

Policy Name: Data Submission	Policy Number: 8.1
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8 Data management

8.1 Data submission

8.1.1 Completing forms

8.1.1.1 Alliance general instructions: all forms (electronic CRFs and paper forms)

All data forms and supporting documentation as required by the study are submitted to the Alliance Statistics and Data Center (SDC) using either Rave (for Alliance studies) or the legacy ACOSOG, CALGB, and NCCTG systems. 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>) or in the electronic data capture system used for the study. Do not store electronic copies of the form on your computer; always download the most recent copy from the Alliance website. Forms for intergroup studies are distributed by the coordinating group and may be obtained from their website, the Cancer Trials Support Unit (CTSU) website (<https://www.ctsu.org>), or iMedidata. If you are unable to locate an intergroup form, contact the responsible coordinating group.

When submitting copies of hospital records (path reports, lab results, etc.) make ONE-SIDED COPIES ONLY. Remove all patient identifiers and write the Alliance study and patient number on each page. For Rave, the supporting documents can be uploaded to the eCRF or faxed to the CTSU for appending to the form in Rave.

8.1.1.2 Instructions for forms submitted during treatment 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 accompanied by required documentation as specified in the protocol for the same time period. Check the data submission schedule in the forms package for

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required data. 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, the time period covered by the forms should be from day one of each treatment phase/cycle up until the administration of the subsequent treatment. 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 phase/cycle.

Follow-up and response forms

1. Record the dates of objective status, e.g., response or progression, only during the time period in which the event occurred.
2. The criteria for assessing response are specified in the protocol. For example in many solid tumor studies, overall objective status is determined per RECIST criteria by combining target lesions, non-target lesions, target lymph node lesions, non-target lymph node lesions and any new lesions or sites of disease.

Once a patient achieves a “PR” or “CR” they remain a “PR” or “CR” until the criteria for progression are met.

3. Supporting documentation of response, relapse or progression must be submitted as required by the protocol.

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 Alliance and the Cancer Therapy Evaluation Program (CTEP) websites (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Use only these criteria to identify events and

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determine grade severity. The version of the CTCAE is specified within the protocol, forms, and data entry screens.

- The forms used with the CTCAE are study-specific. Each form provides a list of solicited events for which grade must be coded. Additional fields are provided for specifying other events that occur.
- Code the grade that reflects the most severe adverse event or most abnormal lab value occurring during the reporting period.
- 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 3 or 4 alopecia).
- Each event included in the CTCAE is linked to a MedDRA code. Refer to the protocol for the MedDRA code version.

Adverse Event Expedited Reporting System (AdEERS)

Expedited adverse events are reported using the NCI’s Adverse Event Expedited Reporting System (AdEERS), located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers.htm. Guidelines for AdEERS reporting are included in each protocol.

Only file one AdEERS 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. Events reported in AdEERS should also be reported on the study-specific adverse event form if submission of the form is still required by the protocol.

8.1.2 Submission of data forms

The Alliance requires capture of data per protocol for all patients on Alliance treatment studies. Data continue to be submitted per protocol until the patient reaches the endpoints defined in the protocol (e.g.,

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relapse/progression), or until follow-up is discontinued per protocol instructions.

8.1.2.1 General data submission instructions

For patients on phase 1, 2, and 3 studies, data submission is required as indicated by the general rules in [table 8-1](#). **However, data submission requirements specified in the protocol take precedence over those indicated in the table.** For example, if a study includes treatment with a drug that may cause chronic toxicity, the protocol may require collection of adverse event data after study endpoints have been reached.

For all patients registered to phase 1, 2, and 3 treatment studies, survival information must be provided as specified in the protocol. Survival data must continue to be submitted until indicated otherwise by the protocol, that is until the patient reaches a follow-up truncation point stated in the protocol or until follow-up is discontinued for the entire protocol. Survival dates and dates of death must contain the day, month and year the patient was last known to be alive.

Death of a patient is reported on the forms specified in the study-specific data submission schedule.

Overdue data

For studies using Medidata Rave, study-specific delinquency lists are available in real time via the Rave task summary. For studies not using Rave, reports of delinquent data provided by the Alliance SDC are available on the [Alliance website](#) to main members. In addition, the institution evaluation report is sent to sites twice annually in conjunction with the Alliance group meetings; this includes an assessment of timeliness of data submission.

New malignancies

All new malignancies that occur following treatment must be reported via [AdEERS](#). For legacy ACOSOG, CALGB, and NCCTG studies, submit new malignancy data as specified in the protocol.

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Table 8-1. Alliance data submission guidelines *

Status	Example	Type of Data					
		Baseline/ On-Study	Off Treatment	Adverse Event +	Endpoint Data Relapse/or Progression	New Malignancy +	Survival
Typical Patient Pathway	Patient on or has completed RX, but has not reached follow-up completion as defined in protocol	X	X	X	X	X	X
Ineligible	Patient registered to study and deemed ineligible after SDC review	X	X	X	X	X	X
Canceled (Patient did not receive any protocol treatment)	Patient participating in a non-tx cancer trial (DCP) and did not receive protocol therapy	X	X				
	Patient did not receive any protocol treatment and participating in a phase 1 trial	X	X				
	Patient did not receive protocol treatment on a non-randomized phase 2 trial	X	X				
	Patient did not receive protocol treatment on a randomized phase 2 trial	X	X		X		X
	Patient did not receive protocol treatment and participating in a phase 3 trial	X	X		X		X
Withdrew Consent #	Patient received some protocol treatment and withdrew consent for clinical follow-up	X	X				X
	Patient received some protocol treatment and withdrew consent for all further follow-up	X	X				
Lost to Follow-up #	Patient received some protocol therapy and was deemed lost to follow-up	X	X				

* Data submission requirements specified in the protocol take precedence over those indicated in this table.

+ Required if the patient received protocol therapy

All data is required until the patient withdrew consent or is deemed lost to follow-up

8.1.2.2 Registered patients who never receive treatment (canceled patients)

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

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may not be removed from an Alliance protocol after being registered. Patients will be given a status of “canceled” if no protocol treatment is ever given.

For canceled patients, the institution provides the SDC with sufficient paperwork to document the reason why treatment was never given. Upon receipt of the documentation, a data manager reviews it and determines the status of the patient. Data submission requirements for canceled patients are provided in [table 8.1](#).

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 complete, supporting documentation is submitted, and any remaining issues or queries are resolved. Copies of all data required by the protocol and subject records must be submitted to the accepting institution.

Both sites will be responsible for their data. The transferring institution is eligible for audit of all patient data submitted up to the date of transfer. The accepting institution is responsible for submitting all subsequent data required by the protocol after the informed consent is signed.

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 Alliance Patient Transfer Form, which can be found on the [Alliance website](#). The completed Alliance Patient Transfer Form must be sent to the Alliance SDC, per the instructions on the form.

The sites should follow the CTSU guidelines for patients registered via the CTSU. Both the treating investigator at the

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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.

The Alliance database does not reflect the transfer until the completed transfer form has been signed by both institutional treating investigators and has been received at the Alliance SDC. For patients registered through the CTSU, the CTSU will forward the transfer information to the Alliance SDC. The Alliance database continues to reflect accrual from the institution that registered the patient.

8.1.2.4 Withdrawn consent to treat or follow

If a patient refuses further protocol treatment after therapy has begun, the institution continues to submit all data required by the protocol unless the patient specifically withdraws consent to be followed. A research participant's discontinuation or refusal of research treatment or intervention is not a withdrawal of consent to participate in the research study. This participant is still considered to be part of the study and should be followed per protocol/group policy.

A patient may, on rare occasions, withdraw consent for continued protocol participation. A verbal or written withdrawal of consent by the patient must be documented in the patient's research record. A patient's refusal to comply with follow-up visits or requirements is not considered to be an implied withdrawal of consent. Institutions must follow the Confirmation of Lost to Follow-up procedure (section 8.1.2.5) for a noncompliant patient who has not specifically withdrawn consent.

The institution must have written documentation that clearly states the level of withdrawal for follow-up. Written documentation can include one or more of the following:

- A signed and dated letter from the study participant documenting the withdrawal of consent (preferred).
- A clinic note from the research record documenting the date of phone conversation with study participant and the withdrawal of consent.

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- A signed and dated letter from the Principal Investigator or treating physician on institution letterhead documenting the withdrawal of consent.
- A signed and dated letter from the study participant’s power of attorney or guardian documenting the withdrawal of consent on the participant’s behalf.

The statement indicates whether the patient is withdrawing consent solely for clinical follow-up or if both clinical and survival follow-up are refused. The following is the suggested wording for the refusal statement:

“[Patient’s initials, Alliance ID #] withdrew consent to be followed with respect to (clinical status/clinical and survival status) on Alliance study (study #). Treating Physician’s signature_____ Date signed_____”

A copy is kept in the patient’s record at the follow-up institution. Based on information provided in the statement, the patient is removed from requirements for further follow-up of the appropriate type. All required study data up to and until the date consent withdrawal declared is expected to be submitted to the lead group/sponsor. 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 participant may rescind their consent withdrawal. Upon rescission of the consent withdrawal:

- Study participant’s status is re-activated.
- Documentation may be provided in same fashion as for consent withdrawal designation.
- Reminders and data expectancy are reactivated.

8.1.2.5 Confirmation of lost to follow-up status

Institutions may confirm that a patient is lost to follow-up using specific procedures. Patients that are confirmed lost to follow-up are removed from calculations of institutional performance related to timeliness. However, the percentage of patients deemed lost to

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follow-up is included in the metrics for institutional performance related to data quality.

Note: Study participants who refuse aspects of participation or withdraw consent from further participation should not be designated as lost to follow-up. The guidelines for patient withdrawal/consent withdrawal should be followed in these situations.

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

After a period of two years in which the institution has tried with unsuccessful results to contact a patient, the patient may then be declared lost to follow-up. Institutions may confirm that a patient is lost to follow-up. Recommended contact strategies include:

- Contact the patient by phone (e.g., residence, work, cell). Search the patient's medical record.
- Contact patient's primary care physician (e.g., family doctor) if permitted. Check the Social Security Death Index (<http://www.stevemorse.org/ssdi>) or appropriate registries for the region for information about the patient's death.
- Contact people listed for the patient (e.g., family members) if permitted.
- Send a letter by certified mail (<https://www.usps.com/ship/insurance-and-extra-services.htm>) with request for return receipt to the patient at the last known domestic address, or by registered priority international mail with request for return receipt to the patient at the last known non-US address.

For the patient to be confirmed lost, the institution must provide the Alliance SDC with the Alliance Confirmation of Lost to Follow-up form, which asks for limited details about the procedures used by the institution. The form must indicate **both** of the following items:

1. No date of death can be found in the Social Security Death Index.

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2. The certified or registered international letter has been returned unclaimed or marked addressee unknown, or it has been received (as documented by return receipt) but has resulted in no response from the patient over a one month period after it was received.

The Alliance SDC does not require submission of additional details of the attempts to contact the patient, but documentation of the attempts made during the 2 years should be retained in the patient's institutional research record for purposes of audits. For an audit, evidence of diligent effort to contact the patient may include:

- A copy of the Web page from the Social Security Death Index indicating that no information was found for the patient, *and*
- A certified or registered international letter returned to the institution unclaimed or marked addressee unknown. Alternatively, if the letter is delivered, but a response from the patient is not obtained by the institution within one month, the return receipt acknowledging the letter was received is evidence of due diligence. Because certified and registered international mail do not require the signature of a specific individual at the destination address, date of receipt of the letter should not be used to update the survival date of the patient. Even if the signed name on the return receipt for the certified or registered international mail appears to be that of the patient, it is not appropriate to update survival based on the signature on the returned receipt because of the level of uncertainty in signature verification.
- A telephone log or other documentation of attempts to contact the patient via telephone.

8.1.2.5.2 Continuing responsibilities for data submission

Patients that are confirmed lost to follow-up are removed from calculations of institutional

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performance related to timeliness. However, the percentage of patients deemed lost to follow-up is included in the metrics for institutional performance related to data quality (see section 2.10).

Retrospective data submission

If a patient is confirmed lost, the institution continues to be responsible for submitting protocol-required data (e.g., on-study, treatment, follow-up information) for the period from patient registration through the date of last contact with the patient.

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. The data manager will inactivate the Lost to Follow up form and advise the site as to the appropriate forms for completion and submission.

8.1.3 Submission of samples, specimens, and modality materials

Specimens and modality materials (e.g., karyotypes, images) are to be submitted to the modality office or repository as specified in the Alliance protocol. Procurement, processing, submission schedules, and shipment instructions are provided in each protocol, as well as in the Alliance Biospecimen Management System (BioMS). Alliance patient ID number, study number, institution, and specimen ID should appear on submitted materials, unless otherwise specified in the protocol.

If a registered patient refuses further protocol treatment but agrees to be followed, samples may 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 can withdraw consent to (1) further specimen collection, and/or (2) 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. Attempts will be made by the repository staff to retrieve any

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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 sections 11.2 and 11.3 for additional information.

8.1.4 Submission of samples for intergroup studies

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
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8.2 Receipt and distribution of data forms by SDC

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

Data for studies coordinated by other network groups are submitted directly to the coordinating group.

Policy Name: Quality Assurance Performed by Data Management Unit	Policy Number: 8.3
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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 coding, as well as intra- and interform consistency. A careful review of the data also is conducted to evaluate protocol compliance, e.g., patient eligibility, stratification and treatment. When discrepancies are found or data are missing, data 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, all pre-study tests and laboratory values. Eligibility is based on data available at the time of patient registration. If laboratory values subsequently change, the patient does not become ineligible. However, if laboratory values were erroneous at the time of registration, the patient may be declared ineligible.

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 resolve the problem. If the statistician cannot resolve the problem, the statistician will contact an executive officer or the group chair for determination. The data manager will notify the institution of any patients deemed ineligible.

Policy Name: Alliance Case Evaluation Process	Policy Number: 8.4
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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, clinical review by the study chair on the accuracy and consistency of key adverse event and outcome data reported by the treating institution for an individual patient (case) entered on a treatment study. The evaluation, which is required by the NCI, provides a centralized review of the data forms and other supporting documents by a medical expert, and ensures accurate data.

The patient (case) on a specific treatment study, not the institution, is the unit of evaluation. It is not the intent of the case evaluation process to evaluate the institution. Institutional evaluation is an independent process and is described in section 2.10.

8.4.1 Objectives

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

- Treatment 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 director of statistics 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 usually performed only once per patient. A patient summary report is created when a patient reaches an endpoint defined in the study. The study chair is notified when a report is generated. The study chair can perform the review in real time or in small batches. If the reviews are performed in batches, the schedule for the review is determined by the study team. The entire case evaluation process for the study must be completed prior to the final statistical analysis to be used for publication of results.

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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. All exceptions must be approved by directors of data management and statistics. In particular for some trials, review of all protocol specified events may be required.

Abstracts submitted to professional society meetings are exempt from these requirements. For most internal purposes (e.g., routine progress reports, interim analyses), it is not essential to have completed the number of case evaluations required for an external publication.

8.4.3 Case evaluation form

The study chair completes the case evaluation form to record his/her evaluation of the case based on an assessment of the patient summary report of data coded on the case report forms, and any other supporting documentation. 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 violations or inadequate reporting.

8.4.3.1 Patient summary report

Provided by the SDC, the patient summary report is a computer-generated review of 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 8-2](#) outlines the data topics included in the report.

Table 8-2. Data topics in the patient summary report

Treatment Compliance	Study Endpoint(s)	Study-Specific For Other Studies	Adverse Events (when applicable)	Additional Items
<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Primary and critical secondary endpoints • Examples: clinical tumor response, pathologic tumor response, disease recurrence or progression, death • Date(s) of endpoint(s) 	<ul style="list-style-type: none"> • Examples: skeletal-related event, lymphedema, submission of final questionnaire • Date(s) of endpoint(s) 	Phase 1 studies: <ul style="list-style-type: none"> • AEs of all grades Phase 2 studies: <ul style="list-style-type: none"> • Question: AEs of grade 2+ or AEs of grade 3+ Phase 3 studies: <ul style="list-style-type: none"> • AEs of grade 3+ 	<ul style="list-style-type: none"> • Determined by study team • Approved by directors (Data Management, Statistics) • Case by case basis

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8.4.4 Procedures

The data manager, who is assigned to the specific study, monitors and coordinates all case evaluation procedures. A patient summary report is generated at the time of case evaluation. The study chair reviews the data in the patient summary report to complete the case evaluation form. The study chair may also review the case report forms as part of the review process. A study chair's access to additional case report form data is based on study phase. Study chairs will have full access to data for phase 1 and 2 studies. Study chairs will not have access to case report forms for phase 3 studies.

The data manager reviews discrepancies and other problems noted by the study chair, and queries the site if necessary.

The study statistician will be notified if the study chair has not completed their review according to the agreed upon timeline. Serious delinquency of the study chair will be reported to the committee chair. Possible consequences for serious delinquency are prevention from serving as future study chair and loss of authorship on the primary manuscript.