10   STUDY SPECIFIC PRE-IMPLEMENTATION, SITE ACTIVATION AND STUDY INITIATION

After finalization of an HPTN protocol, a number of pre-implementation steps must be completed before a study can be initiated. These can broadly be categorized into study-specific Network requirements and study-specific site activation requirements.

Study-Specific Network Requirements: Certain steps must be taken by the HPTN central resources, protocol team members, and the Division of AIDS (DAIDS) to prepare a study for opening. Several of these steps require collaborative work; chief among these is development of the study case report forms (CRFs), any additional data capture methods or surveys, and Study-Specific Procedures (SSP) manuals, described further in Section 10.1. All such study-specific Network requirements must be met prior to the first site being activated to begin enrollment into a study.

Study-Specific Site Activation Requirements: Key pre-implementation activities involved in the study activation process are described in greater detail in Section 10.2.

Once all study-specific site activation requirements are met at a site and documented, the HPTN Leadership and Operations Center (LOC) Clinical Research Manager (CRM) will issue a study-specific Activation Notice (see Section 10.2.9) confirming that all requirements have been met and indicating that the site may initiate study implementation. No study procedures may be undertaken before the activation notice is received. After issuing the study-specific Site Activation Notice, the LOC CRM will provide site staff with a copy of the documentation upon which activation was based.

10.1   Network Requirements

10.1.1   Clinical Trials Agreement

A Clinical Trials Agreement (CTA) is the agreement negotiated between a collaborating pharmaceutical partner and the study sponsor (typically DAIDS), to document the responsibilities and rights of each party in the agreement. The agreement includes, but is not limited to, Investigational New Drug (IND) application sponsorship, safety and data monitoring, and access to data.

The DAIDS Regulatory Affairs Branch (RAB) and the Regulatory Support Center (RSC) handle the development of CTAs for HPTN studies, and the negotiation of these agreements between DAIDS and product manufacturers or other cosponsors. Development of a CTA typically begins once a protocol is approved by the DAIDS Prevention Science Review Committee (PSRC). The RSC and RAB will seek input and review of CTAs by the DAIDS Medical Officer for that study; and as necessary, HPTN LOC, SDMC, and LC, and/or the investigators, prior to finalizing. The status of a CTA may be tracked on the NIAID Clinical Research Management System.

Copies of executed CTAs are provided to the manufacturer, the HPTN SDMC and LOC. Study sites are not expected or required to maintain copies of CTAs in their onsite essential documents files; these are maintained by DAIDS and the cosponsor(s).

10.1.2   ClinicalTrials.gov Registration

For DAIDS-held IND studies, the responsibility to meet the ClinicalTrials.gov reporting requirements falls within DAIDS and is assigned to a DAIDS contractor. For non-IND studies, the Network is responsible. Additional details about the ClinicalTrials.gov registration process, including a checklist that must be completed and submitted to DAIDS RSC at the time of Full Regulatory Review and to the assigned DAIDS contractor once Version 1.0 is approved can be found at: https://rsc.niaid.nih.gov/networks-protocol-teams/clinicaltrialsgov-checklist. See Section 9.2.2.4 for instructions to submit the checklist to DAIDS RSC and Section 9.2.2.7 for instructions to submit the checklist to the assigned DAIDS contractor.

10.1.3   Protocol-Specific Monitoring Plan Confirmation

Before any enrollment may proceed for any study, DAIDS must confirm that the protocol-specific monitoring plan is in place. DAIDS will lead the contracting of this plan providing the monitors with the plan for study monitoring.

10.1.4   Safety and Other Committee Establishment

Per Section 14.2.2, the protocol team leadership will ensure that all safety oversight groups and reviewers (i.e., Clinical Management Committee, Independent Safety Reviewers) are in place prior to study initiation, as appropriate to the safety oversight needs of the study as specified in the study protocol.

10.1.5   eCRF Development

The SDMC is responsible for developing eCRFs or EDC for each protocol. eCRFs, used with electronic data capture, are designed to collect the data used to address protocol-specified study objectives. Typical HPTN eCRF development processes are as follows:

- Development of eCRF content typically begins when the protocol is deemed stable, usually version 1.0
- The internal SDMC study team puts together a data collection plan based on protocol objectives and reporting needs
- Standardized eCRF content and examples from previous studies are gathered for protocol team review by the SDMC Clinical Data Manager (CDM)
- The draft eCRF content and relevant study materials (e.g., Schedule of Forms) are reviewed by the protocol team and additional content is developed, as needed
- As needed, finalized eCRF content is translated by the study sites or contractor (ideally before any planned operational walkthrough or pre-study operations visit, as needed). The translation process is initiated and coordinated by the SDMC. Back-translations, especially for behavioral questionnaires, will be reviewed by the SDMC and the behavioral scientists if applicable

10.1.6   Additional Data Capture Methods

Some types of studies may require methods of data collection in addition to, or instead of, EDC or eCRFs such as an "[Audio]-Computer Assisted Self-Interview" ([A]CASI, electronic pill boxes and SMS), surveillance data or evaluation metrics. The protocol chair and team will assess whether additional methods of data capture are required and if so, whether the SDMC, a contractor, or some other Network resource will be responsible for designing the required system. If the SDMC develops the system, development will follow steps similar to the design of eCRFs.

10.1.7   Study-Specific Procedures (SSP) Manuals

10.1.7.1   SSP Manual Development

In addition to study protocols, SSP manuals (generally referred to as just SSP) are prepared as stand-alone instructional and reference resources to guide conduct of HPTN studies at each site. SSP manuals contain links to applicable DAIDS policies and manuals (such as the DAIDS SCORE Manual and the Manual for Expedited Reporting of Adverse Events to DAIDS) and provide detailed standardized instructions for conducting protocol-specified procedures. The manuals are available upon request to the US FDA, other government and regulatory authorities, and site IRBs/ECs.

Development of SSP manuals proceeds in parallel with eCRF development beginning when a protocol is nearly finalized. Manuals are generally finalized shortly after the first study-specific site training. All manuals should be finalized prior to activation of the first participating site.

The LOC CRM is responsible for posting the manuals in an accessible location for the study team and study leadership; however, assembling and finalizing the individual manuals is the responsibility of the responsible network partner. For example:

- The SDMC CDM is responsible for the manual related to data collection/management, randomization, any additional methods of data collection (e.g., ACASI) developed by the SDMC and the protocol reporting plan

- The LC and/or other representative are responsible for the manual related to laboratory processing, testing, etc.

- The LOC will develop and manage the Study Management Overview; Accrual, Follow-up and Retention; and Clinical, Safety and AE Management manuals

- The DAIDS PAB protocol pharmacist is responsible for the development of the Pharmacy Study-Specific Procedures (SSP) Manual related to study product management by the site pharmacist. The PAB protocol pharmacist also provides significant input on other SSP manuals related to participant study product use. See Section 23 for responsibilities of the HPTN Pharmacist.

All manuals follow a common template table of contents that is tailored to the needs of each study.

Regardless of primary authorship assignments, every SSP manual must be circulated for review by study leadership (e.g., network resources, sponsor, and protocol chair) prior to finalization to ensure clarity, consistency, and compliance across all aspects of the study.

After incorporating all team and site input as needed, the primary author of each manual will send a finalized Version 1.0 (following good documentation practices for versioning and dating) to the LOC CRM for electronic posting. The LOC CRM will also create and maintain a master version control log for all SSP manuals.

10.1.7.2   SSP Manual Amendments

If a need for modifications to an SSP manual is identified after distribution of Version 1.0, the responsible author will revise the text and circulate the draft for review and comment from protocol team members as needed/applicable prior to finalizing a new version. The LOC CRM will post the final, revised manual and update the master version control log to document the change. The LOC CRM will inform the study team and site staff that the electronic file(s) containing the revised manual (with new version number and version date) and version control log have been posted on the study's collaborative electronic space and instruct the site staff to replace the existing manual with the new manual in all electronic and printed working copies of the SSP manual. The old manual should be moved to archive files.

It is the responsibility of the IoR to ensure that all manuals are updated and that updated procedural information is communicated to all applicable study staff in a timely manner.

10.1.8 Pre-study Site Assessment Visits

Prior to site-specific study activation and/or initiation of an HPTN study, staff from the LOC, SDMC, LC, Clinical Site Monitors and/or DAIDS may conduct one or more pre-study site assessment visits to ascertain site readiness for study implementation. Not all studies or study sites will need this visit. The need for this visit will be assessed on a case-by-case basis. The focus of the visit may vary depending on the stage of the study's development, the type of study to be conducted, and

specific requirements for study conduct. The timing of these visits will be planned with the site investigator and staff to allow participation of key site study staff.

The LOC CRM, SDMC staff, and LC staff members assess site facilities, operations, procedures, and available staff. They work with site investigators and staff to identify needs for study implementation (clinic, pharmacy and laboratory facilities, staffing needs, IT and data management best practices, etc.) and develop local plans for meeting them. Staff from the LOC, SDMC, and LC may visit together or separately. Depending on the complexity of the protocol and the site development and infrastructure, the LOC, SDMC, LC and/or DAIDS may make multiple visits.

Following the visit, the LOC, SDMC, or LC staff member typically generates a visit report and distributes it to the site investigators, DAIDS, and the other Network entities. The LOC CRM, SDMC CDM, and/or LC representative work with the site staff to address any issues raised by the visit(s) and documented in the visit report(s). Action items from pre-activation visits may also be documented in the study-specific site activation checklist (see Section 10.2).

10.1.9 Study-specific Training

LOC, SDMC, LC staff members, and the DAIDS PAB Pharmacist collaborate with site staff to plan and implement study-specific training. This training is described in Section 11.4 and may be virtual or in person. Study-specific training must be completed as a requirement for study-specific site activation (see Table 10-1 below).

10.1.10 FDA Submission and Safe to Proceed Notice

♦   For studies under a new IND, the sponsoring agency will submit the application to the US [Food and Drug Administration](#) (FDA). For these studies, completion of a US FDA 30-day review period/safe to proceed notice is required prior to the study opening.

10.2   Study-Specific Site Activation Requirements

Table 10-1 lists the activities that must be completed by each site in order to begin implementation of a specific HPTN study. These requirements are further described in the remaining sub-sections below.

Table 10-1 HPTN Study-specific Activation Requirements

A. For protocol-specific sites, verify OCSO site approval (refer to Section 16)

B. Pharmacy approval of site readiness from the DAIDS PAB Pharmacist may include:

- Confirmation of Pharmacy Establishment Plan and appropriateness for study
- SOP for study product management and approval from the DAIDS PAB (if applicable) (For studies where product may be managed by the HPTN Pharmacist, see Section 23.)
- All applicable import approvals for study products (non-US sites only)
- All applicable export approvals for study products (non-US sites only)
- Training for site pharmacists, if required by PAB
- Specific requirements for a particular study product
- Protocol specific prescriptions templates, as applicable

♦   For studies involving the HPTN pharmacist, see Section 23 for activation requirements

C. Data management approval from the Statistical and Data Management Center (SDMC) of site readiness based on the following:

- SOP(s) for data management, covering computer security, access and authentication, information security, data collection and handling, and data collection training.

- SOP for data quality assurance/quality control (QA/QC) procedures

- SOP for randomization procedures, if applicable

- Availability of required SDMC-provided materials including access to web-based EDC or survey software, randomization, and associated training modules, including the Targeted Source Document Verification (TSDV) (if required per OCSO)

D. Laboratory approval from Laboratory Center (LC) of site readiness, based on the policies found on the DAIDS Clinical Research Laboratory and Specimen Management website, which may include:

- Laboratory Quality Management Plan

- SOP for study-specific specimen management plan and "chain of custody" related to clinical/safety testing and management of samples for the study endpoints

- Confirmation of current CVs (or resumes) of key laboratory personnel

- Verification of Laboratory Data Management System (LDMS) set-up and training

- Verify current International Air Transport Association (IATA) specimen shipping certification for all staff members involved in the specimen management plan

- Good Clinical Laboratory Practice (GCLP) training for the appropriate laboratory staff

- The following for non-CLIA accredited laboratories

- proficiency in performing protocol-required tests

- appropriate validation and documentation of validation for protocol analytes

- any other applicable certifications

E. Site-specific SOPs confirmed in place by LOC for:

- Study source documentation

- Obtaining informed consent from potential study participants

- Participant eligibility determination

- Participant safety monitoring and adverse event/serious adverse event (AE/SAE) reporting (if applicable) and follow-up

- Participant accrual

- Participant retention

- Communication with responsible IRB/EC

- Communication with affiliated additional locations, if applicable

- Audits and Inspections

- Emergency unblinding (if applicable)

- Study-specific SOPs (if applicable)

F. Other requirements confirmed by the LOC:

- For DAIDS-sponsored studies with more than one US site: Single Institutional Review Board (sIRB) approval of the protocol and informed consent forms (including local language versions, back-translations and local language Translation Confirmation Documents, where applicable). For studies with no more than one US site, and for all non-US sites: local IRB/ethics committee (EC) approval, and (if applicable), regulatory authority approval, (e.g., Ministry of Health, drug controller/regulatory agency)

- Protocol registration approval from the Regulatory Support Center (RSC) Protocol Registration Office (PRO), based on the following:

- Signed FDA Form 1572 or DAIDS Investigator of Record Form

- CV of the Investigator of Record (IoR)

- Confirmation received from investigator that completion of Human Subjects Protection (HSP) training for key study staff is current (see Section 11.1)

- Confirmation received from investigator that completion of GCP training for key study staff is current (see Section 11.2)

- Study staff signature sheet, roster, and delegation of duties

- Confirmation received from investigator that current CVs (per DAIDS policies) for key staff are available on site

- For IND studies, verification that Financial Disclosures are on file for all relevant staff that are on the Form FDA 1572 (see Section 7)

- Completion of study-specific training

- Resolution of any other action items identified in any other site preparation activities

- Others as needed (site- and study-specific)

10.2.1   Informed Consent Forms, IRB Approval and Protocol Registration

The DAIDS Protocol Registration Manual includes detailed instructions on obtaining site protocol registration, including the content and formatting of ICFs that must be submitted, as well as documenting and submitting IRB/EC approvals. Section 8 further describes IRB/EC and human subjects requirements for HPTN research studies.

10.2.2   Standard Operating Procedures and/or Plans

As a condition for study activation, site- and study-specific standard operating procedures (SOPs) and/or plans that describe the requirements and operations of a particular study must be in place. A set of standard SOPs are typically required for any HPTN study (see Table 10-1); additionally, study-specific SOPs may be required depending on the nature of the study, as determined by the protocol team. The Activation Checklist will specify which SOPs are required. If a site has established site SOPs that adequately cover required procedures for specific studies, these may be used to fulfill the study activation requirements. In order for these SOPs to cover any HPTN study, they should be generic and not reference the study name or number from any specific study(ies). Sites may consider developing a library of standardized SOPs that could be applicable to any HPTN studies. If a generic SOP needs modification to make it study-specific, a study-specific addendum or appendix should be added.

Details of what must be included in study-specific SOPs will be described in each study's SSP manuals.

10.2.3   Delegation of Duties Log

Sites must create and maintain a study-specific Delegation of Duties log. This log must comply with requirements as outlined in the DAIDS SCORE Manual.

10.2.4   Study Product Acquisition and Shipment to Sites

Study product for HPTN studies is typically received from the manufacturer or other source and stored and distributed to the study sites by the DAIDS Clinical Research Product Management Center (CRPMC). The DAIDS Pharmaceutical Affairs Branch (PAB) has established the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks which describes the required pharmacy and study product management standards for the conduct of DAIDS clinical trials and includes requirements for personnel, facilities, equipment, and processes. (For studies where product may be managed by the HPTN Pharmacist, see Section 23.)

Before study product is sent to a non-US study site, documentation of local drug authority approval for importation of the product for the study use must be obtained and submitted to the DAIDS PAB. It is the responsibility of the IoR and Pharmacist of Record to know the necessary local requirements and to obtain the necessary approvals including those that may provide waivers for import fees. To aid sites in obtaining local approvals, the CRPMC will provide a *pro forma* invoice upon request, detailing the quantity, lot numbers, expiration dates (when available), value, and other details of all products and related materials to be shipped to the site for use in the study. Sample product labels will also be provided by the DAIDS PAB upon request for use in obtaining local approvals, if necessary.

Non-US study sites are encouraged to provide information to the DAIDS PAB pharmacist on the protocol team that may be helpful in shipping products to the study site, including suggestions for preferred couriers and specific wording to be used on the shipping documents to avoid unnecessary customs delays or fees.

For studies involving study products that are not under an IND with the US FDA, export approval from the US FDA may also be required before study product can be shipped to certain countries.

This approval may be sought by either the manufacturer or the local drug authority and takes approximately 8-12 weeks after receipt of the request by the US FDA.

For most studies, study product should be available at the site before the site is activated and begins screening and enrollment. However, depending on the length of the screening process and other details such as shelf-life, a site may be activated prior to study product availability at the site, if approved by DAIDS. Each study team will determine at what point a site may be activated with regards to study product availability. Questions regarding shipment of study products to sites should be directed to the DAIDS PAB Pharmacist of the protocol team. (For studies where product may be managed by the HPTN Pharmacist, see Section 23.)

10.2.5 Study Product Management

General information and guidelines for study product management are included in the latest version of the [Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks](#) is accessible on the DAIDS website. All sites conducting studies with study products are required to have a copy of this document on file. The Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks details the documentation requirements associated with study product receipt, control, accountability, dispensing, and final disposition. The manual also details the responsibilities of the Pharmacist of Record. The pharmacist at each site who is designated the Pharmacist of Record for a particular study will manage and control the study products used in that study. These responsibilities include, but are not limited to, developing and maintaining a study product management system.

More detailed instructions and procedures for the handling of study products for an individual study may be provided in the protocol and Pharmacy SSP Manual. Questions regarding the management of study products should be directed to the DAIDS PAB Protocol Pharmacist. (For studies where product may be managed by the HPTN Pharmacist, see Section 23.)

10.2.6 Pharmacy Establishment Plans

A Pharmacy Establishment Plan is required for each site conducting an HPTN study involving study product(s). A copy of the DAIDS Standard Pharmacy Establishment Plan form can be found in the [Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks](#). An electronic copy is made available to the site via DAIDS PAB. The Pharmacy Establishment Plan (PEP) and applicable PEP Module(s) must be approved by the DAIDS PAB as a condition for shipping study product to a site and for initiation of study procedures. This plan is submitted directly by the site Pharmacist of Record to the DAIDS PAB for review and approval.

The Pharmacist of Record is encouraged to work with study investigators and other local staff members to complete the DAIDS Pharmacy Establishment Plan. Questions regarding the completion and review of Pharmacy Establishment Plans should be directed to the DAIDS PAB. (For studies where product may be managed by the HPTN Pharmacist, see Section 23.)

10.2.7 Essential Documents

HPTN study sites must maintain a number of administrative and regulatory documents pertinent to each HPTN study in which they participate. These documents commonly are referred to as essential documents. Although sites are allowed some flexibility in their filing systems, all required documents should be stored in an organized manner and must be easily retrievable for review by the Clinical Site Monitor and other authorized individuals. Study sites are encouraged to begin organizing and filing required documentation upon receipt of the final study protocol and must maintain complete and accurate files from that time forward, in accordance with the record retention requirements stated in the study protocol. DAIDS requirements and additional guidance on management of essential documents is provided in the [DAIDS SCORE Manual](#).

10.2.8 Study Material Translation

Certain study-related materials may be translated into local languages for HPTN studies involving non-English speaking participants. As a general rule, informed consent forms, community education materials, advertisements, questionnaires, interview forms, and other materials administered or distributed directly to study participants must be translated. The IoRs are responsible for ensuring that study site staff and participants are provided with all required study-related information in a language that is understandable to them.

SSP manuals, in whole or in part, also may need to be translated for some sites in some studies. Study sites are responsible for completing all translation tasks unless otherwise arranged with the HPTN LOC, LC and/or SDMC.

Translations are completed after the English versions are finalized. Translated informed consent forms must be submitted for protocol registration as described in the DAIDS Protocol Registration Manual.

10.2.9 Study-specific Site Activation Notification

When a site has completed all study activation requirements (see Table 10-1), the LOC CRM will send an HPTN Site Activation Notice to the site. Upon receipt of this notification the site may initiate the study. Only upon receipt of this notification may a site initiate recruitment and screening of study participants. In multi-site studies, sites are individually activated as documented fulfillment of activation requirements at each site is completed (i.e., activation of a site need not await readiness of the others).