1.0 PURPOSE

1.1 This document identifies the requirements for closing a study, cleaning data, and preparing for study analysis.

2.0 SCOPE

2.1 This SOP applies to all ACTG studies and substudies and includes procedures for study closure to followup, data cleanup, and analysis.

3.0 DEFINITIONS

3.1 Core Protocol Team: A subgroup of the protocol team, which generally includes the chair(s), vice chair(s), statistician(s), data manager(s), Division of AIDS (DAIDS) Clinical Representative/Medical Officer, protocol pharmacist, and clinical trials specialist (CTS).

3.2 Writing Team: A subgroup of the protocol team members who collaborate to write an abstract or manuscript summarizing results of the study protocol. Under certain circumstances, specialists who are not protocol team members may be included.

3.3 Protocol Team Handbook: Guidelines for protocol development and implementation of ACTG studies; found on the ACTG member website.

3.4 Statistical Analysis Plan (SAP): A document that expands the data analysis plan in the protocol document, defines outcome measures, and lists tables and summaries that will be included in the analysis report.

3.5 Primary Analysis Report: Final analyses of the primary endpoints and other components, as agreed upon by the protocol core team and defined in the SAP. This document is drafted by the statistician(s). When the protocol chairs are satisfied with the report, it is considered an acknowledgement of the final Primary Analysis Report, which, in turn, starts the timeline for submission of the primary manuscript to the ACTG Publications Office.

3.6 Data Cleanup: All activities pertaining to verifying data accuracy, such as queries and database edit checks sent via quality assurance (QA) reports.

4.0 RESPONSIBILITIES

4.1 Scientific Committee (SC) Leadership

• Provides oversight of study conduct, closure, and analysis
• Provides guidance to protocol team regarding any study closure issues
4.2 Core Protocol Team

- Adheres to all ACTG policies and procedures related to study conduct, closure, and analysis preparation
- Addresses all unresolved issues related to study closure (e.g., confirm procedure for reporting adverse events, unblinding)
- Identifies Writing Team

4.3 Protocol Statistician(s)

- Develops the statistical analysis plan in close collaboration with the protocol chairs and/or core protocol team; distributes the SAP to the Core Team and others identified to be on the writing team. (Refer to SOP ACTG-111, “Publications and Disclosure of Study Results,” for additional information related to study analysis.)
- Works with the Data Management Center and team on study closure and data cleaning

4.4 Data Management Center (DMC)

- Ensures data completeness
- Distributes queries to sites to resolve data discrepancies
- Distributes monthly QA reports

4.5 ACTG Network Coordinating Center (NCC)

- Coordinates study closure process
- Distributes appropriate communications regarding study closure and data analysis (See Appendix I)

4.6 Clinical Research Sites

- Submit study closure letters to their Institutional Review Board (IRB) or Ethics Committee (EC) for review
- Respond to data queries in a timely manner to resolve data discrepancies
- Consult with their IRB/EC to determine whether the study needs to remain active in order to respond to data queries and/or review participant letters. (If determined this is the case, the site should contact the team to determine if all data queries have been completed and all participant letters have been distributed prior to deregistration.)
- Deregister with the DAIDS Protocol Registration Office. Sites should check the most current version of the DAIDS Protocol Registration Manual for guidelines on these procedures.
- Follow specific study closure instructions provided by the study team (Appendix I)
5.0 POLICIES

5.1 The decision-making process required to close the study is set forth in the statistical considerations section of the protocol.

5.2 Under standard closure, the dates included in the timeline must be set sufficiently in advance to permit the DMC to initiate data completion and cleanup tasks with the clinical research sites (CRSs). The study closure timeline should be prepared by the CTS, in consultation with the statistician(s), data manager(s), core team, and the writing team; the final version is distributed by the CTS.

5.3 Some of the procedures outlined in this SOP may need to be modified and adapted in a study that has been modified or terminated by the ACTG Executive Committee at an interim analysis review, based on the recommendation of the Data and Safety Monitoring Board, the ACTG Study Monitoring Committee, or the protocol team. In certain cases when a study is closed as a matter of urgency, the timeline and the study closure letters should be forwarded to the chair of the SC responsible for the study for review.

5.4 The DAIDS Clinical Representative/Medical Officer, as an active member of the protocol team, should be copied on all protocol communications related to study closure to provide the linkage for official NIAID communication.

5.5 Any disagreement among parties arising during study closure or analysis-preparation should be resolved at the SC chair level or through the appeals process (SOP ACTG-120, "Grievance and Appeal Policy and Procedure").

6.0 PROCEDURES

<table>
<thead>
<tr>
<th>Event</th>
<th>Responsible Party</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Message sent regarding scheduling of pre-closure conference call and notification to team to download the Study Closure and Publication and Disclosure of Study Results SOPs</td>
<td>CTS</td>
<td>16 to 17 weeks prior to Closed to Follow Up (CFU) date. Note: For studies that are rapidly closed to followup for safety reasons or lack of efficacy, the timeline will need to be modified and events will occur as expeditiously as possible.</td>
</tr>
<tr>
<td>Pre-closure conference call held: consideration of study-specific issues related to study closure, formation of writing team (see Appendix I)</td>
<td>Protocol team</td>
<td>15 to 16 weeks prior to CFU or equivalent to period between clinic visits +3 to 4 weeks, if &gt;12 weeks.</td>
</tr>
<tr>
<td>Study closure and analysis timeline developed</td>
<td>CTS, Data Manager (DM), Statistician, Core Team,</td>
<td>13 to 14 weeks prior to CFU or equivalent to period</td>
</tr>
<tr>
<td>Event</td>
<td>Responsible Party</td>
<td>Timeline</td>
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<td>----------------------------------------------------------------------</td>
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<tr>
<td>Writing Team</td>
<td>writing team</td>
<td>between clinic visits +2 weeks, if &gt;12 weeks</td>
</tr>
<tr>
<td>Study closure letters drafted (see Appendix I)</td>
<td>CTS and protocol team</td>
<td>13 to 14 weeks prior to CFU or equivalent to period between clinic visits +2 weeks, if &gt;12 weeks</td>
</tr>
<tr>
<td>Assessment of laboratory testing to be performed in time to meet the goals of the primary analysis and assurance of access to required specimens for testing</td>
<td>Protocol team</td>
<td>Once the CFU date is determined. If, for instance, batch testing is to be performed for genotypic drug resistance testing, the team should make the request far enough in advance to ensure completion of batch testing in time for inclusion in the draft analysis.</td>
</tr>
<tr>
<td>Study closure notification letters sent to CRSSs</td>
<td>CTS</td>
<td>12 weeks prior to CFU or equivalent to period between study visits if &gt;12 weeks</td>
</tr>
<tr>
<td>Finalization of study analysis plan</td>
<td>Protocol chair(s) and statistician(s)</td>
<td>12 weeks prior to CFU</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NOTE: This may be done prior to study CFU, at the discretion of protocol chairs and statisticians if the primary endpoint occurs prior to study closure.</td>
</tr>
<tr>
<td>Monthly QA reports sent</td>
<td>DMC</td>
<td>6 to 10 weeks prior to CFU, according to routine (every 4 weeks) schedule</td>
</tr>
<tr>
<td>Optional specific data queries sent to CRS leaders and coordinators</td>
<td>DMC</td>
<td>8 weeks prior to CFU</td>
</tr>
<tr>
<td>Completion of study followup for all participants</td>
<td>CRS staff</td>
<td>CFU</td>
</tr>
<tr>
<td>Data entry termination</td>
<td>DMC</td>
<td>4 weeks after CFU. The only exceptions made to this timeline would be for lab data for the primary study endpoints for which the testing requires an unusually extended period of time.</td>
</tr>
<tr>
<td>Event</td>
<td>Responsible Party</td>
<td>Timeline</td>
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<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Routine QA reports sent</td>
<td>DMC</td>
<td>Per routine schedule, 6 to 10 weeks after CFU</td>
</tr>
<tr>
<td>Queries sent to CRSs based on data monitoring plan</td>
<td>DMC</td>
<td>7 weeks after CFU</td>
</tr>
<tr>
<td>Remind CRSs of Data Closure/ Data Complete date</td>
<td>DMC</td>
<td>8 weeks after CFU</td>
</tr>
<tr>
<td>Deadline for site responses and corrections to database</td>
<td>CRS staff</td>
<td>9 weeks after CFU</td>
</tr>
<tr>
<td>NOTE: Timeline may be shortened to 4 weeks after CFU under exceptional circumstances, with the approval of the SASC.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Database checked for corrections and queries on key data items sent, as needed</td>
<td>DMC</td>
<td>10 weeks after CFU</td>
</tr>
<tr>
<td>Conference call held to review data completeness</td>
<td>Protocol chair(s), statistician(s), and data manager; protocol chair(s) communicate any necessary action to CRSs and PIs.</td>
<td>10 weeks after CFU</td>
</tr>
<tr>
<td>Study data closure/data complete (data-entry screens close)</td>
<td>DMC</td>
<td>12 weeks after CFU</td>
</tr>
<tr>
<td>Unblind study subjects, if applicable</td>
<td>See SOP ACTG-123, &quot;Unblinding Subjects&quot;</td>
<td>See SOP ACTG-123, &quot;Unblinding Subjects&quot;</td>
</tr>
<tr>
<td>Primary analysis report to protocol chair(s); notification to ACTG Publications Office</td>
<td>Protocol statistician</td>
<td>5 to 6 months after CFU</td>
</tr>
<tr>
<td>Draft manuscript/abstract submitted to ACTG Publications Office</td>
<td>Writing team chair</td>
<td>3 months after the Primary Analysis Report sent to protocol chair(s) (Refer to SOP ACTG-111, “Publications and Disclosure of Study Results” for additional information and timeline.)</td>
</tr>
<tr>
<td>List of secondary analyses documented in the protocol, newly planned analyses, and potential secondary manuscripts or abstracts submitted to SC chair, SC coordinator, and ACTG Publications Office for SC Leadership review,</td>
<td>Protocol team</td>
<td>Within 6 months of the date that final Primary Analysis Report is received by protocol chair. NOTE: Secondary analyses that are not included in this list must be submitted as a Data Analysis Concept Sheet (DACS). Refer to</td>
</tr>
</tbody>
</table>
### Event Responsible Party Timeline

<table>
<thead>
<tr>
<th>Event</th>
<th>Responsible Party</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>prioritization, and timeline determination.</td>
<td></td>
<td>SOPs ACTG-106 and ACTG-111.</td>
</tr>
</tbody>
</table>

### 7.0 REFERENCES

- ACTG Conference Call Usage Guidelines
- Protocol Team Handbook
- SOP ACTG-105, Protocol Development and Finalization
- SOP ACTG-106, Data Analysis Concept Sheet (DACS) Development and Review
- SOP ACTG-111, Publications and Disclosure of Study Results
- SOP ACTG-120, Grievance and Appeal Policy and Procedure
- SOP ACTG-123, Unblinding Subjects
- SOP ACTG-124, Study Data and Safety Monitoring Review

### 8.0 INQUIRIES

Questions and comments regarding this policy may be directed to the ACTG Network Coordinating Center at: ACTGSOPS@s-3.com.
Appendix I - Communications Regarding Study Closure

The following standard communications are distributed to CRSs during the process of study closure. Team leadership is required to write/review/approve letters distributed for routine study closure. The purpose of the letters is to communicate study-specific information and give instruction to the site, pharmacy, and participants. Study-specific issues should be discussed and agreed to by the team on the pre-closure conference call. For studies that are closed prematurely, the SC leadership must also review and approve the documents. Template communications are available at the ACTG Network Coordinating Center.

1. Notification of Upcoming Study Closure

2. Instructions to CRSs

3. Instructions to Pharmacists

4. Letter to Study Participants

1.0 Notification of Upcoming Study Closure

The initial notification is to inform all participating CRSs of impending study closure approximately 13-14 weeks before the date that all participant followup visits are expected to have been completed. The timing of notification may be adjusted for a study with followup visits less frequent than every 3 months or for a study that closes prematurely. The following information should be included in the initial notification:

1. Anticipated date of closure

2. Reason for closure

3. Initial instructions that the team may wish to provide prior to detailed site instructions

4. Notification that additional details will follow

2.0 Site Instructions for Study Closure

The site instruction letter is to provide CRSs with more specific instructions, guidelines, and a timeline for closure of the study to followup. This communication is distributed to all participating CRSs approximately 12 weeks before study closure to followup and includes information for participant followup and data cleanup. The following information should be included in the site instructions:

1. Study closure timeline – include approximate dates for

   - Last participant study visit
   - Last data entry
   - Timeline for completion of generic and study-specific case report forms (CRFs)
   - Data queries and cleanup
   - Database closure
   - Unblinding, if known
• Data analysis and reporting of results, if known

2. Instruction to notify IRB of study closure

3. Specific instructions for followup, CRFs, and specimens

• Refer to protocol for final visit evaluations and expedited adverse event (EAE) reporting requirements.
• Provide CRF instructions, if needed (eg, special study-specific forms, form completion that differs for on-treatment vs. off-treatment, no treatment, instructions for special cases).
• Provide information on continued specimen storage, or specimen shipment instructions (eg, specimens to be sent, name and address of recipient, shipping conditions, timeframe).
• Provide instructions for processing stored/batched specimens.

4. Availability of rollover protocol (protocol should be sent out at time of this letter)

• Note if there will be a rollover protocol, and who will sponsor it.
• Discuss how it will be structured (randomized/blinded or open-label).
• Provide entry criteria, if applicable.

5. List of any other protocols currently available and appropriate for entry

6. Discussion of timing for unblinding and dissemination of results

7. Reminder about site deregistration process

3.0 Study Closure Letter for Study Participants

Approximately 12 weeks prior to study closure, a sample letter to study participants is forwarded to all participating CRSs, primarily to thank study participants for their participation and to inform them of study closure procedures. Sites will follow IRB instructions for distribution to study participants. The following information should be included in the participant letter:

• General thank you for participation
• Final visit date
• Reason for closure
• Final study product dispensed
• Approximate unblinding date, if known and if applicable
• Availability of study product after study closure, if applicable
• Process for dissemination of preliminary study results
• Other study options, if known and if applicable

4.0 Instructions to Site Pharmacists for Study Closure

The pharmacy instructions are intended to inform the site pharmacists of the impending closure of the study and to provide guidelines on further dispensation, transfer, or return
of study product. The letter is sent to all participating CRSs approximately 12 weeks prior to study closure so that sites can forward the information to the site pharmacist. This letter should be written by the protocol pharmacist with assistance from the CTS and protocol team. The following information should be included in the pharmacy instruction letter:

- Date of closure
- Reason for closure
- Instructions to determine the amount of study product needed to complete the study
- Availability of study product after study closure
  - How it is to be dispensed, if extension provided
  - Information on assistance programs to obtain medication or financial aid, if study product will not be provided
- Disposition of remaining study product
  - Transfer of remaining study product to other studies
  - Return of remaining study product to CRPMC or destruction of remaining study product as appropriate
- Entity to contact for questions