12 STUDY IMPLEMENTATION

Once a site has completed study-specific training of site study staff and received a study activation notice from the Leadership and Operations Center (LOC), the site may initiate study procedures. Detailed study implementation guidelines are included in the Study Specific Procedures (SSP) Manual for each study (see Section 10.7).

This section includes general guidelines, applicable to all HPTN studies, on participant accrual and follow-up (Section 12.1), data collection and documentation (Sections 12.2 and 12.3), and reporting (Section 12.5).

12.1 Participant Accrual and Follow-up in HPTN Studies

12.1.1 Accrual

Study-wide and site-specific participant accrual targets may be specified in HPTN protocols and/or SSP Manuals, based on the scientific objectives and statistical considerations of each study. Unless otherwise specified, study-wide accrual periods are considered to begin on the first day of participant enrollment at any participating study site; site-specific accrual periods are considered to begin on the first day of participant enrollment at that site. For many studies, the time from the first day of participant screening through the end of participant accrual will also be tracked and reported.

In addition to the total number of study participants, multi-site studies typically have an estimated number of participants to be enrolled at each participating study site indicated in the protocol, often with provisions to shift enrollment targets across sites in response to actual site performance in meeting accrual targets. Protocol teams should consider whether to specify a maximum number of enrolled participants for any site to ensure that one or more sites or populations of interest are not inappropriately over represented in the study data. The Protocol Chair(s) and biostatistician will take the lead in making this determination with the protocol team and work with the LOC Clinical Research Manager (CRM) and Statistical and Data Management Center (SDMC) Clinical Data Manager (CDM) to ensure that the determination is operationalized in the SSP Manual as needed. In studies for which enrollment targets are shifted across sites, sites will inform their Institutional Review Boards/Ethics Committees (IRBs/ECs) of increases or decreases in their enrollment targets in accordance with IRB/EC requirements. At a minimum, updates are provided to IRBs/ECs at least annually in the context of obtaining continuing review of ongoing studies.

In some cases, HPTN protocols include guidelines for adding participants to achieve a certain number of fully evaluable participants. In this setting protocol teams should consider whether to specify a maximum total number of enrollees. The Protocol Chair(s) and biostatistician should take the lead in making this determination with the protocol team, and work with the LOC CRM and SDMC CDM to ensure that the determination is specified in the study protocol and operationalized in the SSP Manual as needed.

The LOC CRM and SDMC CDM discuss accrual plans with site staff during study-specific training. They will emphasize the importance of closely monitoring the accrual process at each site and managing the last several weeks of the accrual period (when inadvertent over-enrollment is most likely to occur). For example, training materials may highlight the need to inform potential study participants screened toward the end of the accrual period that even if they meet the criteria for enrollment, there is no guarantee that they will be enrolled in the study if the study quota is reached before the participant is enrolled.

For each HPTN study, the SDMC generates routine study enrollment and retention reports from the primary study database (see also Sections 12.5.2 and 12.5.3) as specified in the study reporting plan in the SSP Manual. Protocol teams are responsible for reviewing the SDMC enrollment and

retention reports on an ongoing basis during the study accrual period and taking action as necessary to ensure that accrual and retention targets are met.

12.1.2 Enrollment

For each HPTN study, screening and enrollment procedures are described in detail in study protocols and SSP manuals. Information pertinent to participant screening and enrollment that is applicable to all HPTN studies is provided in the remainder of this section.

From both a statistical and operational perspective, it is important to define the effective point of enrollment in a research study in the study protocol and/or SSP manual. A few examples of the definition of enrollment are as follows:

- The point in time when a participant provides informed consent for study participation (adequately completed with signature and date)
- The point in time when a participant is assigned to a study treatment group

Written informed consent must be obtained from all HPTN study participants prior to the performance of any protocol-specified screening or enrollment procedures. See Section 8.5 for additional information on the informed consent process.

It is the responsibility of each IoR and designated staff to establish study-specific participant recruitment plans or Standard Operating Procedures (SOPs) for each HPTN study, and also plans to ensure that only persons who meet study eligibility criteria are enrolled in HPTN studies. See Table 10-1 for further guidance on the content of such SOPs.

The Division of AIDS (DAIDS) policy on essential documents (Requirements for Essential Documents at Clinical Research Sites Conduction DAIDS Funded and/or Sponsored Clinical Trials) requires study sites to document HPTN study screening and enrollment activities on screening and enrollment logs. Screening and enrollment logs may be maintained separately or combined into one log. Sample logs that may be adapted for local use at participating study sites typically are provided in SSP manuals.

For all HPTN studies, the SDMC will either provide participating study sites with a list of participant identification numbers (commonly referred to as "PTIDs") or PTIDS will be assigned by the Electronic Data Capture system (EDC) at screening or enrollment, as appropriate to the study. Detailed information on the assignment, structure, and format of the PTIDs to be used in each study, and instructions for assigning PTIDs to individual study participants, are provided in SSP manuals.

The DAIDS policy on essential documents specifies that participant initials be recorded on screening and enrollment logs, in addition to PTIDs. In agreement with DAIDS, participant initials need not be recorded on screening and enrollment logs if doing so presents a potential threat to participant confidentiality. However, in such cases, a separate document must be available to document the link between a participant's name and PTID.

12.1.3 Over-enrollment

In addition to ensuring that accrual targets are met, protocol teams also are responsible for ensuring that accrual targets are not substantially exceeded. During the study accrual period, based on both the site-generated and SDMC-generated accrual reports, the Protocol Chair(s) and biostatistician, together with the LOC CRM and SDMC CDM, are responsible for proactively addressing potential over-enrollment and under-enrollment issues. Accrual and over-enrollment/under-enrollment issues are discussed during routine protocol team conference calls, meetings, etc. Toward the end of the accrual period the Protocol Chair(s) and biostatistician take the lead in determining with the protocol team whether to allow eligible participants who initiate, but do not complete, the study screening process before the accrual target was met to complete

the screening process and enroll in the study after the accrual target was met. In most cases, over-enrollment greater than 5% of the target study sample size or more than 50 participants — whichever is smaller — should not occur. Protocol teams should consult the HPTN Study Monitoring Committee (SMC) if higher rates of over-enrollment are to be considered and should seek approval from the HPTN EC and local regulatory authorities. The LOC CRM maintains documentation of this consultation in the LOC study implementation files.

Over-enrollment is not permitted as a means to "make up for" participant loss-to-follow-up, unless specifically directed by the SMC, EC or the DAIDS Data and Safety Monitoring Board (DSMB). Adjustments to the sample size initially estimated in the study protocol may be made at the recommendation of the SMC, EC and/or the study DSMB, based on actual event rates observed among enrolled participants. If the sample size required to achieve the power specified in the study protocol is adjusted per recommendation of the SMC, EC or DSMB, the over-enrollment specifications will then apply to the final adjusted sample size.

12.1.4 Investigator-initiated Termination of Participants

HPTN study participants may withdraw their consent to participate in HPTN studies at any time, for any reason. However, to avoid biasing study results, investigator-initiated termination of HPTN study participants should occur only under extraordinary circumstances. For instance, termination may be considered if there is potential for harm to study staff or severe disruption of study operations.

In studies involving investigational products or interventions, IoRs will not routinely terminate study participants solely because the participants, for any reason, are non-adherent to the protocol-specified regimen for use of the investigational product or intervention.

In all cases, prior to terminating a participant from an HPTN study, the IoR will seek approval of members of the protocol team designated in the study protocol; at a minimum, the Protocol Chair, DAIDS Medical Officer, LOC CRM and protocol statistician should be consulted in conjunction with the protocol specific Clinical Management Committee. Designated members of the protocol team will assess the scientific, operational, and statistical implications of the requested termination and determine whether the termination may take place.

A designated member of the protocol team will document the team's determination in writing (email or meeting minutes are acceptable) for purposes of onsite documentation, and the determination of the designated protocol team members will rule. Site staff must always record reasons for termination in participant study records.

12.1.5 Participant Unblinding

There are three types of unblinding procedures, unblinding of individual participants for medical reasons during conduct of a study, unblinding of selected HPTN LC staff to identify samples for testing and unblinding of all participants at the end of a study in order to analyze the data and to inform the participants.

12.1.5.1 Unblinding of Individual Participants - Blinded Clinical Trial

Whether non-emergency unblinding of individual participants for medical reasons is allowed during the conduct of a clinical trial must be stated in the protocol and the procedures documented in the SSP. In general, non-emergency unblinding of participants during conduct of a clinical trial is not allowed unless there are compelling medical or safety reasons to do so, e.g., knowledge of the blinded information is necessary for treatment of severe adverse events.

12.1.5.1.1 Emergency Unblinding

In general, unblinding of participants during conduct of a clinical trial should be avoided unless there are compelling medical or safety reasons to do so, e.g., knowledge of the blinded information is necessary for treatment of severe adverse events. Emergency unblinding during the course of a trial has serious implications for study conduct and analysis. As such, site IoRs/designees should carefully consider whether or not emergency unblinding is warranted before proceeding. Simply stopping the study product agent in the case of oral dosing or no longer providing injections or infusions in the case of long-acting agents is often sufficient to provide effective clinical management of an event (though adverse events attributed to long acting agents may take longer to resolve). Regardless, the need for emergency unblinding is expected to be rare. If the site IoR or designee determines that a participant that has sustained a serious adverse event requires unblinding in order to ensure proper management of the participant's condition, the site IoR or designee may perform an emergency unblinding to obtain the participant's study treatment assignment. Until the unblinded treatment assignment is obtained, the participant's clinical management should proceed as if the participant were assigned to active study product in cases where the study is active vs placebo or should proceed as either of the active agents in cases where the study involves an active control arm.

A study-specific mechanism for emergency unblinding will be specified in each study's Study Specific Procedures Manual (SSP). For studies with clinical databases that are set up in an electronic data capture (EDC) system, such as Medidata Rave, site IoRs/designees may be able to unblind a participant's treatment assignment via the EDC system. User-specific permissions to this unblinding feature in the EDC system are restricted to the IoR or designee at each clinical research site. Designated users will be required to undergo specific training on emergency unblinding procedures within the EDC system by the SDMC. If and when an IoR or designee performs emergency unblinding of a participant in the EDC system, the audit trail of the request, including PTID, user, date, time, and reason for unblinding, will be captured within the EDC system itself. In some cases, additional documentation may be needed, such as completion of a CRF.

Once a specific participant is unblinded, the following steps should be taken (unless the protocol or SSP have further instructions):

1. The site IoR or designee must notify the Protocol Chair(s), Protocol Statistician, HPTN PI and co-PI, DAIDS Medical Officer, and protocol management team within the time specified in that particular study's SSP Manual.
2. The site IoR or designee must notify – in an expedited manner – all responsible IRBs/Independent Ethics Committees (IEC) for the site that unblinding has occurred.

In all cases, the minimum number of personnel required for the immediate management of the participant should be unblinded to the treatment assignment. Staff who become unblinded may no longer be involved in the attribution of adverse events or other participant assessments for study-related purposes. If a participant has been unblinded, the participant should be encouraged to remain on study and if at all possible on study product unless medically contraindicated.

12.1.5.1.2 Unblinding of Selected HPTN LC Staff

In some studies (e.g., some PrEP studies), selected staff at the HPTN LC will be unblended to identify samples that need to be tested for a specific analyte (e.g., a specific PrEP agent used in only one study arm). In this case, unblinding will be limited to a single staff person who is not part of the study team; unblinding information will be used solely to select specimens for testing and will not be shared with any study team members. Data from testing on unblinded specimens will be submitted to the SDMC for analysis.

12.1.5.1.3 Unblinding of Participants after Study Completion

The protocol team, in conjunction with the SDMC and LC, determines the timing of participant unblinding. Except in unusual circumstances, the unblinding of participants cannot occur until all participants have completed their final data collection visit.

For Phase I/II trials participants may be unblinded prior to complete database lock, as per the protocol team and SDMC.

For Phase IIb or III trials intended to contribute to a regulatory submission, unblinding of participants cannot occur until the study database at the SDMC is formally locked for the primary analysis.

Phase IIb or III trials that are not intended to contribute to a regulatory submission or that have been terminated before completion due to DSMB or sponsor decision may unblind participants after all participants have completed their final data collection visit and before database lock. This decision is the responsibility of the protocol team, in consultation with the DSMB when applicable.

The protocol team should determine the method of informing participants of their blinded random assignment. In some situations, "Dear Participant" letters will be appropriate. In settings where mailing letters is not possible or appropriate (e.g., for reasons of confidentiality) it will be necessary to plan for disclosure of randomization to participants in person. If disclosure of the random assignment requires counseling of the participant or could cause distress, it should be done in person. The study site staff may consult with their Community Advisory Board (CAB) in order to determine the most appropriate method of unblinding participants and in developing participant letters or counseling materials. The protocol team will make a good faith effort to inform all trial participants of their individual treatment assignment.

The protocol statisticians at the SDMC will generate unblinding lists for each site per SDMC SOPs. The lists will be provided to the study site via password protected electronic file.

12.2 Data Collection

Study site staff are responsible for the collection, storage, timely submission, and quality assurance of study data collected at their site and documenting the plan for these tasks in a Data Management SOP. All *study data should be collected in accordance with applicable specifications of the DAIDS* policy: Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials, the DAIDS SOP for Clinical Site Data Collection and Reporting and study specific SSPs.

In addition, the site is responsible for maintaining all documentation critical to the conduct of the study, known as "essential documents", in accordance with the DAIDS policy: Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Research.

12.2.1 Participant Research Records

The United States (US) Code of Federal Regulations (CFR) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) E6 guidance (use drop down menu in webpage) requires study site staff to maintain adequate and accurate participant "case history records" containing all information pertinent to the study for each HPTN study participant.

12.2.1.1 Participant Research Record Contents

Participant research records should contain all of the following elements:

- Basic participant identifiers such as PTID or initials

- Documentation that the participant provided written informed consent to participate in the study prior to the conduct of any study procedures
- Documentation that the participant met the study's eligibility criteria
- A record of the participant's random assignment (if applicable)
- A record of the participant's exposure to investigational products (if applicable)
- A record of all contacts, and attempted contacts, with the participant including all clinic visits, off-site visits (e.g., at home or work), and all verbal and written contacts
- A record of all procedures performed by study staff during the study
- Complete source documents
- All case report forms (CRFs) and other study data collected from the onset of screening through end of participation, including data collected and entered into an electronic data capture (EDC) system
- Study-related information on the participant's condition before, during, and at the conclusion of study participation, including:
    - subjective data obtained directly from the participant (e.g., interview responses)
    - objective data ascertained by study staff (e.g., exam and laboratory findings)
    - objective data obtained from non-study sources (e.g., medical records, including electronic medical records (EMR) or electronic health records (EHR))

In addition to the above, the DAIDS policy for source documentation requires that all protocol deviations involving participants be documented in participants' study records, along with reasons for the deviation and attempts to prevent or correct the deviations, if applicable. See Section 12.5.11 regarding requirements for reporting protocol deviations.

12.2.1.2 Concept of Source Data and Source Documentation

The ICH/GCP guidance defines source data and source documentation as follows:

- The term "source data" refers to all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- The term "source documents" refers to original documents, data and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subjects' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies of transcriptions certified after verification as being accurate and complete; microfiche; photographic negatives; microfilm or magnetic media; x-rays; subject files; and records kept at the pharmacy, the laboratories, and medico-technical departments involved in the trial).

Source documents are commonly referred to as the documents — paper-based or electronic — upon which source data are first recorded.

HPTN study sites must adhere to the standards of source documentation specified in the DAIDS policy: Requirements for Source Documentation in DAIDS Funded and/or Sponsored Trials. 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. Source documentation includes original documents and certified copies that include documentation pertaining to a participant while on study.

For each HPTN study, participant case history records typically will consist of some or all of the following:

- Narrative chart notes
- Visit checklists or flow sheets
- Laboratory reports
- Medical records or clinic charts, including electronic medical records (EMR) and electronic health records (EHR)
- CRFs and electronic study data (eCRFs)
- Randomization log or other documentation (when applicable)
- Investigational product dispensing and accountability records (when applicable)
- Other source documents and data collection tools or questionnaires

As a condition for study activation, each site must establish an SOP for source documentation that specifies the use of these documents as source documents.

Supplemental information on use of chart notes, visit checklists, and CRFs or eCRFs, and EDC as source documents is provided below. Also provided below is information related to investigational product dispensing and accountability records, document organization, and record retention requirements.

12.2.1.3 Chart Notes

Chart notes must be used to document the following:

- 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

All chart notes or other tools created for the study used as source documentation must document the PTID of the study participant to whom it pertains, the identity of the study staff member who entered information, and the date of the entry. Study sites are strongly encouraged to adopt a common format — such as the Subjective-Objective-Assessment-Plan (SOAP) format for all chart notes, to help ensure adequacy and consistency of note content and maximize adherence to GCP standards: Example SOAP Chart Note. Alternative standardized formats are acceptable and may be adopted by study sites; however, sites are encouraged to also adhere to the DAIDS policies on source documentation.

12.2.1.4 Visit Checklists

The SSP Manuals typically include a series of visit checklists to guide the staff performing procedures at each study visit (in accordance with the protocol). In some studies, visit checklists are also a convenient tool for study staff to fulfill the requirement of documenting all procedures performed with each study participant. The LOC CRM is responsible for developing these checklists with input from the SDMC CDM, Laboratory Center (LC), and the sites. Study sites are allowed to develop site-specific versions of these checklists. Any site-specific visit checklists should be provided to the LOC CRM for review prior to use.

Note that checklists alone often are not sufficient for documenting all procedures. For example, chart notes may be required to document procedures performed at unscheduled study visits to explain why procedures, in addition to those specified on a checklist, may have been performed or why procedures specified on a checklist were not performed. Chart notes also may be required to

document the content of counseling sessions and/or other in-depth discussions with participants (e.g., related to adherence to protocol requirements).

Study procedures for which visit checklists are used as source documentation must contain the PTID, the initials or signature of the authorized study staff member completing the procedures, and the date the procedure was completed. Individual study staff members must initial only those procedures that they complete. In addition, if procedures listed on a single checklist are completed across multiple dates, the date upon which each procedure is completed must be clearly noted. Additional detailed guidance related to proper use of visit checklists is provided in each SSP Manual.

12.2.1.5 CRFs and Electronic Data Capture CRFs (eCRFs)

The SOP for source documentation requires that a site must document which paper CRFs or eCRFs, if any, will be used as source documents. Study staff must follow the specifications of this SOP consistently for all study participants throughout the study. In the event that study staff are not able to record source data directly onto forms designated as source documents, or directly enter the data into the study database, the following procedures should be undertaken:

- Recording the data onto an alternate source document
- Entering the alternate source document into the participant's study chart
- Transcribing the data from the alternate source document onto the appropriate CRF or entering into the study database via EDC
- Recording a chart note stating the reason why an alternate source document was used

12.2.1.6 Electronic Records

Electronic Records are any combination of text, graphics, data, audio, pictorial, or other information in digital form that is created, modified, maintained, archived, retrieved, or distributed by a validated computer system (21 CFR 11.3). When data are entered directly into a computer, the electronic data in the computer becomes the essential document. A paper record (printout/hard copy/"print screen") of the electronic data is considered to be a copy. Requirements for documentation, record keeping and record retention apply to electronic records the same as they do for paper systems.

Examples of electronic records include but are not limited to:

1. Participant data, reports, and/or results
2. E-mail communications pertaining to a participant or protocol management (e.g., 171 directives from protocol chairs, CRS investigators to study nurses, etc.)
3. IRB/EC correspondence pertaining to a participant or the study
4. Audio Computer-Assisted Self-Interview (ACASI) questionnaires

Each electronic record needs to be associated with an originator type, otherwise known as an authorized data originator. An authorized data originator could be a person, a computer system, a device, or an instrument that is authorized to enter, change, or transmit data into the electronic record. [CRS must] develop and maintain a list of all authorized data originators. This list must be made available for study-related monitoring, audits, IRB/EC review, and regulatory inspection by authorized individuals at each clinical research site. In the case of electronic participant-reported outcome (ePRo) measures, list the participant (e.g., unique participant identifier) as the originator. Examples of data originators include, but are not limited to:

1. Clinical investigator(s) and delegated clinical study staff

2. Participants or their legally authorized representatives
3. Consulting services (e.g., a radiologist reporting on a computed tomography (CT) scan)
4. Medical devices (e.g., electrocardiograph (ECG) machine and other medical instruments such as a blood pressure machine)
5. Electronic health records (EHRs)
6. Automated laboratory reporting systems (e.g., from central laboratories)
7. Other technology

12.2.1.7 LDMS Specimen Tracking Sheets Provided by the LC

The LDMS Specimen Tracking Sheet is designed to accompany specimens from the clinic to the site's laboratory and facilitate entry of specimens into LDMS. A study-specific LDMS Specimen Tracking Sheet can be provided by the LC, but sites may elect to use their own laboratory requisition forms instead.

12.2.1.8 Product Dispensing and Accountability Records

As indicated in Section 10.11, the receipt, dispensing, and final disposition of all investigational product supplies used in HPTN studies must be documented by designated study site staff in accordance with the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* as well as any supplemental instructions provided in the study protocol and/or SSP Manual.

12.2.1.9 Document Organization

All participant study records must be stored securely at the study site in accordance with the specifications of the study protocol. See Section 8.9 for additional considerations related to participant confidentiality.

12.2.1.10 Record Retention Requirements

For studies (such as HPTN) that are DAIDS /supported and/or sponsored, the institutions, 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 human subjects (e.g., when all subjects 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 under an Investigational New Drug Application (IND), the same guidelines apply with the addition that the investigator or designee must retain clinical research records for two years after 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, for two years after the investigation is discontinued and FDA is notified.

No records may be destroyed without written permission from DAIDS or the sponsor (if not DAIDS).

For more information, see DAIDS Policy on Storage and Retention of Clinical Research Records. For all studies, retention of study records must also be in accordance with local regulatory requirements as well as local IRB/EC policies and procedures. **No study records are permitted**

to be destroyed before the study to which the records relate are 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 RSC website page for CRF management.

12.2.2 Electronic Data Entry and Data Management

The SDMC uses Medidata Rave Electronic Data Capture (EDC) for CRF data entry and management for most HPTN studies. Medidata Rave is a web-based system that provides:

- eLearning modules and on-screen help
- Real-time field-level and cross-form edit checks
- Viewing, updating, querying, and locking data
- Automatic calculations (e.g., BMI, pill counts, toxicity grading)
- Real time access to data and standard reports
- Printing of paper CRFs, as needed
- Allows for multiple languages
- Automatic data back up
- User and role-specific permissions
- Integrated randomization system (Balance)
- Investigator of Record sign-off and Emergency Unblinding

Site staff who do not already have a Medidata account will be required to complete the appropriate eLearning modules before being granted access to HPTN studies in Rave. Additional details about the implementation of HPTN studies in Medidata Rave will be in study SSP manuals.

12.2.3 Other Methods of Data Collection

The HPTN SDMC may occasionally use other systems for collection of study data, either in additional to, or instead of, Medidata Rave. When this is the case, information and procedures for the data collection tools will be included in the SSP.

12.3 Standard CRF Elements and Forms

All HPTN CRFs and eCRFs have been designed using standards and conventions developed by the SDMC. Certain CRFs have been standardized within the HPTN to ensure that all required data is collected and to create as much consistency as possible between protocols. These elements also align to the extent possible to the Clinical Data Interchange Standards Consortium (CDISC) standards as required by NIAID. Instructions for study staff on correct completion of each of these CRF elements are included in Case Report Form Completion Guidelines (CCGs) with additional information provided in SSP Manuals and online in the Medidata system.

Included in SSP Manuals and online in the Medidata system.

To date, the following CRFs are considered standard in the HPTN:

- Adverse Event
- Social Impact
- Select Laboratory Results modules (e.g., CBC, differential, chemistries)

- Concomitant Medications
- Pre-existing Conditions (may also be called Medical History)
- Pregnancy History and Report
- Pregnancy Outcome
- Protocol Deviation
- Missed Visit
- Participant Transfer
- Participant Receipt
- Termination

12.4 Study Team Communications

After initial release of a study protocol and SSP Manual, several types of study-related communications may be issued to report on study progress or provide further clarification of protocol-specified procedures and study documentation requirements. Such communications may include, but are not limited to, the following:

- *Conference call and meeting summaries*: Protocol teams, and in some cases, 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 6.2
- *Protocol Clarification Memoranda (Memos), Letters of Amendment, and full amendments with an attendant summary of revisions*: These documents are developed and issued as described in Section 9.3. Development of these documents is coordinated by the LOC CRM, and final versions are distributed to all protocol team members and study sites. Final versions also are posted on the HPTN website
- *SSP Manual updates*: These updates are developed and issued as described in Section 10.7. Like the initial version of an SSP Manual, development of the updates is coordinated by the LOC CRM, and final versions are posted on the HPTN website.
- *Data Communiqués*: These documents are developed and issued by the SDMC CDM to clarify issues related to study data collection. Final versions are distributed to all study sites for filing in the SSP Manual and are posted on the HPTN website. They are considered an official part of the SSP Manual
- *Laboratory Communiqués*: These documents are developed and issued by the LC HPTN QAQC representative to clarify issues related to laboratory procedure. Final versions are distributed to all study sites for filing in the SSP Manual and are posted on the HPTN website. They are considered an official part of the SSP Manual.
- *Reports:* Data reports on study progress, protocol adherence, data quality, etc., are developed and issued by the SDMC in accordance with the study reporting plan (see Section 12.5)
- *Study implementation questions*: Site questions about study implementation should be directed to the LC, LOC CRM and the SDMC CDM. They will determine between them who is the most appropriate person to respond. They will also forward the query to another party for a response if deemed appropriate. In cases where the LC representative, LOC CRM and SDMC CDM determine that the question and answer may be relevant or informative to staff from other study sites, they will forward the

information to relevant site staff. They also may raise the issue for discussion during study-related conference calls and/or issue a more formal communication (e.g., SSP Manual update, Clarification Memo, or Data Communiqué) to properly address the issue

All of the above-listed communications are issued with specific instructions for filing and further distribution as appropriate. Recipients are responsible for filing copies of documents as instructed and for communicating relevant information contained in the documents to all applicable study staff members, collaborators, etc.

12.5 Reporting

The HPTN has developed a standardized reporting for tracking study progress and site performance.

A study reporting plan is prepared by the SDMC CDM and statisticians prior to the start of the study. The reporting plan lists the types and frequencies of reports to be produced for a given study. The approved reporting plan is included in the study SSP Manual. Reports that are generally included are:

- Enrollment and retention Data management quality
- SMC
- DSMB

12.5.1 Confidentiality of Study Data

The disclosure of study end points during an ongoing study should be limited to designated committees (e.g., closed SMC, DSMB) to avoid bias in study conduct and/or interpretation of data.

12.5.2 Enrollment, Visit Completion, Loss to Follow-Up & Retention Reports

During the protocol accrual period, the SDMC routinely generates protocol-specific enrollment reports showing projected and actual participant enrollments. The SDMC also generates protocol-specific reports on participant visit completion, as an estimate of retention, for each scheduled study visit. Details of these reports are included in the reporting plan included in the SSP Manual and are available online.

12.5.3 Data Quality Control

For EDC, much of the data QC is performed by real-time field-level and cross-form data checks programmed into the system by SDMC CDM. In addition to these real-time checks, data queries regarding items that require more clarification by site staff will appear in the CRS data manager and/or study coordinators Rave Task Summary. In general, site staff should respond to these queries within 7 days, or 48 hours regarding queries on safety data and AEs.

12.5.4 Data Management Quality Reports

The SDMC routinely generates reports on site-specific and protocol-specific data management performance. These reports include:

- Total number of CRF pages submitted during the report period
- Mean days to submit CRF data
- Percentage pages submitted within 7 days of study visit
- Total number of items queried by the SDMC
- Query rate (the number of queried items per 100 CRF pages)

- Percentage of queries responded to within 7 days
- For studies with AE reporting, percentage submitted within 3 days of site awareness

12.5.5 SMC Reports

The SMC reviews all protocols approximately every six months (see Section 4.3.2 for reporting frequency). The LOC CRM is responsible for identifying the date of each SMC review and for arranging SMC conference calls and documenting the SMC review. The SDMC prepares reports (blinded if necessary) for these reviews that include:

- Trial design
- Accrual
- Demographics and other baseline characteristics
- Summaries of expedited adverse event/serious adverse event/adverse event/data or social impact reporting
- Protocol and intervention adherence
- Participant retention
- Laboratory performance, specimen storage and quality assurance (QA) testing (with input from the LC)
- Data quality and timeliness
- Reportable protocol deviations
- Review of aggregate safety data as a closed review for all studies with a biomedical intervention without DSMB oversight. The SMC composition for these studies should include clinicians experienced in the review of safety data, who are not affiliated with the protocol team or HPTN. The SMC will review safety data only during a closed session with no study team or sponsors present
- Endpoint summary

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 SDMC report. Such addenda are prepared only at the request of the SMC or SDMC and are typically prepared by the LOC CRM and/or other protocol team members.

After the SMC review, the LOC distributes a summary to the protocol team, and at that time the SMC report may be shared with members of the protocol team.

12.5.6 Data and Safety Monitoring Board (DSMB) Reports

A DAIDS DSMB periodically reviews data reports from all Phase IIb/III HPTN trials and other selected studies. The primary responsibilities of the DSMB are to:

- Safeguard the interests of study participants
- Preserve the integrity and credibility of the trials in order that future participants will benefit from optimal prevention therapy
- Ensure that definitive and reliable results will be available in a timely way to the medical community

To do this, the multidisciplinary panel of DSMB members conduct comprehensive reviews to evaluate the:

- Study design and statistical analysis plan
- Accumulated efficacy data, typically according to formal interim analysis plan
- Integrity of the trial with regard to accrual, eligibility, compliance, and retention

Typically, a report is prepared by the SDMC for review by the DSMB. It is composed of an open report in which data are presented aggregated across treatment arms and a closed report containing data presented by treatment arm, blinded or unblinded. Topics covered in the report include:

Open report (data not reported by arm):

- Trial design and history
- Accrual
- Baseline characteristics
- Adherence
- Participant status and retention
- Serious and non-serious adverse events
- Data quality and timeliness
- Reportable protocol deviations
- SMC review summary

Closed report (data reported by arm — masked or unmasked):

- Accrual
- Baseline characteristics
- Retention
- Adherence
- Participant status and termination
- Efficacy endpoints
- Safety endpoints
- Other secondary outcomes

After the DSMB review, a summary is distributed by the LOC to investigators for submission to the site IRBs/ECs, unless otherwise directed by DAIDS.

12.5.7 Modification of Study Recommended by DSMB

When the DSMB recommends modification to a study, this information will be immediately communicated to National Institute of Allergy and Infectious Diseases (NIAID) and to HPTN leadership. This leadership team includes:

- Network PI/Co-PI
- LC PI
- LOC Project Director

- SDMC PI
- Others as deemed necessary

Prior to NIAID's release of a press release or public statement, it is imperative that the DSMB findings remain confidential. In an effort to ensure study confidentiality, all study team members must sign a confidentiality agreement.

Recognizing that in some cases DSMB findings may require immediate action, communication of DSMB results with network constituents and study participants will be coordinated with the Protocol Chair, HPTN leadership and NIAID in a timely fashion. Advance communication planning and development of possible DSMB outcomes will expedite this process.

12.5.8 Reporting of Protocol Deviations

The HPTN has established a process for staff at HPTN study sites, the LOC, the LC and the SDMC to document the occurrence of protocol deviations and to report them to the protocol team, particularly those that might otherwise not be evident in the study data or reported otherwise. Reportable protocol deviations are defined by the HPTN as individual incidents, trends or omissions that result in:

- Significant added risk to the participant
- Non-adherence to significant protocol requirements
- Significant non-adherence to GCP

Examples of reportable protocol deviations are:

- Enrollment of an ineligible patient
- Informed consent not obtained prior to performing protocol-specified procedures
- Non-compliance with study randomization and blinding procedures
- Protocol-specified procedures not followed by site staff
- Breach of participant confidentiality
- A protocol-specified laboratory assay consistently not being performed (a single missed assay during one participant visit would not be considered a reportable protocol deviation)
- A site-specific laboratory assay is deliberately added to protocol requirements by the investigator to be conducted for all participants

Participant non-compliance with the study protocol, including treatment specifications, is not considered to be a reportable protocol deviation, but should be discussed by the protocol team.

After consultation with LOC, SDMC, and LC representatives, all deviations that meet the above criteria will be recorded on the Protocol Deviation case report form and submitted to the SDMC for entry into the study database. For studies using Medidata Rave for data entry and management, it is acceptable to create a pdf version of the eCRF to use a as Protocol Deviation report for communication with DAIDS and the site IRB/EC.

Full documentation of all protocol deviations including reportable deviations for each study should be maintained at the site and reported as needed to the local IRB/EC. A brief description of the deviation is sent via email to the Protocol Chair, IoR, Site Study Coordinator, Site QA/QC Coordinator(s), LOC CRM, SDMC PM, LC representative, Prevention Science Program (PSP)/Office of Clinical Site Oversight (OCSO) representative for the site, the DAIDS Medical Officer for the study and, if the deviation involves an investigational product, the DAIDS Protocol Pharmacist. NIH staff will determine whether the event is a Critical Event and the form must be completed.

The Clinical Site Monitor identifies protocol non-adherence events and violations in their monitoring reports, and some of these may also be reportable protocol deviations; however, there is not a one-to-one correlation between events reported by the Clinical Site Monitor and those to be reported through the HPTN protocol deviation reporting system. The Clinical Site Monitor may report protocol non-adherence events and violations that encompass every infraction of the protocol. For example, if a blood specimen is drawn for ALT, but is not processed by the laboratory, it is a non-adherence event according to the Clinical Site Monitor. This would not be a reportable protocol deviation. If, however, an ALT is to be drawn at each patient visit and is not being done at all, this would be a reportable protocol deviation.

12.6 Release of HPTN Study Data from the SDMC

Analysis of data related to the protocol objectives is the responsibility of the SDMC. In order to ensure rapid, high quality analysis and dissemination of study results, the protocol statisticians at the SDMC conduct these analyses centrally. Premature distribution of the data has the potential to:

- Jeopardize the integrity of the trial
- Compromise the quality of study results that are disseminated
- Divert the resources of the SDMC from the preparation, dissemination and support of protocol analyses

This section describes how HPTN study data is released by the SDMC without compromising the interests of trial participants or the integrity and credibility of the trial.

12.6.1 Release of Data During the Conduct of a Study

No study data beyond baseline will be available to the site, protocol team or any other body, other than as reports to the DSMB and to the SMC, or to the LC as needed, to perform protocol-related activities and assessments (e.g., for QC activities, to assist with protocol testing, and for assessments related to protocol objectives). Exceptions to this rule require approval by the Leadership Group/Executive Committee and/or the DSMB, as appropriate. Baseline data may be published or presented only after all sites have completed enrollment.

Publication or presentation of site-specific follow-up data or results during the trial is not approved under the HPTN Publications Policy (Section 21) and should not occur unless authorized by the HPTN Leadership group and/or Executive Committee. It is the responsibility of the site Principal Investigator (PI) and the IoR to ensure that inappropriate dissemination of results or analysis of data does not occur.

After enrollment is complete, and by request, the SDMC makes participant-level baseline data available to sites as electronic files, either securely posted on the SDMC web-portal, or through the Medidata Rave system. Publication of these data are per the Publication Policy (Section 21).

Certain types of data are never available while the study is ongoing:

- Data that constitute primary or secondary endpoints
- Coding (e.g., by MedDRA) of AEs
- PTID identified data from Computer-Assisted Self-Interviews (ACASI or CASI)
- Laboratory data not submitted on a CRF (e.g., submitted directly to the SDMC by the LC or other central laboratory)
- For blinded trials, the participant's random assignment

12.6.2 Release of Data after Completion of a Study

12.6.2.1 Final Release of Site-specific Data to Site Investigators

Final site-specific study data sets can be requested from the SDMC by the site investigators once the database is cleaned and locked and all intended manuscripts reporting primary results of the protocol objectives have been approved by the Manuscript Review Committee (MRC) for publication. All manuscripts based on HPTN study data, with the exception of Public Use datasets, must be reviewed by the MRC (see Section 21). The HPTN LC will inform the MRC of laboratory-related publications that do not report primary or secondary protocol results. The SDMC will not check or validate the accuracy of data summaries and analysis computations completed outside the SDMC.

12.6.2.2 Release of Data to Protocol Team and Scholars for Analysis

In general, the HPTN SDMC conducts analysis of primary and secondary objectives data for publication. Data sets for specific analyses to be conducted by HPTN investigators and HPTN Scholars without the assistance of the HPTN SDMC may be released after completion of primary and secondary publications. Release of these data are approved by the Protocol Publications Committee (PPC) and follow the Protocol Publications Guidelines (see Section 21). Submission of a Proposal that documents the data requested is also reviewed by the PPC.

12.6.2.3 Final Release of Data to Investigators after Trial Completion

The complete study database can be released for use by HPTN investigators once the manuscripts reporting the results of the protocol objectives have been approved by the MRC for publication. The study database must be locked prior to release, and unless otherwise requested, the datasets will be de-identified. The HPTN LC must approve the decision to lock laboratory results data sets that were submitted directly to the SDMC (non-CRF lab data) and must approve the final release of data sets that include such laboratory data.

The timeline for release of the data is negotiated with the SDMC and the protocol team, taking data cleaning, database lock and study analysis commitments into consideration. In general, the study database will be posted on the SDMC web portal for use by HPTN Investigators. All manuscripts based on HPTN study data, with the exception of Public Use datasets (see Section 21) intended for wide dissemination, must be reviewed by the MRC. The HPTN LC will inform the MRC of laboratory-related publications that do not report primary or secondary protocol results. The SDMC will not check or validate the accuracy of data summaries and analysis computations completed outside the SDMC.

12.6.3 Limited Release of Data to Non-HPTN Investigators

For pre-specified purposes, e.g., ancillary studies external to the HPTN or grant applications, investigators may request approval for release of data to HPTN and non-HPTN entities (information on approval of ancillary studies can be found in Section 17.2). These requests require approval of the HPTN leadership group.

- Release of follow-up data prior to the final study visit and study unblinding (if applicable) requires additional approval of the Protocol Chair, the SDMC PI, the LC PI, and the EC and would typically be approved only in extraordinary circumstances.
- Release of data after the final study visit but prior to database lock and completion of publications requires additional approval of the Protocol Chair(s), LC PI, and the protocol statistician.
- Release of baseline data after completion of enrollment requires only approval of the Protocol Chair(s), LC PI, and the protocol statistician(s).

- The timeline for release of the data is negotiated with the SDMC and the protocol team, taking data cleaning, database lock and study analysis commitments into consideration.

12.6.4 Release of Data from a Study Conducted Under an IND

The Clinical Trials Agreement (CTA) governs the release of study data to the pharmaceutical partner. The guidelines in this policy will hold for IND studies unless otherwise specified by the CTA. Data cannot be released from the SDMC unless it is in agreement with the terms of the CTA.

12.6.5 Public Use Datasets

Federal research sponsors often require that data be made available to the public in the form of "Public Use" datasets that have been prepared by the SDMC for wide scale dissemination. Data from HPTN studies may be released as a Public Use dataset after all analyses and publications of study objectives by the protocol team are considered complete by the protocol team and public release is approved by the Protocol Chair(s), , the HPTN Executive Committee and NIH as the study sponsor. See Section 21 regarding publications based on an HPTN study Public Use data set.

Increasingly, scientific journals require posting of the dataset used in an analysis for publication, either on the journal's website or on a public website or portal. If required by the journal, the SDMC will prepare a de-identified analysis dataset for posting. Any publications that result from such publicly posted publication datasets are not reviewed or approved by the HPTN MRC per the HPTN Publication Policy (Section 21).

12.6.6 Other Release of Data from HPTN Studies

Requests for release of data not covered in Sections 12 and 21 must be negotiated with the SDMC PI and the EC. Approval from the LC PI is required for release of any data sets that include laboratory data submitted by the HPTN LC.