Policy Name: Data Submission	**Policy Number:** 8.1
Section: Data Management – 8	**Date Revised:** December 16, 2024

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.

Policy Name: Receipt and Distribution of Data Forms by SDC	**Policy Number:** 8.2
Section: Data Management – 8	**Date Revised:** December 16, 2024

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.