13. STUDY IMPLEMENTATION

A study site may initiate study implementation as soon as it receives the *Registration Notification Approval* from the Division of AIDS (DAIDS) Protocol Registration Office (PRO) and the *Study Activation Notice* from the Microbicide Trial Network (MTN) Leadership and Operations Center [LOC (FHI 360)]. Study procedures are directed by the protocol and guided by the Study-Specific Procedures (SSP) Manual for each study (as described in Section 11.13 of this Manual).

This section includes general guidelines on study implementation related to participant accrual, follow-up, data collection and documentation, study-related communications and reporting and are applicable to all MTN studies. The general laboratory aspects of implementation are described in Section 14 of this Manual.

13.1 Participant Accrual

This section describes the creation and management of accrual targets, and procedures which occur during the screening and enrollment process for each Clinical Research Site (CRS).

13.1.1 Accrual Targets

The Statistical and Data Management Center (SDMC) establishes participant accrual targets for each study according to the study's scientific objectives and statistical considerations. Specific participant accrual targets for a given study are outlined in the study protocol and/or SSP Manual. For studies with event-driven designs, adjustments to the sample size may be made at the recommendation of the Study Monitoring Committee (SMC) and/or Data and Safety Monitoring Board (DSMB), based on actual event rates observed among enrolled participants. However, changes in the sample size of the overall study and/or the length of the participant's study involvement must be reported by protocol and informed consent form (ICF) amendment to the site's Institutional Review Boards/Independent Ethics Committees (IRB/IEC) for approval prior to initiating the change.

In addition to the participant accrual target, MTN protocols and/or SSP Manuals may specify an estimated number of participants to be enrolled at each participating study site, often with provisions to shift enrollment targets across sites in response to site performance. Protocol teams should consider whether to specify a maximum number of enrolled participants for any site to ensure that no site inappropriately influences the study data. The Protocol Chair(s) and Protocol Statistician take the lead in making this determination with the protocol team and work with MTN LOC (FHI 360) and the SDMC to ensure its inclusion in the SSP Manual as applicable. In addition, for studies utilizing web-based randomization (e.g., Medidata Balance), the SDMC may set up randomization caps within the system to ensure enrollment does not exceed the pre-specified limits.

The SDMC and MTN LOC (FHI 360) will review accrual specifications during study-specific training, emphasizing the importance of closely monitoring the accrual process at each site and carefully managing the completion of accrual. For example, training may highlight the need to inform potential study participants who are screened toward the end of the accrual period that, even if they meet the enrollment criteria, they are not guaranteed enrollment in the study if the study quota is reached before they are enrolled.

Unless otherwise specified, study-wide accrual periods begin on the first day of participant enrollment at any participating study site; site-specific accrual periods begin on the first day of participant enrollment at that site. For most studies, the time from site-specific study activation to the first day of participant screening, and the time from first screening to first enrollment, will be tracked and reported. Participating study sites are responsible for establishing a study-specific participant accrual Standard Operating Procedure (SOP) for each MTN study and for updating this SOP as needed to meet accrual targets. See Section 11.4 of this Manual for further guidance on the content of this SOP.

Protocol teams are responsible for ensuring studies do not exceed the overall sample size as specified in the protocol. The scientific and ethical review process in place for each MTN study involves the consideration and approval of the number of participants to be enrolled in the study.

- For studies that require a certain number of fully evaluable participants for analysis purposes, the protocol may specify the overall sample size as the number of evaluable participants needed. In these studies, the total number of participants allowed to enroll in

the study will include both original participants who enroll and are fully evaluable, as well as those who enroll as “replacement” participants to make up for previously enrolled participants who do not meet criteria to be considered “fully evaluable.” For example, if a study sample size is 24 participants and 3 of the original 24 enrolled are not considered fully evaluable, the protocol team may enroll additional “replacement” participants as needed to achieve 3 more fully evaluable participants and reach the protocol-specified target of 24 evaluable participants. The study-specific definition of “fully evaluable” will be documented in the protocol and/or SSP Manual.

- For studies with event-driven designs, an increase to the sample size to achieve the total target number of events as defined in the protocol may be made at the recommendation of the SMC and/or DSMB, based on actual event rates observed among enrolled participants.

Protocol teams should consult the SMC and/or DSMB (if applicable) if they are considering increasing the overall sample size that is specified in the protocol. Changes in the sample size of the overall study and/or the length of the participant’s study involvement must be reported by protocol and ICF amendment to the site’s IRB/IEC for approval prior to initiating the change. In addition, for studies utilizing web-based randomization (e.g., Medidata Balance), the SDMC may need to adjust randomization setup and limits within the system.

> **NOTE:** Over-enrollment is not permitted as a means to make up for participant loss-to-follow-up unless specifically addressed in the protocol or directed by the DSMB.

The Protocol Chair(s) and Protocol Statistician will take the lead in making the determination on the criteria for replacement participants and ensure its inclusion in the study protocol, as applicable.

For studies in which enrollment targets are shifted across sites, sites will inform their IRBs/IECs of increases or decreases in their enrollment targets and will update their site-specific study ICF(s), in accordance with IRB/IEC requirements. At a minimum, updates should be provided at least annually as part of the continuing review of ongoing studies.

13.1.2 Screening and Enrollment

MTN study protocols and SSP Manuals describe study-specific screening and enrollment procedures in detail. This section provides information pertinent to participant screening and enrollment that is applicable across all MTN studies.

13.1.2.1 Obtaining Informed Consent

Written informed consent must be obtained from all potential MTN study participants prior to the conduct of any protocol-specified screening or enrollment procedure. See Section 9.6 of this Manual for additional information on the informed consent process.

13.1.2.2 Assigning Participant Identification Numbers

The SDMC uses a unique participant identification number (PTID) to identify each study participant in the study database. Depending on the data management software used in the given study, the SDMC will either provide sites with a list of PTIDs (e.g., for studies with paper

case report forms), or site staff will generate a PTID (e.g., Subject ID in Medidata Rave) for each participant in the study database. The site is responsible for assigning one unique PTID to each study participant and ensuring that each PTID is assigned only once.

After a participant has been assigned a PTID, he or she maintains that same PTID throughout the entire study. However, because PTIDs are study-specific, if a participant enrolls in a later MTN study, he or she will be assigned a different PTID for that study. Of note, study co-enrollment is forbidden unless specifically allowed by the relevant study protocols. Specific instructions on obtaining/generating and assigning PTIDs to study participants are provided in each study's SSP Manual.

13.1.2.3 Determining Participant Eligibility

The Investigator of Record (IoR) and other designated study-site staff are responsible for ensuring that only persons who meet study eligibility criteria are enrolled in an MTN study. As a condition of study activation, study sites must establish an SOP that describes how they will fulfill this responsibility. See Section 11 of this Manual for further guidance on the content of SOPs.

13.1.2.4 Defining Enrollment

From both a statistical and operational perspective, it is important to define the point at which enrollment in a research study becomes effective. For example, in some studies, enrollment is effective when a participant provides informed consent for study participation. For other studies, enrollment is effective when a participant is assigned to a study treatment group. The *effective point of enrollment* for each MTN study is defined in the protocol and/or SSP Manual.

13.1.2.5 Screening and Enrollment Logs

The U.S. National Institute of Allergy and Infectious Diseases (NIAID) DAIDS policy on *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* requires study sites to document screening and enrollment activity on screening and enrollment logs. This policy and the associated appendix can be accessed at the following websites:

- https://www.niaid.nih.gov/sites/default/files/daids-essentialdocpolicy.pdf
- https://www.niaid.nih.gov/sites/default/files/essentialdocappndx.pdf

Study sites may maintain screening and enrollment logs separately or combine them into one log. Template logs that may be adapted for use in MTN studies are provided as part of each study's implementation materials. The DAIDS policy specifies that participants' initials must be recorded on screening and enrollment logs, in addition to PTIDs. However, per a DAIDS-approved MTN policy, participants' initials do not need to be recorded on screening and enrollment logs if it presents a potential threat to participant confidentiality. In such cases, a separate log must be available to document the link between a participant's name and PTID. This log must be stored in a secure location.

13.1.2.6 Tracking Screening and Enrollment

The IoR or designee should monitor the accrual process at his or her site throughout the screening and enrollment period. Protocol teams are also responsible for reviewing the screening and enrollment data and implementing any necessary actions to address under- or over-enrollment issues and to ensure that accrual targets are met. Reporting methods of accrual information may differ for each study. The protocol team will agree on the methods for reporting

in advance of study implementation, and these methods will be specified in the SSP Manual for each study.

13.2 Follow-Up Visits

This section addresses participant retention, follow-up visit procedures, and procedures for participant transfer to a different study site.

13.2.1 Participant Retention Targets, Definitions and Tracking

Participant retention targets are specified in the protocol and SSP Manual for each study and are based on the scientific objectives and statistical considerations of the study. The SSP Manual also includes study-specific retention definitions and tips for maximizing participant retention. Participant-retention targets must be met to minimize biases in study results due to inaccurate or missing data. MTN study sites are responsible for establishing a study-specific participant retention SOP for each MTN study and for updating this SOP as needed to meet retention targets. See Section 11 of this Manual for further information on the content of SOPs.

The IoR or designee must monitor retention rates at his or her site during each study follow-up period. In addition, the SDMC generates retention reports from data that are entered in the study database. (See also Section 13.5 of this Manual.) Protocol teams are responsible for reviewing these reports throughout the study follow-up period and for taking any necessary actions to ensure that retention targets are met.

13.2.2 Scheduling Follow-Up Visits

Each MTN study protocol specifies the expected duration of participant follow-up and the number and type of study visits that are scheduled to take place during follow-up. For each protocol-specified follow-up visit, a target visit date and, if applicable, an allowable visit “window” is defined in the study protocol and/or SSP Manual for that study. Visit windows are defined as the period of time near the target date during which visit procedures may be performed. For example, if a follow-up visit is targeted to take place on study day 90, and a ±14-day window is specified for the visit, every effort should be made to conduct the visit on day 90, but the visit could take place at any time between days 76 and 104. To facilitate the scheduling of follow-up visits, the SDMC may provide study sites with a study visit-scheduling tool tailored to the specific study design. Depending on protocol specifications, a visit may be considered missed if the scheduled follow-up visit does not take place during the allowable visit window.

13.2.3 Follow-Up of Pregnancy Outcomes

For MTN studies in which a study product is used by women of reproductive age, the outcomes of any pregnancies that occur during follow-up must be ascertained and reported on case report forms (CRFs). The protocol will specify requirements and procedures for reporting outcomes that occur after each pregnant participant’s scheduled study-exit visit.

13.2.4 Participant Transfers Between Study Sites

Participant transfers between study sites may be permissible in some MTN studies. Transfer procedures will be detailed in a study’s SSP Manual, when applicable. General responsibilities for coordinating and executing transfers are listed below.

The site from which the participant is transferring is responsible for notifying the receiving site about the transfer, as well as the SDMC, MTN LOC (FHI 360), MTN Director of Pharmacy Affairs and the MTN Laboratory Center (MTN LC) staff. After the two sites have discussed and agreed on the logistical details of the transfer, the following steps will be completed:

- The SDMC notifies the transferring site of all outstanding data quality control (QC) notes for the transferring participant. The transferring site will resolve these QC notes.
- The transferring site explains the transfer arrangements to the participant and obtains written permission to provide copies of his or her study records to the receiving site. If the participant has already moved and cannot return to provide written permission to release his or her records, the transferring site sends the release to the receiving site for completion by the participant.
- The transferring site delivers certified copies of all the participant's paper study records to the receiving site via courier or overnight mail service. If the study involves blinded assignment to a study product, the pharmacy records must be delivered separately from the clinic records. The transferring site Pharmacist of Record (PoR) must deliver certified copies of the participant's pharmacy records directly to the PoR at the receiving site. The transferring site will document all materials that it sends to the receiving site and inform the receiving site of the shipment date and expected arrival date. The receiving site will confirm receipt of the shipment.
- The transferring site completes the *Participant Transfer CRF*.
- Upon receipt of the *Participant Transfer CRF* in the study database, the SDMC makes the appropriate database updates to reflect the change in site follow-up responsibility. The participant's original PTID and follow-up visit schedule remain unchanged, as does the participant's random assignment (if applicable).
- The receiving site establishes contact with the participant, obtains the participant's written informed consent to continue in the study at the receiving site and completes the *Participant Receipt CRF*.
- For participants assigned to a study product, an authorized prescriber at the receiving site prepares a prescription or a signed and dated note to pharmacy staff stating that the participant has provided written informed consent to take part in the study at the receiving site and that the prescriber authorizes the participant to continue use of the study product per the study protocol at the receiving site. Upon receipt of the original prescription or note, pharmacy staff at the receiving site dispenses the study product to the participant according to the product-assignment documentation received from the pharmacy at the transferring site.
- The transferring site retains responsibility for storing and shipping all specimens collected from the participant prior to participant transfer, unless the MTN LC instructs otherwise.

13.3 Data Collection and Documentation

MTN study staff are responsible for the collection, storage, timely submission and quality assurance of data at their site. All data should be collected and managed in accordance with the protocol, SSP Manual and DAIDS policies on *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* (see the website in Section 13.1.2.5) and *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. The SOP for *Requirements for Source Documentation* and associated appendix can be accessed at the following website addresses:

- https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf

- https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf

13.3.1 Participant Research Records

U.S. regulations and guidelines for Good Clinical Practice (GCP) require study staff to maintain adequate and accurate participant research records for each participant enrolled, containing all information pertinent to the study.

13.3.1.1 Contents of Participant's Research Records

A participant's research records should contain all the following elements:

- Basic participant identifiers
- Documentation that the participant provided written informed consent to screen for and participate in the study prior to the conduct of any screening or study procedures
- Documentation that the participant met the study's selection/eligibility criteria
- A record of the participant's random assignment (if applicable)
- A record of the participant's exposure to study products (if applicable)
- A record of all contacts and attempted contacts with the participant
- A record of all procedures performed by study staff during the study
- Study-related information on the participant's condition before, during and at the end of study participation, including:
    - Data obtained directly from the participant (for example, interview responses)
    - Data ascertained by study staff (for example, exam and lab findings)
    - Data obtained from non-study sources (for example, non-study medical records)

In addition to the above, the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* (see the website link above) requires that all protocol deviations be documented in participants' research records, along with reasons for these occurrences and actions taken to prevent or correct these or future occurrences, if applicable.

13.3.1.2 Concept of Source Data and Source Documentation

The term *source data* refers to all information in original records and in certified copies of original records related to clinical findings, observations or other activities in a clinical study that are necessary for reconstructing and evaluating the trial. Source data are contained in source documents (such as original records or certified copies).

The term *source documents* refers to original documents, data and records (such as hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries and/or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies of transcriptions certified after verification for accuracy and completeness; microfiche; photographic negatives; microfilm or magnetic media; X-rays; participant files; and records kept at the pharmacy, laboratories and medico-technical departments involved in the study). Source documents are commonly referred to as the paper-based or electronic documents upon which source data are first recorded. MTN study sites must adhere to the standards of source documentation specified in the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* (see the website link above). This policy contains both requirements and recommendations. Study sites must comply with all requirements and are advised, but not required, to comply with all recommendations.

Participants' research records for MTN studies often consist of the following types of source documents (as defined in the site's study-specific Source Document SOP):

- Narrative chart notes
- Baseline and follow-up medical history documents
- Visit checklists or procedural flow sheets
- Random assignment documentation (if applicable)
- Documentation of the provision and receipt of study product (if applicable)
- Laboratory testing logs and result reports
- CRFs provided by the SDMC
- Other source documents (such as site-specific worksheets, interview recordings/notes, or non-study medical records)

Supplemental information on the use of chart notes, visit checklists and CRFs provided by the SDMC is provided below.

13.3.1.3 Chart Notes

Study staff must document every attempt to contact a study participant (for example, in-person, via telephone, or any other method), the date, type, purpose and location of the contact, and specify the general status of the participant. Chart notes or site-specific source documents should be used for this documentation. Each entry should be signed and dated. The time at which a contact and/or a procedure occurs may be specified when necessary to document adherence to protocol requirements. Additionally, chart notes must be used to document the following:

- The informed consent process (unless an informed consent cover sheet or other source tool is developed)
- Procedures performed that are not recorded on other source documents
- Pertinent data about the participant that are not recorded on other source documents
- Protocol deviations that are not otherwise captured on other source documents
- Clinical information that is not otherwise captured on other source documents
- Any other relevant documentation necessary to supplement available information

Study sites are strongly encouraged to adopt a common format, such as the *Subjective-Objective-Assessment-Plan* (SOAP) format, for all chart notes to ensure the adequacy and consistency of note content and to maximize adherence to GCP standards. See https://www.ncbi.nlm.nih.gov/books/NBK482263/ for a description of SOAP notes, released by the National Center for Biotechnology Information (NCBI), part of the U.S. National Institutes of Health (NIH).

13.3.1.4 Visit Checklists

Each study site will be provided template visit checklists that may be adapted for use as convenient tools to guide study visits and to fulfill the requirement of documenting procedures performed at study visits. Visit checklists alone, however may not be sufficient for documenting all procedures. For example, chart notes may be required to explain why procedures in addition to those listed on a checklist were performed, or why procedures listed on a checklist were not performed; to document any procedures performed at interim visits; and document the content of counseling sessions and/or other in-depth discussions with participants (such as discussions related to adherence to protocol requirements).

When visit checklists are used as source documentation to document the completion of study procedures, they must be completed in accordance with standard source-documentation requirements. Tips for completing visit checklists in accordance with these requirements are as follows:

- Enter the PTID, visit date and, if applicable, visit code on the checklist; if source data are recorded on both the front and back of the checklist, enter the PTID and visit date on each page.
- Staff should only enter their initials beside the procedures that they perform. Initials should not be entered beside procedures performed by other staff members.
- If all procedures listed on a checklist are performed on the same visit date, the date need not be entered beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date beside each procedure as each is performed.
- If a procedure listed on the checklist is not performed, enter “ND” for not done or “NA” for not applicable beside the item, and record the reason on the checklist (if not self-explanatory). Initial and date the entry.

Study sites may adapt template visit checklists to site-specific versions to better reflect local staffing plans, logistics and procedures — provided the checklists comply with the study protocol and SSP Manual. All site-specific checklists should be provided to MTN LOC (FHI 360) for review and approval prior to use.

13.3.1.5 Case Report Forms Provided by SDMC

The CRFs developed for each MTN study are designed for use with the data-management system that will be used for the given study. The SDMC provides these forms to each participating site. As a condition of study activation, a study site must specify the forms that it intends to use as source documents in its study-specific Source Document SOP. Study staff must follow the specifications of this SOP consistently for all study participants. If study staff members are not able to record/enter source data directly on forms designated as source documents, the following procedures should be undertaken:

- Record the data onto an alternative source document.
- Enter the alternative source document into the participant’s study chart.
- Transcribe/enter the data from the alternative source document onto the appropriate form.
- Record a chart note stating the relevant study-visit date and the reason why an alternative source document was used.

13.3.1.6 Documentation of Study Product Accountability and Dispensing

Designated pharmacy staff must document the receipt, dispensing and final disposition of all study product and study supplies that are used in MTN studies. This documentation must comply and be maintained in accordance with guidelines provided in the *Pharmacy Guidelines and Instructions Manual* for MTN Clinical Trials as well as any supplemental instructions provided in the study protocol and/or SSP Manual.

13.3.1.7 Storing Documents

Participant research records must be stored securely at the study site, in accordance with the protocol and SSP Manual for the entire implementation period of the study. See Section 9.7 of this Manual for additional considerations related to participant confidentiality.

13.3.1.8 Record-Retention Requirements

Once all study follow-up procedures have been completed and the study database has been locked, any transfer of study records to an off-site long-term storage facility must be approved by a DAIDS Office of Clinical Sight Oversight (OCSO) representative. However, no records are permitted to be discarded or destroyed without prior written authorization from the MTN Protocol Team, provided by the MTN LOC (FHI 360) CRM in consultation with DAIDS and the MTN Executive Committee. Study records are the property of the MTN. See Section 18 in this Manual for additional details.

13.3.2 The Data Management System and Case-Report Forms

The SDMC selects the data management system (e.g., Medidata Rave) that will be used to receive and manage study data collected at sites for a given study. Each site collects study data by completing study CRFs in an electronic format, on paper or both, as specified in the SSP Manual and site Source Documentation SOPs.

13.3.2.1 Case Report Form Processing

Electronic Data Capture (EDC)

For studies utilizing EDC, site staff will enter study data manually into the electronic CRFs (eCRFs) within the study database (e.g., Medidata Rave). As specified in each site's Source Documentation SOP, data may be entered directly into the study database (i.e., eCRF is source), collected first on paper CRFs then entered into the study database, and/or entered into the study database based on other non-CRF source documents (e.g., lab reports, testing logs, chart notes, etc.).

The CRFs in the study database are set up within pre-defined study visit folders sorted by visit name and visit number. Paper CRFs, if utilized, include a designated place to record the participant ID, the name/number of the corresponding study visit and the visit date.

Within Medidata Rave, two types of queries will be generated: system queries and manual queries. System queries are automatically generated at the time data is entered and saved if the data entered does not conform to pre-programmed logic, is incomplete or contains inconsistent data. Manual queries are created in the study database by designated Rave users, such as the SCHARP Clinical Data Manager (CDM), SCHARP Clinical Safety Associate (CSA) and the Clinical Site Monitoring Group (i.e. the PPD study monitor).

DataFax

Each DataFax CRF is identified by a barcode that denotes the protocol number and type of form. Pages do not need to be faxed in sequence. DataFax processes images by separating a fax into individual pages, adjusting each page to correct for proper alignment and rotation, and identifying each page based on the barcode information and other key items (such as PTID and visit code). DataFax stores and tracks each image of a CRF.

DataFax uses intelligent character recognition (ICR) to extract data from checkboxes and enter numbers into numerical fields. The SDMC staff review each CRF at least twice, comparing the data entered by the ICR process with the actual data image and correcting any discrepancies. Data in text and comment fields are entered manually.

Data fields that require clarification, correction or verification are flagged with QC notes, which are included in QC reports that are regularly emailed to study sites for resolution. To resolve QC notes, site staff must make corrections or clarifications on the original CRFs and re-fax them to the SDMC. QC reporting schedules are determined based on the size and progress of the study and are specified in study reporting plans. See Section 13.5 of this manual.

13.3.2.2 Distribution of Case Report Forms

Prior to study initiation, the SDMC will provide the study site with a PDF file containing the full set of blank CRFs, applicable to the selected Data Management System, for IRB/IEC approval as needed, and for on-site printing and data collection, as needed (i.e., in the event that paper CRFs are used). See Section 13.3.2.7 of this Manual.

Once a study is under way, the protocol management team or SDMC may need to update one (or more) of the study-specific CRFs. In this situation, the SDMC is responsible for updating CRFs, as needed. Revised CRF pages in the PDF file(s) are assigned an updated version number and/or revision date, depending on the type of revision. The SDMC will issue a data communiqué and/or update the Data Collection section of the SSP Manual to communicate issuance of an updated data collection tool or CRF, and/or to notify the protocol team of updated CRF completion guidelines, as needed. If IRB/IEC approval is required for new or revised CRFs, study-site staff are responsible for obtaining approval and informing the SDMC and MTN LOC (FHI 360) when approval is obtained. Once all required approvals are obtained, study-site staff can remove and destroy all previous versions of the CRFs and implement the new version according to SDMC instructions.

13.3.2.3 Storage of Paper Case Report Forms

Study sites should store paper CRF supplies in an organized fashion, in a safe and secure location, that allows easy access to them and enables study-site staff to conduct an inventory at any time during the study. DataFax forms are designed for storage in a standard two- or three-ring binder, with the holes punched on the left side of the form. This may be useful for organizing participants' files. Alternatively, the CRFs may be stored in ordinary file folders. The site SOP for data management for each study should include specific details regarding the storage of forms.

13.3.2.4 Standard Elements in Case Report Forms

When possible, CRFs used in MTN studies are designed within standards and conventions developed by the SDMC, and in alignment with CDISC/CDASH standards. Standard elements include PTID format, visit codes and laboratory-result formats. Some CRFs have standardized content and formatting to ensure that required data for a given study are collected in a consistent manner. The SDMC may modify these forms to accommodate study-specific requirements for collecting data. Examples of standardized forms include:

- Adverse Event (AE) Log
- Concomitant Medications Log
- Medical History Log
- Pregnancy Report and History
- Pregnancy Outcome
- Missed Visit
- Participant Transfer

- Participant Receipt
- Termination
- Protocol Deviation Log

13.3.2.5 Completion and Review of Case Report Forms

For DataFax studies, form-specific instructions are provided on the back of each form. For Medidata Rave studies, form-specific instructions are provided in the study's *CRF Completion Guidelines* (CCG) document, which the SDMC provides for each study. The CCG provides detailed instructions and guidelines on skip patterns, form completion and data entry in EDC (if applicable). Study-site staff must perform internal data reviews on CRF data, as specified in the site's data management SOP, to ensure data accuracy and completeness. Each SSP Manual provides guidance regarding these site study data reviews to maximize data quality and minimize the number of QC notes that are generated by the SDMC for site resolution.

13.3.2.6 Handling Missing and Unknown Data

In compliance with Good Documentation Practices (GDP) and ICH E6 GCP, every effort should be made to complete all CRF requests for information during the participant's study visit. Any required data items left blank on a CRF, other than those resulting from appropriately followed skip patterns, are considered a GDP/GCP violation and will result in a data query (QC). Each SSP Manual provides detailed instructions for handling missing data in various situations, such as when a participant refuses to answer a question, does not know the answer to a question or is inadvertently not asked a question.

13.3.2.7 Completion of Case Report Forms

The SDMC routinely reports on data management quality performance of sites, as specified in Section 13.5.4 of this Manual.

In order to ensure that study documentation is able to be completed in a timely manner, as required, and participant visit schedules are maintained, it is important for sites to ensure the availability of all required resources.

- For EDC studies (e.g., Medidata Rave), site staff are responsible for obtaining and maintaining internet connectivity and internet-capable equipment, such as laptops, tablets and desktop computers, to facilitate timely entry and cleaning of data in the study database.
  - If internet connection or Metadata Rave is out of service, site staff use paper CRFs

- For DataFax studies, the SDMC Technology Systems and Services staff support maintaining the CRF data-transmission processes between the study sites and the SDMC. This includes:
  - Assisting sites with troubleshooting data-transmission problems if they occur, and developing alternate data-transfer methods, if necessary
  - Providing support and supplies, as appropriate, for maintaining and operating data-transmission systems
  - Tracking the completion and entering of CRFs to the SDMC

13.4 Study-Related Communications

After the initial release of a study protocol and SSP Manual, several types of study-related communication may be issued to report study progress or clarify study procedures and documentation requirements. Communications should comply with the *MTN Good Documentation Practices Policy* (see Section 9.2.2 of this Manual) as required and may include, but are not limited to, the following:

- Conference calls and meeting summaries: Protocol teams and other designated study working groups take part in routine meetings and conference calls throughout the period of study implementation. Summaries of these meetings and conference calls, which often document key protocol-related and study-implementation decisions and action items, are prepared and distributed as described in Section 6.3 of this Manual.
- *Protocol Clarification Memos, Letters of Amendment and Full Amendment*s: These documents are developed and issued as described in Section 10.3 of this Manual. MTN LOC (University of Pittsburgh [Pitt]) coordinates development of these documents. The final versions are posted on the MTN website.
- *SSP Manual* updates: These updates are developed as described in Section 11.13 of this Manual. MTN LOC (FHI 360) coordinates SSP Manual development and updates. The final versions are posted on the MTN website.
- *Data Communiqués*: The SDMC develops these documents to clarify and communicate data decisions and procedural revisions during the study. Final versions are posted on the MTN website as part of the relevant section of the SSP manual.
- Study implementation questions and answers: Site staff may direct questions about study implementation to the study management team per instructions in the SSP Manual. The management team responds to the originating site and determines whether all sites should be informed of both the question and response. Additionally, the management team may raise the question for discussion during study-related conference calls and/or issue a more formal communication (such as an Operational Guidance document) if needed to properly address the issue.
- *Reports*: The SDMC develops and issues data reports on study progress in accordance with the *Study Reporting Plan*. See Section 13.5.

All of these communications are issued with instructions for on-site filing and/or distribution, as appropriate. Recipients are responsible for filing documents as instructed and for communicating relevant information contained in the documents to all applicable study staff.

13.5 Reporting

The MTN uses a standardized reporting system for tracking study progress and site performance. The SDMC prepares a *Study Reporting Plan* in conjunction with the study protocol statisticians. The protocol team reviews the plan prior to study initiation. The reporting plan lists the types and frequencies of reports to be produced for each study. The reporting plan is included in the SSP Manual. Reports that may be used should comply with the *MTN Good Documentation Practices Policy* (see Section 9.2.2 of this Manual) as required and include the following:

- Screen-out reports
- Enrollment reports
- Retention reports
- Missed Visit listing/summary reports
- QC reports
- Procedure Completion reports
- Data Management Quality reports
- Protocol Safety Review Team (PSRT) reports
- SMC reports
- Interim Study Review (ISR) reports
- DSMB reports
- Protocol Deviation Listings
- Specimen Monitoring reports
- Data Summary reports

Certain information in MTN studies will be considered confidential, and reporting will, in some cases, be limited to designated committees (such as the PSRT, SMC and DSMB). Regarding study endpoints, in particular, adherence to confidentiality policies is necessary to avoid bias in study conduct and/or interpretation of data. All protocol team members and study staff are expected to strictly adhere to such policies.

13.5.1 Screen-Out and Enrollment Reports

Screening and enrollment data in MTN studies may be captured in two ways: on CRFs entered into the study database or, for behavioral studies, manually in real time by the BRWG representative or designee throughout the period of study accrual. When reported via CRF, the SDMC generates Screen-out and Enrollment reports from data entered into the study database. When accrual information is reported manually, MTN LOC (FHI 360) or the BRWG representative or designee works with the Protocol Chair(s), MTN LOC (Pitt) and the SDMC (if applicable) to determine the relevant accrual information to be reported and the frequency (for example, weekly, biweekly, or monthly) for site reporting and report distribution. MTN LOC (FHI 360) or the BRWG representative or designee then compiles information received from each study site into a cross-site report and distributes the report to the protocol team and MTN LOC (Pitt) for reporting to IND-holder(s) for the study and to the Network Evaluation Committee.

In addition to using the report to assess accrual performance at all sites, MTN LOC (FHI 360) and the SDMC also review the report to identify significant discrepancies between site- and SDMC-reported enrollment information. Discrepancies may indicate problems with data submission or entry at the sites, problems receiving, processing or reporting the data at the SDMC, or both. SDMC-reported enrollment data may lag behind site-reported enrollment data due to the time needed for data submission or entry, cleaning, and reporting.

13.5.2 Retention Reports

During the study implementation period, the SDMC routinely generates study-specific reports on participant retention and loss to follow-up for each scheduled study visit. Details of these reports are included in the reporting plan in each SSP Manual.

13.5.3 Quality Control Reports

In accordance with the study reporting plan developed for each study, the SDMC provides study-specific QC reports to each study site. These may be e-mailed to sites (e.g., for DataFax studies) or provided within the study database (e.g., Medidata Rave). For EDC studies (e.g., Medidata Rave), sites may review their current QCs at any time via their site's Task Summary in the study database. The frequency of QC report generation is outlined in the study SSP Manual. For EDC studies, sites may generate the report within the study database at any time. For studies where the QC reports are e-mailed to site staff, the QC report schedule may be adjusted in preparation for SMC and DSMB reviews. QC reports identify data items that are inconsistent, missing or out-of-range. Site staff review the QCs and correct/update study data on the CRF(s) as appropriate in response to a query. For studies utilizing EDC, site staff are encouraged to make the appropriate updates directly in the database to resolve a query, or if further clarification is needed, enter into the database a query response back to the person who initiated the query (e.g., SDMC Clinical Data Manager or PPD monitor). By providing a response to the query within the study database, site staff provide an audit trail within the database that contains information relevant to the query and its resolution. If needed, site staff also may email SDMC Clinical Data Management staff.

Site staff should address all QCs in a timely manner as specified in the site's study-specific Data Management SOP.

13.5.4 Data Management Quality Summary Reports

The SDMC routinely reports on a site's data management performance for each study. Data Management Quality Summary Reports include information on the following:

- Timeliness of data entry [e.g., total number or proportion of CRF pages faxed or electronic CRFs (eCRFs) completed within 7 days of the visit date]
    - Although, GDP (Section 9.2.2 of this Manual) requires contemporaneous entry of study information, the completion date is extended to 7 days to allow for return of laboratory test results.
- Accuracy and correctness of data entry [e.g., query rate (total number of queries per 100 pages faxed or number of manually placed queries in EDC system per 100 eCRFs)]
- Timeliness of query resolution (e.g., percent of all queries resolved or percent of manually placed queries resolved in EDC within 7 days)
- Timeliness of AE data entry (e.g., proportion of AEs faxed or reported in EDC within 3 days of the date the AE is reported to the site)

If concerns arise about a site's data management quality, the SDMC Clinical Data Manager will work with the site to develop strategies for improving performance.

13.5.5 Protocol Safety Review Team Reports and Clinical Quality Control

For MTN studies that involve a PSRT (as discussed in Section 15.2.2 of this Manual), the SDMC convenes a study-specific safety strategy meeting (usually a conference call) with members of the PSRT. The purpose of the meeting, which occurs prior to study start, is to

determine the specific safety criteria that will be used to trigger SDMC safety alerts, including the frequency of the alerts, as well as the format of the safety-data reports that will be used for routine review by the PSRT during a trial. Safety alerts may include weekly updates from SDMC Clinical Safety staff to the PSRT on events that meet specific criteria (e.g., grade 3 and higher lab values) as determined during the safety strategy meeting. The frequency of PSRT-report generation is based on the frequency of the PSRT review, which in turn is based on the study protocol and/or SSP Manual.

The SDMC Clinical Safety staff review clinical data submitted on CRFs and place clinical queries (clinical QC notes) on any data items that need verification or further clarification from the site clinician. Site clinical staff review and address the clinical queries via updates or notes of explanation on the appropriate CRFs. For studies utilizing EDC, site staff are encouraged to make the appropriate updates directly in the database to resolve a query, or if further clarification is needed, enter into the database a query response back to the SDMC Clinical Safety Staff to provide further information which may help resolve the query. By providing a response to the query within the study database, site staff provide an audit trail within the database that contains information relevant to the query and its resolution. If needed, site staff also may e-mail SDMC Clinical Safety or Clinical Data Management staff. Clinical QCs are considered high priority. As part of their Data Management SOP for each study, sites should specify how they will ensure appropriate and expeditious responses to these QCs.

13.5.6 Study Monitoring Committee and Interim Study Review Reports

The SMC or ISR committee reviews MTN studies at an interval determined by the protocol and/or as needed. See Sections 16.8 and 16.9 of this Manual. The SDMC prepares reports for these reviews. The reports address the following:

- Study design
- Participant accrual
- Baseline characteristics
- Serious and expedited AEs and social harms
- Protocol and intervention adherence
- Participant retention
- Laboratory performance and quality assurance
- Study endpoints

The SMC and ISR Reports present data aggregated across study treatment arms (that is, they are blinded). But for Phase I, Phase II and observational MTN studies that are not subject to routine DSMB review, members of the SMC or ISR may review safety data by study arm. When such reviews are conducted, the data will be compiled in closed-data reports that are distributed to SMC or ISR members only, unless the SMC or ISR requests or authorizes further distribution.

Additional information about study conduct, site-specific issues and materials other than study data collected by the SDMC may be included as an addendum to the SMC Report. Such addenda are prepared only at the request of the SMC or SDMC. The MTN LOC (FHI 360) generates, distributes for review, finalizes and stores a summary of the SMC or ISR meeting according to Section 9.2.2 of this Manual. MTN LOC (FHI 360) distributes the approved summary to the protocol team, ideally within seven working days from the review date.

13.5.7 Data and Safety Monitoring Board Reports

An independent DSMB chartered by DAIDS/NIAID is responsible for reviewing safety and efficacy data as well as overall study conduct of all ongoing MTN Phase IIb and Phase III studies. See Sections 1, 15 and 16 of this Manual. The DSMB evaluates the following:

- The study design and statistical analysis plan
- Integrity of the study regarding accrual, eligibility, adherence and retention
- Accumulated safety and efficacy data, typically according to a formal interim analysis plan

Generally, the DSMB Reports are created in two different ways: (i) an open report in which data are aggregated across treatment arms, and (ii) a closed report in which data are presented by treatment arm (blinded or unblinded). All DSMB Reports must comply with Good Documentation Practices (see Section 9.2.2 of this Manual).

Topics covered in the open report (data not reported by treatment arm) include the following:

- Study design and history
- Participant accrual
- Eligibility
- Baseline characteristics
- Adherence
- Participant status and retention
- AEs
- Data quality and timeliness
- Summary and recommendations

Topics covered in the closed report (data reported by treatment arm — blinded or unblinded) include the following:

- Study design and history
- Participant accrual
- Eligibility
- Baseline characteristics
- Adherence
- Participant status and retention
- AEs
- Safety and efficacy endpoints
- Data quality and timeliness
- Summary and recommendations