NCI Oral DARF



Investigational Agent Accountability Record
Oral agents ONLY

National Institutes of Health
National Cancer Institute
Division of Cancer Treatment and Diagnosis
Cancer Therapy Evaluation Program

PAGE NO.
CONTROL RECORD ☐
SATELLITE RECORD ☐

Name of Institution:	Investigator Name:	CTEP Investigator ID:
Protocol Title:	NCI Protocol No: / Local Protocol No:	Dispensing Area:
Agent Name:	Dose Form and Strength:	Bottle size (e.g., # tablets/bottle):

Line No.	Date	Patient's Initials	Patient's ID No.	Dose	Quantity Dispensed or Received	Balance Forward / Balance	Manufacturer and Lot No.	Recorder's Initials	Expiration Date (if available)	Date Patient Returned	Quantity Patient Returned	Recorder's Initials
1.												
2.												
3.												
4.												
5.												
6.												

Current Inventory Section For Drug Accountability Purposes Only

For use by site per Institutional Policy, if applicable

Updates to tables 17-2, 17-3, 17-4, 17-5, 17-6, 17-7, 17-8, and 17-9

Section 17.5.7.4 Review of patient case records

Minor editorial changes

New addition to 'Assessment of patient cases should include'

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

Section 17.5.7.4.1 Examples of critical, major and lesser deficiencies

Extensive updates to 'Informed Consent-Major Deficiencies', 'Treatment-Major Deficiencies', 'Disease Outcome/Response-Major Deficiencies', 'Adverse Events – Major Deficiencies', and 'General Data Management Quality- Major Deficiencies'

New Section added:

Correlative Studies, Tests, and Procedures – Major Deficiencies

- **Protocol-specified laboratory tests or other parameters not done, not reported or not documented**
- **Protocol-specified diagnostic studies including baseline assessments not done, not reported or not documented**

- **Protocol-specified research (Quality of Life forms, collection of research samples, etc.)/advanced imaging studies not done or submitted appropriately**

Updates to table 17-12 Final rating for patient case review

Section 17.5.9.1 Audit evidence of scientific misconduct
Minor editorial changes

Section 17.5.9.2 Action taken based on audit results
Minor editorial changes

Section 17.5.9.3 Report submission to CTMB
Minor editorial changes

Section 17.5.9.4 Changes to the Alliance database subsequent to audit
Minor editorial changes

Appendix B - Abbreviations

Abbreviation	Full Term
1572	Statement of Investigator (Form FDA 1572)
ABBR	Alliance Biorepositories and Biospecimen Resource
ACoS	American College of Surgeons
ACOSOG	American College of Surgeons Oncology Group
ACS	American Cancer Society
AER	Adverse Event Report
AIS	Audit Information System
Alliance	Alliance for Clinical Trials in Oncology
ANFU	Acceptable needs follow-up
ASCII	American Standard Code for Information Interchange
BioMS	Biospecimen Management System
BIQFSP	Biomarker, Imaging and Quality of Life Studies Funding Program
BLA	Biologic License Application
CALGB	Cancer and Leukemia Group B
CAO	Chief administrative officer
CAP	College of American Pathologists
CAPA	Corrective and Preventive Action
CCOP	Community Clinical Oncology Program
CCP	Cancer Control Program
CCSC	Core Correlative Science Committee
CE	Continuing Education
CFO	Chief financial officer
CFR	Code of Federal Regulations
CI	Clinical Investigator
CIB	Clinical Investigations Branch
CIRB	Central Institutional Review Board
CLIA	Clinical Laboratory Improvement Amendments
CoC	Commission on Cancer
COI	Conflict of Interest

Abbreviation	**Full Term**
CPOP	Central Protocol Operations Program
CR	Complete Response
CRA	Clinical research associate
CRADAs	Cooperative Research and Development Agreements
CRFs	Case report forms
CRP	Clinical research professional
CS	Correlative Science
CSA	Clinical Supply Agreement
CSM	Correlative Science Manual
CT	Central Time
CTAs	Clinical Trial Agreements
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTEP-AERS	CTEP Adverse Event Reporting System
CTMB	Clinical Trials Monitoring Branch
CTSU	Cancer Trials Support Unit
CV	Curriculum Vitae
DARF	Drug Accountability Record Form
dbGaP	Database of Genotypes and Phenotypes
DCCPS	Division of Cancer Control and Population Sciences
DCP	Division of Cancer Prevention
DCTD	Division of Cancer Treatment and Diagnosis
DNA	Deoxyribonucleic acid
DSMB	Data Safety and Monitoring Board
DTL	Delegation of Tasks Log
ET	East Coast Time
FCOI	Financial conflict of interest
FDA	Food and Drug Administration
FDF	Financial Disclosure Form
FWA	Federalwide Assurance
GBC	Group Banking Committee
GCP	Good Clinical Practice

Abbreviation	**Full Term**
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health
HSP	Human Subjects Protection
IAM	Identity and Access Management
ICC	Informed Consent Content
ID	Identification
IDE	Investigational Device Exemption
ID.me	Identity
IND	Investigational New Drug
IPEC	Institutional Performance Evaluation Committee
IRB	Institutional Review Board
IROC	Imaging and Radiation Oncology Core
IS	Information Systems
ISU	Information Systems Unit
IT	Information Technology
LAPS	Lead Academic Participating Sites
LCTB	Lung Cancer Tissue Bank
LOI	Letter of Intent
LTB	Leukemia Tissue Bank
MAYO	Mayo Clinic Bank
MedDRA	Medical Dictionary for Regulatory Activities
MGA	Multi-Group Audit
NCCCP	NCI Community Cancer Center Program
NCCTG	North Central Cancer Treatment Group
NCDB	National Cancer Data Base
NCI	National Cancer Institute
NCTN	National Clinical Trials Network
NDA	New Drug Application
NIH	National Institutes of Health
NMC	Non-Member Collaborators
OAOP	Online Agent Order Processing

Abbreviation	**Full Term**
OEWG	Operational Efficiency Working Group
OHRP	Office for Human Research Protections
OPEN	Oncology Patient Enrollment Network
ORI	Office of Research Integrity
PBTP	Procedure-Based Therapy Program
PCO	Pathology Coordinating Office
PDF	Portable Document Format
PHI	Protected Health Information
PI	Principal investigator
PMB	Pharmaceutical Management Branch
PPP	Pharmacogenomics and Population Pharmacology
PR	Partial Response
PRO	Patient Reported Outcomes
QA	Quality assurance
QARC	Quality Assurance Review Center
QOL	Quality of life
RCR	Registration and Credential Repository
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
RRA	Request for Rapid Amendment
RSS	Regulatory Support System
RT	Radiologic Technology
RUMS	Roster Update Management System
SAE	Serious adverse event
SAS	Statistical Analysis System
SCRC	Study Concept Review Committee
SDMC	Statistics and Data Management Center
SEI	Sensitive Electronic Information
SMU	Systems Management Unit
SPOREs	Specialized Programs of Research Excellence
STL	Washington University Bank
SUSAR	Suspected Unexpected Serious Adverse Reaction

Abbreviation	**Full Term**
TMA	Tissue Microarray
TRP	Translational Research Program
W-9	Request for Taxpayer Identification Number and Certification (Form W-9)