14 SITE STUDY-SPECIFIC CLOSE-OUT

14.1 Overview, Key Principles, and Definitions

The term "close-out" refers to procedures undertaken to fulfill protocol, administrative, regulatory, and human participant requirements after all participant follow-up in an IMPAACT study has been completed. These procedures may include laboratory testing specified per protocol to be performed after all participant follow-up has been completed, data cleaning and locking the study database, and ensuring appropriate final disposition of study products and stored specimens. These activities and the use of the term "close-out" are independent of study closure with each study site's Institutional Review Boards/Ethics Committees (IRBs/ECs) and other regulatory entities.

Some of the procedures outlined below may require modification for a study that closes earlier than planned according to the study design. For example, early study closure may be recommended by a Data and Safety Monitoring Board (DSMB) or Study Monitoring Committee (SMC) at an interim analysis review or due to the inability to meet accrual goals (see Section 13).

The timeline and procedures described in this section are overlapping but distinct from timelines and procedures for manuscript development and publication procedures. Refer to Section 19 for more information on analysis, ClinicalTrials.gov results entry, manuscript development, and publication procedures.

Table 14-1 provides definitions of terms used when describing activities related to study close-out. Some of these terms are Network-specific; the sources of others are National Institute of Allergy and Infectious Diseases/Division of AIDS (NIAID/DAIDS) or ClinicalTrials.gov.

Table 14-1. Definitions of Terms

Term	Definition
Closed to Follow-up ***[DAIDS Study Status]***	The study has been permanently closed to accrual, all participants have completed study agents/products and all follow-up visits have been completed. Last participant has completed the last study visit and all participants are "off study." Equivalent to "Study Completion" in ClinicalTrials.gov.
Data Entry Termination Date	Date by which sites enter all new case report form (CRF/electronic CRF [eCRF]) data.
Participant Unblinding	"Unblinding a study" may refer to (1) informing participants of their blinded treatment codes, (2) informing the sites of the blinding codes for their participants, or (3) informing protocol chair(s) or other medical investigators of the study results or treatment codes. See Appendix I for a full description of unblinding in IMPAACT studies.
Primary Completion Date	Date that the final participant was examined or received an intervention for the purpose of the final collection of data for the primary outcome measures (per ClinicalTrials.gov).
Study Completion Date	Date that the final participant was examined or received an intervention for the purpose of the final collection of data. Equivalent to "closed to follow-up" date for DAIDS.
Study Database Closure/Data Complete	The CRF/eCRF data and the database are complete to begin the final analysis. Database locked, and routine delinquencies, queries, and edits cease; non-CRF/non-eCRF data that are to be included in the primary publication have been finalized and made available to the party conducting the analysis.

14.2 Timeline for Study Close-Out

In general, the protocol team will begin planning for study close-out approximately four to six months prior to the anticipated closed to follow-up date.

The protocol data manager (PDM) – in consultation with the protocol Clinical Trial Specialist (CTS) – will provide the protocol team with information on the projected primary completion date (PCD) for the study, the projected date for closed to follow-up (i.e., the projected study completion date), and the date range during which the final follow-up study visits should occur, as needed. Initial projections are typically updated upon completion of accrual into the study. Thereafter, projections are updated as needed depending on the study design and planned duration of participant follow-up.

Based on the anticipated PCD and/or closed to follow-up date, the Statistical and Data Management Center (SDMC) will generate a timeline for completion of data entry, resolution of data queries, and locking the study database, to comply with the recommended study analysis timelines provided in Section 19 and the requirements for data entry per ClinicalTrials.gov provided in Section 7. The protocol statistician – in consultation with the PDM and Laboratory Data Manager (LDM) – will provide the timeline to the protocol team approximately six months prior to the anticipated PCD.

The typical close-out timeline is shown below in Table 14-2; however, this may be condensed or modified for studies that have a short duration of follow-up, studies with accrual targets based on determination of evaluability, and/or those that are closed early at the recommendation of the DSMB or SMC.

Table 14-2. Timeline for Study Close-Out Procedures

Event	Timeline *(time from closed to follow-up date)*	Procedures	Responsibilities
Prior to Closed to Follow-Up Date			
Protocol Team Planning for Closed to Follow-Up	Approximately 6 months prior to anticipated closed to follow-up date	• Notify protocol team of upcoming closed to follow-up date • Facilitate discussion of close-out preparations (through pre-closure conference call or standing agenda item on team calls) • Begin work on close-out and analysis timeline and consideration of study-specific issues related to study close-out, including: – Prepare Site Considerations for Study Close-out memorandum – Prepare specimen shipping and testing plan for laboratory specimens – Confirm that Material Transfer Agreements (MTAs) and/or Specimen Transfer Agreements (STAs) are in place/updated as needed to facilitate specimen shipments – Confirm Data Transfer Agreements (DTAs)	PDM CTS Protocol team CTS LDM LC LDM
Considerations for Study Close-Out to Sites	Approximately 2-3 months prior to anticipated closed to follow-up date	• Finalize memorandum to sites • Distribute Site Considerations for Study Close-Out memorandum to sites	CTS with team CTS
Implementation of Site Study-Specific Close-Out Procedures	Approximately 2-3 months prior to anticipated closed to follow-up date	• Develop operational and staffing plans for completion of all required study close-out procedures as listed in the Site Considerations for Study Close-Out memorandum	Sites
Following Closed to Follow-Up Date			
Final Closed to Follow-up Notification	+ 1 week	• Notify protocol team and sites of closed to follow-up completion • Notify the DAIDS Regulatory Support Center (RSC) Clinical Study Information Office (CSIO) of study status change to closed to follow-up	PDM CTS
Final Visit Data Entry	+ 2 weeks	• Enter all participant visit data by this date	Sites
Specimen Request Lists Distributed	+ 2 weeks	• Distribute specimen request lists to sites/laboratories, as applicable to primary outcome evaluation (and secondary or other outcomes as needed)	LDM

Table 14-2. Timeline for Study Close-Out Procedures

Event	Timeline *(time from closed to follow-up date)*	Procedures	Responsibilities
Entry of all remaining data and resolution of all pending data queries	+ 4 weeks	• Ensure data completeness (collection and verification of all available study outcome data) • Distribute queries (e.g., data and laboratory) to sites to resolve data discrepancies	PDM
Notification of Upcoming Study Data Closure/Data Complete Date	+ 10 weeks (4 weeks prior to clinical database closure date)	• Notify sites of the upcoming clinical database closure date	PDM
Submission of Laboratory Data to DMC	+ 12 weeks	• Submit laboratory data to DMC • Confirm laboratory data received by DMC	Assay Laboratories LDM
Clinical Database Closure	+ 15 weeks	• Complete database freeze • Notify sites of data freeze date and request for site Investigator of Record (IoR) signatures • Sign off on CRFs/eCRFs	PDM PDM IoRs
Notification of Completed Database Clean and Locks	+ 21 weeks	• Complete clinical database lock and primary laboratory database lock • Notify protocol team and sites when databases are locked	PDM
Confirmation of Consent for Specimen Storage for Future Use and Distribution of Specimen Destruction Instructions	After all protocol-specified laboratory testing has been performed following closed to follow-up date	• Confirm that all protocol-specified laboratory testing has been completed • Inform sites to develop listing of participant identification numbers (PIDs) for which consent has and has not been provided for specimen storage for future use; DMC can confirm listing is consistent with consent status indicated in study database • Prepare site instructions for specimen destruction • Distribute site instructions for specimen destruction to sites	Protocol team LDM
Note: For more information on analysis, manuscript development, and publication procedures, refer to Section 19.			

14.3 Study Close-Out Communications and Considerations for Sites

The protocol team is responsible for addressing all unresolved issues related to study closure (e.g., confirming procedure for reporting adverse events, unblinding), defining study-specific close-out milestones and requirements, and developing appropriate study-specific close-out communications for sites regarding study closure and data analysis (refer to Table 14-2 for details on procedural timelines and responsibilities). Typically, protocol teams will develop a study close-out memorandum to be distributed to all participating sites along with additional communications as described below.

The PDM(s) – in collaboration with the study sponsor, CTS(s), statistician(s), LDM(s), and Laboratory Center (LC) representatives – will help study sites complete required study close-out data management procedures, distribute appropriate communications regarding study database closure and data analysis, and distribute queries to sites to resolve data discrepancies; for laboratory related queries, the LDMs may distribute communications and queries.

Sites are responsible for completing required study close-out procedures according to the timelines provided by the protocol team. The study-specific Investigator of Record (IoR) is ultimately responsible for ensuring all site requirements are met. Sites will develop operational and staffing plans for completion of all required study close-out procedures as listed in the Site Considerations for Study Close-Out memorandum.

Study close-out communications will be developed by the protocol team, with instructions and considerations tailored to study-specific needs and protocol requirements. The following standard communications are distributed to participating sites during the process of study close-out:

- Site Considerations for Study Close-Out memorandum (*approximately two to three months prior to the anticipated closed to follow-up date*): Detailed considerations for study close-out are distributed to participating sites. The memorandum generally addresses:

  - Reason for closure as well as the anticipated closed to follow-up date
  - Any study-specific guidance related to final participant visits, participant transition plans, and informing participants, parents/guardians, community advisory boards, and other key stakeholders of study plans
  - IRB/EC and other regulatory entity communications
  - Guidance on protocol deregistration
  - Laboratory considerations (e.g., specimen storage, shipping timelines, destruction)
  - Pharmacy considerations (e.g., study product storage, post-study access, disposition)
  - Data management considerations (e.g., timelines for completion of data entry, resolution of data queries, locking the study database, and eCRF IoR signature requirement)
  - Unblinding considerations (if applicable)
  - Regulatory and other essential document considerations, including any study-specific record retention requirements

  The CTS, in collaboration with the protocol team, is responsible for preparing the draft memorandum and coordinating the development, review, and distribution of this memorandum. The protocol team is responsible for contributing to and reviewing the draft memorandum. Sign-off is required from one protocol chair (chair, co-chair, or vice chair), one CTS, one DAIDS MO, and one PDM; if laboratory considerations are included, sign-off from one LDM and one LC representative is required; if pharmacy considerations are included, sign-off from one protocol pharmacist is also required. Sign-off requirements must be completed before the memorandum is distributed to participating sites.

- Final Closed to Follow-up Notification (*approximately 1 week following the official closed to follow-up date)*: A final confirmation notification is distributed to participating sites to include the date that the study closed to follow-up as well as any additional details or clarifications, as needed. This notice is generally distributed to sites by the PDM. The CTS informs DAIDS RSC CSIO of the closed to follow-up date.

- Clinical Database Closed Notification *(approximately 21 weeks following the official closed to follow-up date):* A confirmation notification is distributed to participating sites. This notice is generally distributed to sites by the PDM, and the notice should include:

  - Confirmation that the clinical database for the study is closed
  - Indication that no additional queries to which sites would need to respond are anticipated

14.3.1 IRB/EC and Other Regulatory Entity Communications

Sites are responsible for notifying their IRBs/ECs and other regulatory entities that the follow-up of participants has been completed according to their IRBs'/ECs' and other regulatory entities' procedures. Sites should continue routine communication with these review bodies (e.g., for continuing review, or for submission of other relevant documentation as needed per IRB/EC policies and procedures).

The PDM will provide technical assistance as needed to study site staff who need to access data maintained at the SDMC to fulfill IRB/EC study close-out reporting requirements.

14.3.2 DAIDS Protocol Deregistration

Consistent with the DAIDS Protocol Registration Manual, sites may deregister from a protocol in the following circumstances:

- The CRS no longer has participants on study (all follow-up has been completed) and does not plan to enroll additional participants.
- If no participants were ever enrolled at the CRS and the study has closed to accrual.

Deregistration is not automatic when a study is completed. The deregistration process is independent of a site's closure of a study with its IRBs/ECs; however, site IRB/EC policies should be reviewed prior to deregistration to help ensure that all IRB/EC requirements are met. For example, if an IRB/EC requires continued submission of safety information while data cleaning, analysis, and manuscript preparation are ongoing, deregistration may need to be deferred. NIAID sites may contact their DAIDS OCSO program officer for additional guidance.

When deregistering from studies conducted under an Investigational New Drug Application (IND), sites should also ensure that all applicable financial disclosure forms for all study staff listed on the Form FDA 1572 are reviewed and/or updated as needed. Refer to Section 7 for a full description of processes and requirements for financial disclosure by clinical investigations.

Refer to the current version of the DAIDS Protocol Registration Manual for complete deregistration details: https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual.

14.3.3 Informing Participants and Community Advisory Boards

Participants, parents/guardians, community advisory board members, and other key local stakeholders should be informed of study follow-up completion, consistent with usual site practices and standard operating procedures.

Study results may also be available for dissemination close to or after study close to follow-up. Refer to Section 19 for details describing study result dissemination.

14.3.4 Laboratory Specimen Storage and Shipping

Prior to study closure, the protocol team determines if additional laboratory testing is needed to complete the protocol-specified primary and secondary analyses, consistent with the protocol and statistical analysis plan(s). Each protocol should minimally provide an indication of when stored specimens are planned to be tested; details regarding specimen processing, storage, shipping, and testing are specified in the Laboratory Processing Chart (LPC). Some specimens may be stored at sites until after the study is closed to follow-up and/or they are requested to be shipped by the protocol team. To assist the team in prioritizing and determining specimens to be shipped for final study testing, the LDM will prepare a Status of Batched Laboratory Assays report prior to the anticipated closed to follow-up date.

In preparation for final laboratory testing, all study sites and testing laboratories should initiate efforts well in advance to fully execute all MTAs/STAs needed to permit specimen shipping and testing. The LDM will coordinate communications with study sites to request specimens to be shipped within specified timelines. Sites and testing laboratories are responsible for preparing shipments within the timelines specified in the specimen request letter from the LDM. Testing laboratories are responsible for completing testing and transmitting test results to the DMC within the specified timelines (e.g., through the Laboratory Data Management System [LDMS] or Data Submission System [DSS]). Site- and laboratory-specific specimen inventory quality assurance/quality control (QA/QC) procedures should be performed to ensure complete and accurate records. Any laboratory data queries and delinquencies should be resolved as soon as possible and within two weeks. These processes will help ensure that all required specimens have been shipped, tested, and reported appropriately to complete the study analyses.

14.3.5 Future Use Specimen Storage and Destruction

Specimens remaining after all protocol-specified laboratory testing has been performed may be stored in on-site storage or at NIAID or National Institute of Child Health and Human Development (NICHD) repositories. For some studies, participants (or their parents/guardians) are asked to provide written informed consent for continued storage and future research of these specimens. If such consent has been provided, the specimens will be retained. If such consent has not been provided, the specimens will be destroyed. If requested, the DMC helps sites and/or laboratories confirm the listing of participants who did not provide informed consent for post-study specimen storage and possible future research testing. See Section 17 for further details on specimen storage.

14.3.6 Study Product and Pharmacy

Post-Study Access to Study Product

Plans for post-study access to study product are typically addressed in the study protocol. The protocol team should provide any information necessary to facilitate transition of study participants to non-study sources of care and non-study provided treatment as needed. For studies that close early, the protocol team may need to rapidly address issues related to access to study product as final study visits are conducted.

Final Disposition of Study Product

Directions for final disposition of study drug are typically addressed in the study protocol. If applicable, the DAIDS protocol pharmacist will develop written instructions for final disposition of study product and associated documentation to provide to sites as part of the Site Considerations for Study Close-Out memorandum referenced above. Guidance will generally follow procedures as outlined in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* available here: https://www.niaid.nih.gov/research/daids-clinical-research-pharmacy-and-study-products-management

14.3.7 Data Management

The PDM is responsible for informing the protocol team and sites of the date the final participant completed the final study visit and is off-study, ensuring clinical data completeness (collection and verification of all available study outcome data), distributing queries to sites to resolve data discrepancies, and distributing appropriate communications to all sites indicating the completion date of the study database clean and lock, as well as requesting IoR signatures of eCRFs. The LDM is responsible for ensuring non-CRF laboratory data completeness and distributing queries to laboratories to resolve discrepancies.

Sites are expected to enter all study data within approximately two weeks following the closed to follow-up date and resolve all pending data queries within approximately two weeks of receipt of the query. Exceptions may be made to this timeline for large databases or for laboratory data that may require additional time after the closed to follow-up date. Data queries, including queries to testing laboratories, may be generated as a result of the data cleaning process, and additional queries may be generated later as data analysis proceeds. All sites should continue data management activities, as required, through the period of data analysis. Site-specific QA/QC procedures should be completed in coordination with data lock and data freeze expectations provided by the DMC, and data queries and delinquencies should be resolved as rapidly as possible.

In addition to the Site Considerations for Study Close-Out memorandum, the PDM will communicate with sites in the Notification of Study Data Closure/Data Complete Date four weeks prior to clinical database closure.

Study site staff are responsible for contacting the study PDMs with any questions, issues, or problems.

14.3.8 Unblinding Procedures

If applicable, unblinding of all participant treatment assignments will occur once all primary outcome data (i.e., clinical, virologic, or laboratory-based) and safety data for each participant have been entered and cleaned, all outstanding data queries resolved, and any clinical outcomes reviewed as specified by the protocol.

As appropriate per Appendix I, the statistician and PDM collaborate with the protocol team to confirm plans for unblinding participants. The PDM provides unblinding memorandum(s) to the protocol team for review, and the chief data manager (or designee) prepares the unblinding listings for each site and distributes the listings to each site along with the unblinding memo. Sites should inform participants (or their parents/guardians) of their treatment assignments.

Refer to Appendix I for a full description of definitions, roles and responsibilities, and procedures related to unblinding.

14.3.9 Regulatory and Other Essential Documents

Refer as needed to the DAIDS policy on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials, which is available at the following website: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations.

All study-specific essential documents will need to be prepared and organized for long-term storage. Unless other site-specific organizational systems are in place, essential documents should be organized and categorized, to the extent possible, according to International Conference for Harmonisation Good Clinical Practice (ICH GCP) guidelines (ICH E6, Section 8.4).

During study close-out from IND studies, sites should also ensure that all applicable financial disclosure forms for all study staff listed on the Form FDA 1572 are reviewed and/or updated as needed. Refer to Section 7 for a full description of processes and requirements for financial disclosure by clinical investigations.

14.3.10 Record Retention Requirements

All sites are encouraged to begin planning for long-term storage of participant study records, including source documents and CRFs/eCRFs, early in the study close-out process. Site staff (e.g., coordinators and data managers) are encouraged to work with site quality management officers to develop operational plans and timelines for final QA/QC and organization of all files.

Sites should refer to the DAIDS Policy on Storage and Retention of Research Records, which is available at the following website: https://www.niaid.nih.gov/research/daids-clinical-research-protocol-informed-consent. This policy defines minimum requirements for retaining study records to ensure compliance with applicable regulations, laws, and policies. Requirements differ for IND versus non-IND studies. **In all cases, sites should contact the study sponsor for approval before destroying any clinical study records.**

For studies that are DAIDS supported and/or sponsored, the institution or designee must maintain adequate documentation of all IRB/EC records and clinical research records for at least three years or as designated after the completion of research. The three-year time period begins when all of the following are completed:

- All research-related interventions or interactions with participants (e.g., when all participants are off study)
- All protocol-required data collection and analysis of identifiable private information described in the IRB/EC-approved research plan
- Primary analysis of either identifiable private or de-identified information

For studies conducted under an IND, the same guidelines apply with the addition that the investigator or designee must retain clinical research records for two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the US Food and Drug Administration (FDA) is notified.

US Department of Health and Human Services (HHS) regulations require that records be maintained for at least three years after the study is completed.

No study records are permitted to be destroyed before the study to which the records relate is included on one of the lists entitled "List of Protocols having CRF/Pharmacy Records that will not be stored by DAIDS." There is one list for IND protocols and one list for non-IND protocols. These are studies for which DAIDS no longer has any regulatory obligation. This information can be found on the DAIDS RSC webpage for CRF/eCRF management: https://rsc.niaid.nih.gov/clinical-research-sites/case-report-form-management.

Most importantly, site investigators must retain records in accordance with the most stringent regulation, institutional policy, or local law that applies to the study being conducted.