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.

Policy Name: Suspending a Study	**Policy Number:** 6.8
Section: Study Protocol – 6	**Date Revised:** December 16, 2024

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.

Policy Name: Study Termination with the local IRB	**Policy Number:** 6.14
Section: Study Protocol – 6	**Date Revised:** December 16, 2024

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.

Policy Name: Retrospective Data Collection from Closed or Completed Studies	**Policy Number:** 6.15
Section: Study Protocol – 6	**Date Revised:** December 16, 2024

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.