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 subjects requirements after all participant follow-up in an IMPAACT study has been completed. These procedures may include protocol-specified laboratory testing, data cleaning, 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).

Sites that have completed participant follow-up at their site, are not anticipating future enrollments, and no longer wish to remain active in the study may seek to complete some of the procedures outlined below prior to the study meeting closed-to-follow-up status. In this scenario, the site should communicate their intent to the protocol team.

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

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 (may also be referred to as LPLV) and all participants are "off study." Equivalent to "Study Completion Date" in ClinicalTrials.gov.
Data Entry Termination Date	Date by which sites enter all new case report form (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, and/or (3) informing protocol chair 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 (PCD)	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. May or may not be the same as the closed to follow-up date, depending on the study design.
Rave Database Lock/Primary Laboratory Data Complete	The eCRF data and the primary laboratory data are complete so the final analysis can be completed. The Rave database is locked, and routine queries and edits have ceased; non-eCRF laboratory data that are to be included in the primary analysis have been finalized and made available to the party conducting the analysis.

14.2 Timeline for Study Close-Out

The timeline for study close-out is in relation to the closed-to-follow-up date for the study. The protocol team begins planning for study close-out approximately four to six months prior to the anticipated closed-to-follow-up date. The protocol statistician and the protocol data manager (PDM) – in consultation with the clinical research manager (CRM) – provide the protocol team with information on the projected primary completion date (PCD) and the projected date or date range for closed to follow-up for the study, respectively. Initial projections are typically updated upon completion of accrual into the study. Thereafter, projections are updated as needed.

Depending on the study design, the closed-to-follow-up date may be the same or different than the PCD. See Section 19 for further details on the PCD. The Statistical and Data Management Center (SDMC) works with other team members to generate a timeline for completion of data entry, resolution of data queries, shipping of specimens, testing of specimens, and locking the study eCRF 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 and PDM are responsible for notifying the protocol team of the anticipated and actual PCD and closed to follow-up dates, respectively. The DAIDS Monitoring Operations Branch (MOB) is also included on these notifications, and the CRM invites MOB representatives to participate in team calls and discussions that involve study closure timelines using the DAIDS MOB email alias, ocsomob@mail.nih.gov.

Procedures for data entry and clean-up, resolution of data queries, and database lock, if applicable, for all data are initiated upon confirmation of the PCD and/or closed to follow-up date. The PDM notifies the protocol team and the study sites of the closed to follow-up date. The Operations Center is responsible for informing the DAIDS Regulatory Support Center (RSC) Clinical Study Information Office (CSIO).

The typical close-out timeline is shown 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, studies preparing for a regulatory submission, and/or those that are closed early (e.g., 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 (26 weeks) prior	• Notify protocol team and DAIDS MOB 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, including DAIDS MOB representatives) • 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 export/import permits are in place/updated as needed to facilitate specimen shipments – Prepare Data Transfer Agreements (DTAs)	PDM CRM Protocol team CRM LDM Laboratory Center (LC) LDM
Site Considerations for Study Close-Out Memorandum	Approximately 2-3 months (8-12 weeks) prior	• Finalize memorandum to sites • Distribute Site Considerations for Study Close-Out memorandum to sites	CRM with protocol team CRM
Site Implementation of Study-Specific Close-Out Procedures	Approximately 2-3 months (8-12 weeks) prior	• 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	Approximately 1 week after	• Notify protocol team, DAIDS MOB, and sites of closed to follow-up completion • Notify the DAIDS RSC CSIO of study status change to closed to follow-up	PDM Operations Center
Final Visit Data Entry	2 weeks after	• Enter all participant visit data by this date	Sites

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

Event	Timeline *(time from closed to follow-up date)*	Procedures	Responsibilities
Specimen Shipment Request Lists Distributed	2 weeks after	• Distribute specimen shipment request lists to sites/laboratories, as applicable for primary analysis (including primary and secondary outcome measures) • Determine timelines for specimen shipment requests for exploratory outcome measures, or other testing; issue requests accordingly	LDM Protocol team; LDM
Entry of all Remaining Data and Distribution of Data Queries	4 weeks after	• Ensure data completeness (collection and verification of all available study outcome data) • Distribute queries (e.g., data and laboratory) to sites and laboratories to resolve data discrepancies	PDM PDM, LDM
Notification of Upcoming Rave Database Freeze and Lock	10 weeks after (4 weeks prior to Rave database freeze date)	• Notify sites of the upcoming Rave database freeze and lock dates	PDM
Submission of Primary Laboratory Data to the Data Management Center (DMC)	12 weeks after	• Submit laboratory data to DMC • Confirm laboratory data received by DMC for primary analysis (including primary and secondary objectives)	Testing Laboratories LDM
Monitoring Complete	Prior to database freeze	• Notify DMC that all monitoring, including verification of the Rave data, is complete	DAIDS OCSO MOB or Westat (if applicable) representatives
Rave Database Freeze	15 weeks after	• Complete Rave database freeze • Request site Investigator of Record (IoR) signatures • Sign off on eCRFs	PDM PDM IoRs
Rave Database Lock/Primary Laboratory Data Complete	21 weeks after	• Complete Rave database lock • Confirm primary laboratory data are complete • Notify protocol team and sites when the Rave database is locked, and the primary laboratory data are complete	PDM LDM PDM
Note: For more information on analysis, manuscript development, and publication procedures, refer to Section 19. For more information on specimen storage for future use and distribution of specimen destruction instructions, refer to Section 17.			

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). Protocol teams develop a Site Considerations for Study Close-Out memorandum for distribution to all participating sites along with additional communications as described below.

The PDM – in collaboration with the study sponsor, CRM, protocol statistician, LDM, and LC representative – helps study sites complete required study close-out data management procedures, distributes appropriate communications regarding Rave database lock and data analysis, and distributes queries to sites to resolve data discrepancies; for laboratory-related queries, the LDM distributes 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 IoR is ultimately responsible for ensuring all site requirements are met. Sites 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 are developed by the protocol team, with instructions and considerations tailored to study-specific needs and protocol requirements, as described below:

- 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 and participant transition plans, including post-study access to study product, if applicable
  - IRB/EC and other regulatory entity communications
  - DAIDS protocol deregistration
  - Completion of financial disclosure forms
  - Stakeholder communications (including informing participants, parents/guardians, community advisory boards, and other key stakeholders)
  - Laboratory considerations
  - Management of stored specimens for future use
  - Final disposition of study product
  - Data management considerations
  - Unblinding considerations (if applicable)
  - Regulatory and other essential record considerations
  - Record retention requirements

The CRM, in collaboration with the protocol team, is responsible for preparing the draft memorandum and coordinating its development, review, and distribution. The protocol team is responsible for contributing to and reviewing the draft memorandum. Sign-off is required from one protocol chair (chair, or vice chair), one CRM, one DAIDS Medical Officer (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 one week following the closed to follow-up date)*: a final confirmation notification is distributed to participating sites. This notification includes the closed to follow-up date as well as any additional details or clarifications, as needed. This notice is distributed to sites and the protocol team by the PDM.

- Notification of Upcoming Rave Database Freeze and Lock *(approximately ten weeks following the closed to follow-up date and approximately four weeks prior to the anticipated Study Database Freeze date)*: an initial notification of the forthcoming Rave database freeze and lock dates is distributed to participating sites by the PDM.

- Notification of Rave Database Lock/Primary Laboratory Data Complete *(approximately 21 weeks following the closed to follow-up date)*: a confirmation notification distributed to participating sites. This notice is distributed to sites by the PDM and includes:
  - Confirmation that the Rave database for the study is locked and the primary laboratory data are complete
  - Indication that no additional queries to which sites would need to respond are anticipated

14.3.1 Completion of Study Visits and Additional Contacts

As the final participants are nearing completion of study visits, the protocol team provides guidance to sites on anticipated study completion timelines, with reminders related to final study visits, referrals, transition back to standard of care, post-study contacts, and post-study access, as applicable.

Requirements related to additional study contacts are addressed in the study protocol. The protocol team also provides any guidance or reminders related to additional study contacts, if required per protocol (e.g., pregnancy outcomes, adverse event resolution/stabilization, viral load confirmation). Based on study requirements, the protocol team may also provide an anticipated date of completion of additional study contacts to all sites.

Plans for post-study access to study product are typically addressed in the study protocol. The protocol team provides any information necessary to facilitate transition of study participants to non-study sources of care and non-study provided treatment, as needed. The protocol team may require completion or confirmation of post-study access plans.

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.

14.3.2 IRB/EC and Other Regulatory Entity Communications

Sites are responsible for notifying their IRBs/ECs, including the single IRB (sIRB) if applicable, 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 provides 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. The Operations Center provides assistance with sIRB close-out, as needed.

14.3.3 DAIDS Protocol Deregistration

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

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. Sites are encouraged to deregister as soon as applicable requirements have been met. However, site IRB/EC and regulatory entity policies should be reviewed prior to initiating the deregistration process with DAIDS 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.

14.3.4 Financial Disclosure Forms

Consistent with guidance provided in Section 7, sites should perform a comprehensive review of financial disclosure forms when closing studies conducted under an Investigational New Drug (IND) Application. Sites should ensure that all applicable forms for all study staff listed on any Form FDA 1572 are reviewed and/or updated, as needed. The study-specific form is available on the study-specific webpage.

Refer also as needed to DAIDS guidance: https://rsc.niaid.nih.gov/clinical-research-sites/financial-disclosure-forms.

14.3.5 Stakeholder Communications

As part of ongoing stakeholder communications, sites should inform key stakeholders that the study is closing. This may include communications with participants, parents/caregivers/guardians, or community advisory board members. As participants exit the study, contact information should be updated and permission to contact for future studies and/or results dissemination should be documented.

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.

14.3.6 Laboratory Considerations

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 analysis plan(s). Each protocol minimally provides 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. 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 prepares a Status of Batched Laboratory Assays report prior to the anticipated closed to follow-up date.

In preparation for final laboratory testing, the LDM communicates with study sites, testing laboratories, and repositories to request specimens to be shipped within specified timelines. Sites, testing laboratories, and repositories are responsible for preparing shipments within the timelines specified in the Specimen Shipment Request Letter from the LDM. Testing laboratories are responsible for establishing MTAs with study sites if required, completing testing, and transmitting test results to the DMC within the specified timeline and following the format and transmission method defined in the Data Transfer Agreement

(DTA). 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 discrepancies should be resolved as soon as possible and within two weeks. These processes help ensure that all required specimens have been shipped, tested, and reported appropriately to complete the study analyses.

14.3.7 Management of Stored Specimens for Future Use

For some studies, participants (or their parents/guardians) are asked to provide written informed consent (or permission/assent) for continued storage and future research of biological specimens remaining after all protocol-specified laboratory testing has been performed. These specimens may be stored in on-site storage or at NIAID or NICHD repositories, as applicable.

As part of the quality control (QC)/quality assurance (QA) activities, sites are encouraged to review all study informed consent forms and confirm that all corresponding eCRF entries related to this continued storage and future research of specimens are complete and accurate. The protocol team provides information and instructions for stored specimens after all protocol-specified testing has been completed. Instructions from the protocol team also address specimen destruction as applicable; no specimens may be discarded or destroyed unless or until instruction to do so is received from the protocol team or IMPAACT Network. See Section 17 for further details on specimen storage and destruction at the end of a study.

14.3.8 Final Disposition of Study Product

Directions for final disposition of study drug are typically addressed in the study protocol. At US sites, any remaining study product received from the National Institute of Allergy and Infectious Disease (NIAID) Clinical Research Products Management Center (CRPMC) must be returned to the CRPMC (unless otherwise directed by the sponsor). At non-US sites, any remaining study product received from the NIAID CRPMC must be destroyed following the site's standard operating procedures (SOP) for study product destruction in the presence of a DAIDS authorized witness.

If applicable, the DAIDS protocol pharmacist develops 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 generally follows 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.

14.3.9 Data Management Considerations

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 (i.e., the closed to follow-up date), ensuring clinical data completeness (collection and QC of all available study outcome data), distributing queries to sites to resolve data discrepancies, and distributing appropriate communications to all sites indicating the final data submission/QC/query timelines and planned/final Rave database freeze and lock dates, as well as requesting IoR signatures on eCRFs. The LDM is responsible for ensuring non-eCRF 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 Rave database freeze and lock expectations provided by the DMC, and data queries and delinquencies should be resolved as rapidly as possible. Study site staff are responsible for contacting the study PDMs with any questions, issues, or problems.

Generally, for non-IND studies, the PDM provides participant casebooks to sites following the final data lock date to ensure site IoR has control of and continuous access to the eCRF data. For IND studies, the PDM contacts sites to initiate the site-driven process to generate and download participant casebooks following final data lock to ensure site IoR has control of and continuous access to the eCRF data. For registrational studies only, sites are responsible for notifying the PDMs when the download of all participant casebooks is completed.

14.3.10 Unblinding Considerations

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

As appropriate per Appendix I, the protocol statistician and PDM collaborate with the protocol team to confirm plans for unblinding participants. The PDM provides unblinding memoranda to the protocol team for review, and the DMC/IMPAACT Chief Data Manager (or designee) prepares the unblinding listings for each site and distributes the listings to each site along with the unblinding memorandum. 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.

14.3.11 Regulatory and Other Essential Records

Refer as needed to the DAIDS SCORE Manual, which is available at the following website: https://www.niaid.nih.gov/research/daids-score-manual

Designated site staff prepare and organize all study-specific essential records for long-term storage (and/or regulatory inspection, if applicable). Unless other site-specific organizational systems are in place, essential records should be organized and categorized, to the extent possible, according to International Conference for Harmonisation Good Clinical Practice guidelines (ICH E6). As part of this process, the site IoR reviews all entries on the delegation of duties log for accuracy and once confirmed, signs and dates in the designated area on the log. Sites are strongly encouraged to perform internal QC/QA audits of all essential records in anticipation of document requests and/or regulatory inspections.

14.3.12 Record Retention Requirements

All sites are encouraged to begin planning for long-term storage of participant study records, including source records and 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.

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

The DAIDS Policy on Storage and Retention of Research Records (https://rsc.niaid.nih.gov/clinical-research-sites/daids-record-storage-assessment) and the DAIDS SCORE Manual (https://www.niaid.nih.gov/research/daids-score-manual) define minimum requirements for retaining study records to ensure compliance with applicable regulations, laws, and policies. In circumstances where multiple sets of requirements apply, the most stringent retention requirement must be followed. Requirements differ for IND versus non-IND studies.

US Department of Health and Human Services and Food and Drug Administration regulations along with NIH guidelines require that study records be maintained for at least three years after a DAIDS-supported and/or sponsored study is completed.

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 is notified.

To assist clinical research sites in determining whether a study has met these requirements, the DAIDS RSC maintains a Trial List identifying studies that have fulfilled DAIDS record retention requirements. This information can be found on the DAIDS RSC webpage for Storage and Retention of Clinical Research Records: https://rsc.niaid.nih.gov/clinical-research-sites/daids-record-storage-assessment.