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## 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 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).

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**

| <b>Term</b>  | <b>Definition</b>  |
|--|--|
| <b>Closed to Follow-up [DAIDS Study Status]</b>            | The study has been permanently closed to accrual, all participants have completed study agents/products and all follow-up visits have been completed.<br><br>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.    |
| <b>Data Entry Termination Date</b>                         | Date by which sites enter all new case report form (electronic CRF [eCRF]) data.   |
| <b>Participant Unblinding</b>                              | “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. |
| <b>Primary Completion Date (PCD)</b>                       | 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.  |
| <b>Rave Database Lock/Primary Laboratory Data Complete</b> | 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 publication 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 will begin planning for study close-out approximately four to six months prior to the anticipated closed to follow-up date. The protocol statistician(s) and the protocol data manager (PDM) – in consultation with the protocol clinical research manager (CRM) – will 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 and planned duration of participant follow-up.

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) will work 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 statisticians 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) will also be included on these notifications, and the CRM will invite MOB representatives to participate in team calls and discussions that involve study closure timelines using the DAIDS MOB email alias, [ocsomob@mail.nih.gov](mailto:ocsomob@mail.nih.gov).

Procedures for data entry and clean-up, resolution of data queries, and database lock, if applicable, for all data should be 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 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**

| <b>Event</b>   | <b>Timeline<br/>(time from closed to follow-up date)</b> | <b>Procedures</b>   | <b>Responsibilities</b>  |
|--|--|---|--|
| <b>Prior to Closed to Follow-Up Date</b>                   |  |   |  |
| Protocol Team Planning for Closed to Follow-Up             | Approximately 6 months (26 weeks) prior                  | <ul style="list-style-type: none"> <li>• Notify protocol team and DAIDS MOB of upcoming closed to follow-up date</li> <li>• Facilitate discussion of close-out preparations (through pre-closure conference call or standing agenda item on team calls, including DAIDS MOB representatives)</li> <li>• Begin work on close-out and analysis timeline and consideration of study-specific issues related to study close-out, including:                             <ul style="list-style-type: none"> <li>– Prepare Site Considerations for Study Close-Out memorandum</li> <li>– Prepare specimen shipping and testing plan for laboratory specimens</li> <li>– Confirm that Material Transfer Agreements (MTAs), export/import permits, and/or Specimen Transfer Agreements (STAs) are in place/updated as needed to facilitate specimen shipments</li> <li>– Confirm Data Transfer Agreements (DTAs)</li> </ul> </li> </ul> | PDM<br><br>CRM<br><br>Protocol team<br><br>CRM<br><br>Laboratory Data Manager (LDM)<br>Laboratory Center (LC)<br><br>LDM |
| Site Considerations for Study Close-Out Memorandum         | Approximately 2-3 months (8-12 weeks) prior              | <ul style="list-style-type: none"> <li>• Finalize memorandum to sites</li> <li>• Distribute Site Considerations for Study Close-Out memorandum to sites</li> </ul>  | CRM with protocol team<br>CRM  |
| Site Implementation of Study-Specific Close-Out Procedures | Approximately 2-3 months (8-12 weeks) prior              | <ul style="list-style-type: none"> <li>• 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</li> </ul>  | Sites  |
| <b>Following Closed to Follow-Up Date</b>                  |  |   |  |
| Final Closed to Follow-up Notification                     | Approximately 1 week after                               | <ul style="list-style-type: none"> <li>• Notify protocol team, DAIDS MOB, and sites of closed to follow-up completion</li> <li>• Notify the DAIDS RSC CSIO of study status change to closed to follow-up</li> </ul>   | PDM<br><br>Operations Center   |
| Final Visit Data Entry                                     | 2 weeks after  | <ul style="list-style-type: none"> <li>• Enter all participant visit data by this date</li> </ul>   | Sites  |

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

| <b>Event</b>   | <b>Timeline<br/>(time from closed to follow-up date)</b>  | <b>Procedures</b>  | <b>Responsibilities</b>                                  |
|--|---|--|--|
| Specimen Shipment Request Lists Distributed  | 2 weeks after   | <ul style="list-style-type: none"> <li>• Distribute specimen shipment request lists to sites/laboratories, as applicable to primary outcome evaluation (and secondary or other outcomes, as needed)</li> </ul>   | LDM  |
| Entry of all Remaining Data and Distribution of Data Queries   | 4 weeks after   | <ul style="list-style-type: none"> <li>• Ensure data completeness (collection and verification of all available study outcome data)</li> <li>• Distribute queries (e.g., data and laboratory) to sites and laboratories to resolve data discrepancies</li> </ul> | PDM<br><br>PDM, LDM                                      |
| Notification of Upcoming Rave Database Freeze and Lock   | 10 weeks after (4 weeks prior to Rave database lock date) | <ul style="list-style-type: none"> <li>• Notify sites of the upcoming Rave database freeze and lock dates</li> </ul>   | PDM  |
| Submission of Laboratory Data to DMC   | 12 weeks after  | <ul style="list-style-type: none"> <li>• Submit laboratory data to DMC</li> <li>• Confirm laboratory data received by DMC</li> </ul>   | Testing Laboratories<br>LDM                              |
| Monitoring Complete  | Prior to database freeze                                  | <ul style="list-style-type: none"> <li>• Notify DMC that all monitoring, including verification of the Rave data, is complete</li> </ul>   | DAIDS OCSO MOB or Westat (if applicable) representatives |
| Rave Database Freeze   | 15 weeks after  | <ul style="list-style-type: none"> <li>• Complete Rave database freeze</li> <li>• Request site Investigator of Record (IoR) signatures</li> <li>• Sign off on eCRFs</li> </ul>   | PDM<br>PDM<br>IoRs                                       |
| Rave Database Lock/Primary Laboratory Data Complete  | 21 weeks after  | <ul style="list-style-type: none"> <li>• Complete Rave database lock</li> <li>• Confirm primary laboratory data are complete</li> <li>• Notify protocol team and sites when the Rave database is locked, and the primary laboratory data are complete</li> </ul> | PDM<br>PDM, LDM<br>PDM                                   |
| <p><i>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.</i></p> |   |  |  |

### 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 will develop a Site Considerations for 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, CRM(s), statistician(s), LDM(s), and LC representative(s) – will help study sites complete required study close-out data management procedures, distribute appropriate communications regarding Rave database lock and data analysis, and distribute queries to sites to resolve data discrepancies; for laboratory-related queries, the LDM(s) 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 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 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, 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
  - Guidance on informing participants, parents/guardians, community advisory boards, and other key stakeholders of forthcoming study close-out status, participant transition plans (as appropriate), and plans for disseminating study results (if known; see Section 19)
  - 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 CRM, 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, 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 generally distributed to sites 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 Closure 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 generally 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 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 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. The Operations Center will provide assistance with sIRB close-out, as needed.

### 14.3.2 DAIDS Protocol Deregistration

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

- The clinical research site (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 Site Office of Clinical Site Oversight program officer for additional guidance. National Institute of Child Health and Human Development (NICHD) sites may contact Westat for additional guidance.

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 Review of 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 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>.

### 14.3.4 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.

### 14.3.5 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. 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, export permits, and import permits needed to permit specimen shipping and testing. The LDM will communicate 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 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 will help ensure that all required specimens have been shipped, tested, and reported appropriately to complete the study analyses.

### 14.3.6 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 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 may be retained when approved by the IMPAACT Management Oversight Group (MOG). If such consent has not been



provided, the specimens will be destroyed. See Section 17 for further details on specimen storage and destruction at the end of a study.

### **14.3.7 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>.

### **14.3.8 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 (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.

### **14.3.9 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 are 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 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.

#### 14.3.10 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 guidelines (ICH E6, Section 8.4).

#### 14.3.11 Record Retention Requirements

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

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 is notified.

US Department of Health and Human Services 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 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.**