18 STUDY CLOSE-OUT

The term *close-out* refers to procedures undertaken to fulfill administrative, regulatory, data, laboratory, pharmacy and human subjects requirements after participant follow-up in a Microbicide Trials Network (MTN) study has been completed. Responsibilities and procedures for study close-out are described below.

18.1 Study Close-Out Responsibilities

The general responsibilities of MTN partners for close-out of MTN studies are as follows:

- MTN study-specific management teams are responsible for defining study-specific, close-out milestones and requirements and developing a study-specific closeout checklist.
- MTN Clinical Trials Units (CTUs) and affiliated clinical research sites (CRSs) are responsible for completing required study close-out procedures at their respective site(s). Ultimate responsibility for ensuring that all site requirements are met rests with the site's study-specific Investigator of Record (IoR).
  - The U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS), the MTN Leadership and Operations Center [LOC (FHI 360) and University of Pittsburgh (Pitt)], the Statistical and Data Management Center (SDMC), and the Laboratory Center (LC) are responsible for helping study sites complete applicable study close-out procedures.
- The SDMC is responsible for ensuring collection and verification (if applicable) of all available study endpoint data; cleaning and locking the study database [Case Report Form (CRF) data] and study datasets [such as lab assay results and Audio/Computer Assisted Self Interviews (A/CASI)]; conducting study analyses; producing a Final Study Report (FSR); and providing tables, listings, and figures (TLFs) for a Clinical Study Report (CSR), as needed.

18.2 Study Close-Out Procedures

To facilitate planning for study close-out, the SDMC will provide protocol teams with information on the projected date for the final participant follow-up visit for each participating study site and for the study overall. Initial timeline projections will be made upon completion of accrual into the study. Thereafter, projections will be updated as needed based on the study design and planned duration of participant follow-up.

Each protocol team will begin planning for study close-out approximately one to six months prior to completing participant follow-up at any participating study site. Participating sites will be informed of the proposed close-out timeline and a review of required study close out requirements will be shared with sites as soon as possible so that sites can begin to plan accordingly.

Table 18.1 illustrates the general order in which study closeout procedures are completed and milestones are reached.

Table 18.1: Study Closeout Timeline

Last participant follow-up visit	•Study closed to further data collection visits
Data cleaning	•Resolution of data, clinical, and analysis QCs •Final MedDRA coding of AEs (and WHO-drug dictionary coding of Concomitant Meds, if applicable) •Final Adverse Events/Expedited Adverse Events reconciliation
Statistical Analysis Plan (SAP)	•SAP is finalized prior to database lock
Data cut/freeze for primary analysis	•Programmer freezes dataset •Primary endpoint data (e.g., seroconverter data) complete/stable •Statisticians conduct analyses
Primary analyses	•Primary analyses are based on cut/frozen data •Primary analyses are finalized once the CRF database is locked
Closed results meeting/call	•Statisticians and/or Protocol Chair(s) present results of primary and secondary endpoint analyses
Results made public	•Conference presentation and/or primary manuscript publication •Additional manuscript work begins
Participant unblinding	•SDMC generates unblinding lists •Participants informed of their study randomization assignment
Clinical Study Report (CSR)	•Includes FSR Tables, Listings, and Figures (TLFs) •Additional TLFs generated

For some closeout tasks, there is flexibility in terms of when they can be completed. For example:

- Locking the A/CASI datasets (if A/CASI is used in the study) may occur in tandem with, or at any time prior to, the data cut/freeze for the primary analysis. The same is true for finalization of the Statistical Analysis Plan (SAP).
- Individual assay datasets may be locked on an assay-by-assay basis, as data are submitted, processed and cleaned. Although completion and locking of these assay datasets may take up to a year or more after the last participant follow-up visit (depending on the study and assay), it is expected that all assay datasets used for the primary analysis will be stable (locked or frozen, and not subject to change) for analysis and presentation at the closed results meeting.
- Locking of the CRF database may be delayed until after the closed results meeting, to allow for identification and resolution of any additional data discrepancies.
- Ideally, CRF database lock will occur prior to participant unblinding for blinded studies, or at a minimum, when no further CRF changes are expected prior to unblinding, unless early unblinding is requested by the Data and Safety Monitoring Board (DSMB).

After participant follow-up has been completed, protocol teams and study sites will implement the plans as listed in Tables 18.2 and 18.3, respectively.

Table 18.2: Network Responsibilities for Initiation of Study Close-Out

Lead Responsibility	Task
SDMC	•Develop plans, procedures and materials for verification of primary study endpoints (if applicable).
SDMC	•Develop plan for final study data submission, cleaning and analysis.
SDMC	•Develop plans, procedures and materials for unblinding the protocol team, study staff and participants (if applicable).
SDMC/MTN LOC (FHI 360)/ Protocol Team/ Protocol Chair(s)	•Develop plans for data analysis, manuscript preparation and publication, taking into account that the primary manuscript should be submitted within six months of the study database lock date.
SDMC	•Provide technical assistance (as needed) to study sites that wish to access data maintained at the SDMC to fulfill Institutional Review Board/Independent Ethics Committee (IRB/IEC) study close-out reporting requirements.
SDMC	•When all protocol-required laboratory results are complete per protocol as confirmed by the LC, provide study sites and/or LC with a list of study participants who did not provide informed consent for post-study specimen storage and possible future research testing. (See Section 18.4 for further information.)
Protocol Team	•Develop timeline and plans for return/destruction/disposal/reallocation of site supplies and equipment procured for the purposes of MTN protocol(s); for example, computers, participant-tracking databases, educational and training models and supplies.
MTN LOC (FHI 360)/ Protocol Management Team/DAIDS	•Develop a study-specific close-out checklist, adapting the requirements listed in Table 18.4 into a study-specific close-out checklist for each study. This checklist will be reviewed by the Protocol Management Team and DAIDS. Final checklists are filed with sites' regulatory documentation and serve as formal communication to the management team of the site's close-out status. Additional tools with specific timeline targets and completion dates may be drafted for sites' use prior to completion of the final checklist.
LC	•Develop a plan to complete all required post-study laboratory testing, including testing performed for verification of study endpoints. Inform study sites when all protocol-specified testing has been completed and when study sites may archive or destroy stored specimens (if applicable). In the event that biological specimens are shipped to the LC (or other designated laboratory), the LC (or other designated laboratory) will be responsible for archiving or destroying stored specimens (if applicable).
DAIDS Medical Officer (MO)	•Inform all relevant parties at DAIDS of the projected end date for participant follow-up at each study site; at a minimum, this will include communication to the DAIDS Office of Clinical Site Oversight (OCSO) PO and DAIDS Clinical Site Monitoring Group (CSMG) to begin planning for a final study-monitoring visit.
FHI Pharmaceutical Product Manager	•Develop written instructions for final disposition of investigational study drugs/products and associated documentation (if applicable).
MTN LOC (Pitt) Communications & External Relations	•Develop a communications plan template and associated materials to assist sites in planning for the dissemination of study results (if applicable). See Section 8 of this Manual for further information.

Site responsibilities assumed for study close-out are listed in Table 18.3.

Table 18.3: Site Responsibilities for Study Close-Out

The site will be responsible for completing the following:
• Identify the study close-out reporting requirements of its responsible Institutional Review Board/Independent Ethics Committee (IRBs/IECs). Some IRBs/IECs require submission of a study close-out report upon completion of participant follow-up, whereas others do not consider a study closed until the primary study-data analyses are completed and/or published. Each site will adhere to its IRB/IEC requirements for report submission. In the event that IRB/IEC guidelines do not specify the required content of study close-out reports, the reports should contain the following information: o Date when participant follow-up was completed o Number of participants enrolled in the study o Number of participants who completed the study o Number of participants who withdrew, or were withdrawn, from the study prior to its completion o Information on the adverse events that occurred at the site during the study o If applicable, reference to all Investigational New Drug (IND) Safety Reports submitted to the IRB/IEC during the study o Listing of protocol deviations and/or Critical Events reported by the site (if applicable)
• For randomized, blinded studies, tailor plans, procedures and materials for unblinding study staff and participants to suit local site needs in consultation with site-specific study staff and community representatives (if applicable) and in keeping with timelines and parameters defined by MTN LOC (FHI 360 and Pitt) and DAIDS.
• Tailor plans, procedures and materials for release of study results to study staff, participants and participant communities to suit local site needs in consultation with site-specific study staff and community representatives (if applicable) and in keeping with timelines and parameters defined by MTN LOC (FHI 360 and Pitt) and DAIDS.
• Develop operational and staffing plans for completion of all required study close-out procedures as listed on the study-specific close-out checklist.

Study sites will complete all required study close-out procedures as listed on the study-specific close-out checklist (see Table 18.4). Close-out procedures need not be completed in the order listed on the checklist, and some procedures may require considerably more time (as much as several months) than others. Study sites should complete each requirement in as timely a manner as possible and use the checklist to document progress toward meeting each requirement throughout the close-out process.

In most cases, public dissemination of study results will be coordinated by the MTN LOC (Pitt) Director of Communications and External Relations, in accordance with the terms defined by NIAID (and the National Institute of Mental Health and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, when applicable), as defined by the specific situational timelines, any relevant embargo policies and other parameters described in Section 8 and Section 19 of this Manual.

After all requirements have been met, the study site IoR will sign and date the checklist, file the signed original onsite and email a copy to the MTN LOC (FHI 360) Clinical Research Manager (CRM). Thereafter, all study records must be maintained in accordance with all applicable DAIDS policies and procedures, (e.g., the DAIDS SCORE Manual guidelines for Essential Documents and Source Documentation SOPs), the ICH E6 Good Clinical Practice (GCP) guidelines, all applicable regulations of the U.S. Food and Drug Administration (FDA) (e.g.,

Code of Federal Regulations (CFR), 21 CFR 312.57). See Section 18.2.2 for further information on requirements for record retention.

18.2.1 Data Quality Control Visits

As an MTN study draws to a close, the SDMC will determine whether the number of outstanding data quality control (QC) notes, particularly ones essential to data analysis, warrant a Data Quality Control Visit. When appropriate, the SDMC will contact the site to arrange and conduct the visit.

18.2.2 Long-Term Storage of Study Records

Study records must be maintained on-site for the entire study implementation period. To relocate study records, the following requirements must be met:

- All MTN study records must be maintained throughout the study close-out process; i.e., until the study close-out checklist is finalized and signed by the site IoR.
- All MTN study records must be maintained in accordance with protocol-specified protections of participants' confidentiality and with site IRB/IEC policies and procedures.
- All MTN study records must be filed in a safe, secure and confidential storage area that is easily accessible for prompt retrieval of records if needed.

18.3 Study Record Destruction

Under no circumstances will any study record located at a site be destroyed without prior written authorization, as described below. The destruction of study records may proceed provided the following requirements are met:

- All MTN study records must be maintained a minimum of seven years after final reporting or publication of the study's primary results, in accordance with the requirements of the University of Pittsburgh IRB which approves MTN LOC (Pitt) as the Coordinating Center.
- All MTN study records must be maintained in accordance with protocol-specified protections of participants' confidentiality and with site IRB/IEC policies and procedures. Site staff should follow the strictest retention requirements to which a study record is subject, including U.S. federal or state, country or local laws, regulations or policies.
- All study records of MTN studies conducted under an IND application must be retained for at least two years after the FDA's marketing product approval or disapproval, IND withdrawal or study discontinuation as per 21 CFR 312.62 (c). Requirements stipulated by other regulatory authorities (such as the South African Health Products Regulatory Authority for sites operating in South Africa) may also apply.
- All study records of MTN studies that are not conducted under an IND must be retained for at least three years after completion of research as per 45 CFR 46.115 (b).

When the above conditions are met, the MTN LOC (FHI 360) CRM will contact the study sponsor(s), product development organization(s), protocol chair(s), study statistician and DAIDS MO (if not the sponsor) for their approval to destroy study records. The DAIDS MO will confer with the DAIDS Regulatory Affairs Branch, as needed. Additional information may be found in the DAIDS policy on *Storage and Retention of Clinical Research Records* at: https://www.niaid.nih.gov/sites/default/files/StorageRetentionClinicalResearchRecordsPolicyFinal.pdf

Once the sponsor(s), product development organization(s), protocol chair(s), study statistician and DAIDS MO approve the destruction of study records, the MTN LOC (FHI 360) CRM will obtain approval from the MTN LC and Behavioral Consultant or designee to confirm that sites' local records are no longer needed for analyses. Following receipt of approvals from the above listed individuals, the MTN LOC (FHI 360) CRM will inform the MTN LOC (Pitt) Director of Operations & Fiscal and MTN PI, who will in turn ensure that the request for approval of destruction of study records is included on the agenda of the next scheduled MTN Steering Committee (SC) meeting. All approvals for destruction of study records will be documented according to *Good Documentation Practices Policy*, described in Section 9.2.2 of this Manual.

Following MTN SC approval, the MTN LOC (FHI 360) CRM will notify the sites that the MTN approves sites' record destruction; however, study sites will be reminded to confirm with their institutions and regulatory bodies whether any in-country or local requirements stipulate that study records must be retained for longer periods of time.

18.4 Specimen Destruction

Study site staff must store all specimens collected during a study per protocol until instructed to ship samples by the MTN LC, Protocol Chair(s), DAIDS or Network leadership. Selected samples may be shipped while others remain onsite indefinitely. Refer to Section 14.8 of this Manual for specific guidance regarding specimen destruction.

In select studies, study participants may be asked to provide written informed consent for their specimens to be stored after the end of the study for possible future testing. The specimens of participants who do not consent to long-term storage and possible future testing must be destroyed after all protocol-specified testing has been performed, relevant data have been cleaned, data analyses have been completed and permission is obtained from the SDMC and LC, per section 14.8.1 of this Manual. Specimen destruction that occurs at the CRS must be documented as described in the study close-out checklist.

Table 18.4 Sample Site-specific Checklist for an MTN Study-Specific Close-out

Note: Study-specific Close-out Checklists may include, but are not limited to, the items listed in the Sample checklist. Study-specific close out requirements will be determined in consultation with designated protocol team members (staff from MTN LOC (FHI 360 and Pitt), the SDMC, LC and the Behavioral Consultant or designee).

Site-specific Checklist for an MTN Study-Specific Close-out
❒ In accordance with IRB/IEC requirements, inform all responsible IRBs/IECs/regulatory entities of study closure.
❒ Complete and document all remaining study visits, including any final contacts to provide outstanding test results, counseling, referrals and treatment. Follow all protocol and/or Study Specific Procedures (SSP) Manual requirements for post study contact.
❒ Complete protocol de-registration with the DAIDS Protocol Registration Office, per the DAIDS RSC de-registration guidance, located in the Protocol Registration Manual: https://www.niaid.nih.gov/sites/default/files/prmanual.pdf.
❒ Compile lists of contacts who grant permission to be contacted for future studies, for communicating study results and unblinding information, if applicable.
❒ Complete all required CRFs and ensure that all site study data in the SDMC study database is complete and accurate, to the best of the site's knowledge.
❒ Resolve all outstanding data QC notes and confirm with SDMC that there are no outstanding data or clinical queries.
❒ Once all queries have been resolved, when instructed by SDMC, complete IoR sign-off on all participant casebooks to attest that the data has been reviewed and is deemed to be accurate.
❒ Consult Behavioral Consultant or designee and ensure accurate completion, submission and filing of all qualitative summary reports and transcripts (if applicable).
❒ Consult Behavioral Consultant or designee and confirm all audio files for qualitative assessments have been saved to CD and deleted from site servers.
❒ Consult DAIDS OCSO PO and resolve any pending monitoring findings/queries.
❒ Consult LOC (FHI 360) and resolve any pending assessment visit findings/queries.
❒ Ship all pending and requested biological specimens to the MTN LC (or other designated laboratory).
❒ Resolve all outstanding discrepancies and errors on the Laboratory Data Management System (LDMS) Specimen Monitoring Reports. Confirm with the MTN LC that discrepancies and errors have been resolved.
❒ As applicable, destroy all specimens collected during failed screening attempts. This includes specimens from participants who did not enroll and from first screening attempts for participants who required a new screening attempt before being enrolled. Such action does not require prior notification from the MTN LC or SDMC.
❒ After receiving written approval from the MTN LC, destroy all remaining specimens for participants who did not provide informed consent for long-term specimen storage and future research testing (a list of participant identification numbers will be provided by the SDMC). Document specimen destruction using destruction logs and in LDMS. **Note:** If all specimens have been shipped to the MTN LC and none remain on site, the MTN LC will be responsible for archival or destruction and documentation. If applicable, an MTN LC authorization memo instructs the site to complete study closeout before sample destruction due to delay in protocol required testing. A written inventory of all samples and storage locations should be submitted to MTN LC.
❒ Create a PDF sample disposition record that includes a sample identification and final location/disposition, at minimum. Send an electronic version of the document to the MTN LC. Print a final, hardcopy, sample disposition record for storage and file with other study records. The record, at minimum, needs to include a sample identification and final location/disposition. Each page of the printout should be initialed/dated by the person printing it, testifying that is accurate and complete (to the best of their knowledge).
❒ Conduct final reconciliation of study product accountability records in the pharmacy.

❒ Consult the FHI Pharmaceutical Product Manager and destroy unused study product prescriptions and materials as instructed (i.e. request and/or management slips).

❒ In accordance with the Clinical Trials Agreement and instructions provided by the FHI Pharmaceutical Product Manager, return or dispose of all investigational drug/product supplies.

❒ Confirm with MTN Regulatory that all necessary documentation is in place at MTN LOC (Pitt). This includes but is not limited to financial disclosures (FD) forms and investigator documentation.

❒ Review and prepare all required essential documents for storage, including but not limited to:

- DoD Log (with documentation of final sign-off by IoR). Final IoR sign-off may occur on or about the date of database lock as per SDMC Database Lock Notification Memo.
- FD forms (reflecting any relevant changes that occurred during the course of the study) for the applicable staff duration for the duration of study implementation (e.g., site activation through follow-up closure). In the year following the close of participant follow-up, the study team agrees to follow the MTN FD policy and make changes as necessary
- Logs that link participants' names and ID numbers (which also serve as the completed participant identification code lists required by International Conference on Harmonisation (ICH/GCP) guidelines)
- All qualitative data audio recordings
- All study documents bearing participants' names
- All study documents bearing participants' ID numbers
- All study documentation regarding drug/product receipt, dispensing, accountability and final disposition (if applicable)
- Final report by investigator to IRBs/IECs and local drug regulatory authorities (where applicable)
- Any other key communication/correspondence with the site

Note: The above list represents key required essential documents. The study-specific Close-Out Checklists should include a comprehensive list of required essential documents for storage based on the protocol requirements.

Documents must be stored securely and with adequate protection of participants' confidentiality. No study records may be discarded or destroyed without prior written authorization as per Section 18 of the MTN Manual of Operational Procedures (MOP).

❒ Complete, sign and date this checklist. File original with other study documentation and provide a copy to the MTN LOC (FHI 360) CRM.

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Investigator of Record Signature Date

_____

Investigator of Record Name (Print)