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. Several of these steps require collaborative work among the Division of AIDS (DAIDS) staff, HPTN central resources, protocol team and site study staff members; chief among these is development of the study case report forms (CRFs) and a study-specific procedures (SSP) manual, described in Sections 10.5 and 10.7, respectively.

Once all study activation requirements are met at a site and documented, the HPTN Leadership and Operations Center (LOC) Clinical Research Manager (CRM) will issue a site-specific Study Activation Notice (see Section 10.4) 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 to site staff a copy of the documentation upon which activation was based.

Study-specific Requirements: Table 10-1 lists the activities that must be completed by each site in order to begin implementation of a specific HPTN study. Key pre-implementation activities involved in the study activation process are described in greater detail throughout the remainder of Section 10.

As a condition for study activation, study-specific SOPs that describe the requirements and operations of a particular study must be in place. The Activation Checklist will specify which SOPs are required (e.g., accrual, retention). 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. (See Table 10-1.)

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

Table 10-1 HPTN Study-specific Activation Requirements

I. Required Study-specific Activities, SOPs, and Documentation
A. Verify OCSO site approval (refer to Section 16) B. Pharmacy approval of site readiness from the DAIDS Pharmaceutical Affairs Branch (PAB) may include: • SOP for investigational product management and accountability review and approval from the DAIDS PAB (if applicable) • All applicable import approvals for study products • All applicable export approvals for study products • Training for site pharmacists, if required by PAB • Specific requirements for a particular study agent • Regimens and administration • Protocol specific prescriptions

C. Data management approval from the Statistical and Data Management Center (SDMC) of site readiness based on the following:
- Installation of required data transfer equipment, EDC or survey software
- SOP for data management, including data quality assurance/quality control (QA/QC) procedures
- SOP for randomization procedures, if applicable
- Availability of required SDMC-provided materials (e.g., paper CRFs) or access to web-based EDC or survey software

D. Laboratory approval from Laboratory Center (LC) of site readiness based on the following:
- Study-specific QA/QC procedures
- SOP for study-specific specimen management plan and "chain of custody" related to clinical/safety testing and management of samples for the study endpoints
- Sites in the United States (US) must identify local back up laboratory arrangements. Non-US sites must identify back up for laboratory testing in their Protocol Analyte List (PAL) (see Section 13)
- 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
- Reference intervals Clinical Laboratory Improvement Amendments (CLIA) accreditations for US laboratories performing safety testing/CD4/Viral Load
- The following for non-CLIA accredited laboratories
  - proficiency in performing protocol-required tests
  - appropriate validation and documentation of validation for protocol analytes

E. Study-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)
- Participant accrual plan (may be written as SOP or plan)
- Participant retention plan (may be written as SOP or plan)
- Communication with responsible IRB/EC (may be site-specific SOP)
- Communication with affiliated sub-sites, if applicable (may be site-specific SOP)
- Others as determined by study team

II. Other Required Activities

A. Local regulatory authority approval of the study protocol, e.g., Ministry of Health, drug controller/regulatory agency (if applicable, in addition to IRB/EC approval)

B. Protocol registration approval from the Regulatory Support Center (RSC) Protocol Registration Office (PRO), based on the following:
- Approvals of the study protocol from all Institutional Review Boards/Ethics Committees (IRBs/ECs)

- IRB/EC-approved informed consent forms (including local language versions, back-translations and local language Translation Confirmation Documents, where applicable)
- Signed FDA Form 1572 or DAIDS Investigator of Record Form
- CV of the Investigator of Record (IOR)

C. Completion of US Food and Drug Administration FDA 30-day review period/safe to proceed notice (if applicable)
D. Confirmation received from investigator that completion of Human Subjects Protection (HSP) training for key study staff is current (see Section 11.1)
E. Confirmation received from investigator that completion of GCP training for key study staff is current (see Section 11.2)
F. Study staff signature sheet, roster, and delegation of duties
G. Confirmation received from investigator that current CVs for key staff available onsite
H. Completion of study-specific training; DAIDS approval of resolution of findings/actions identified during training, if applicable
I. Resolution of any other action items identified in any other site preparation activities
J. Others as needed (site- and study-specific)
K. Final DAIDS Branch Chief approval for study activation

10.1 Clinical Trials Agreement

A Clinical Trials Agreement (CTA) is the agreement negotiated between a collaborating pharmaceutical co-sponsor and DAIDS, as the study sponsor, 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. In general, terms in the CTA covering data access and sharing conform to policies developed jointly by the Executive Committee (EC) and DAIDS.

The DAIDS Regulatory Affairs Branch (RAB) and the 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 DAIDS Medical/Program 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).

10.2 Study Product Acquisition and Shipment to Sites

Study products for HPTN studies are 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). Ordering and storage instructions for US sites are found in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.* For non-US HPTN sites, instructions for obtaining study products will be provided by DAIDS PAB on a study-by-study basis.

Before study products are sent to a non-US study site, documentation of local drug authority approval for importation of the products for the study use must be obtained and

submitted to the DAIDS PAB and the HPTN LOC. 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 drugs or biologics 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 drug availability at the site, if approved by DAIDS. Each study team will determine at what point a site may be activated with regards to drug availability.

Questions regarding shipment of study products to sites should be directed to the DAIDS PAB member of the protocol team.

10.3 Study-specific Preparatory, Assessment, and Initiation Visits to Sites

Prior to initiation of an HPTN study, site readiness for study implementation must be ascertained. The LOC, SDMC, LC, Clinical Site Monitor, and DAIDS may conduct visits if needed to assist sites in preparation and to assess and confirm readiness to undertake a specific study. These visits will likely include a combination of the visits described in the following sections. The table below summarizes these visits. The timing of these visits will be planned with the site investigator and staff to allow participation of key site study staff.

Table 10-2 HPTN Pre-study Site Visits

Pre-study Site Visits (typically conducted for sites previously not in HPTN)			
Type of Visit	**Purpose**	**Timing/Requirements**	**Responsible Group(s)**
Pre-study assessment (Section 10.3.1)	To assess site infrastructure, operations, and staffing	Prior to acceptance as a participating site, and prior to finalization of protocol	LOC, SDMC, LC, and/or DAIDS
Pre-study operations (Section 10.3.2)	To obtain site input on day-to-day study implementation and content of study	Following finalization of protocol, when draft CRFs and SSP manual are available, and prior to study-specific training	LOC, SDMC, LC

Pre-study Site Visits (typically conducted for sites previously not in HPTN)			
Type of Visit	**Purpose**	**Timing/Requirements**	**Responsible Group(s)**
	CRFs; to review source document requirements for each procedure		
Special assignment study-specific initiation (Section 10.3)	To be specified in advance by DAIDS/Clinical Site Monitor	Following IRB/EC approval of protocol and prior to study training. See the table in Section 11.4.2	Lab and/ or Clinical Site Monitor
Protocol Training (Section 11)	To participate, as trainers and representatives of the central operations components, in study-specific training	Following Clinical Site Monitor initiation visit. See the table in Section 11.4.2 for a list of specific requirements	LOC, SDMC, LC and any experts/ consultants as applicable

10.3.1 Pre-study Site Assessment Visits

Prior to site-specific study activation, staff from the LOC, SDMC, LC, and/or DAIDS may conduct one or more pre-study site assessment visits. The purpose of these visits is to assess site readiness and assist the site to prepare to undertake a specific HPTN study. 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 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 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.

The pre-study assessment visits may be conducted anytime between the identification of the site as a participant in the protocol and finalization of the protocol. Dependent on the complexity of the protocol and the site development and infrastructure, the LOC, SDMC, LC and/or DAIDS may make multiple visits. Timing and activities for visits will be planned in conjunction with the site staff.

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).

10.3.2 Pre-study Operations Visit

On a study-by-study basis, a pre-study operations visit may take place. Following the pre-study site assessment visit, and after a study protocol is finalized and draft study CRFs or eCRFs have been approved by the protocol team, the LOC CRM, LC and SDMC CDM may conduct pre-study operations visits with at least one participating study site. This is part of the process for finalizing the study CRF/eCRFs and SSP Manual (described in Section 10.5 and 10.7, respectively). Depending on the needs of the study, multiple visits may be conducted. Every effort will be made to involve key study implementation staff from sites in the visits. For some studies, visits may be conducted at each participating study site. For other studies, a single visit may be conducted, and key staff from other sites asked to attend the visit.

The purpose of pre-study operations visits is to obtain detailed site input on both day-to-day study implementation tasks and activities and the content of the study CRF/eCRFs. The visits take place over several days and may include a step-by-step "walkthrough" (time permitting) of the protocol specifications for each study visit and the data collected at each visit. Source documentation requirements associated with each study procedure also are discussed. Input received from site staff is incorporated by the LOC CRM and SDMC CDM into the draft study SSP manual and the study CRF/eCRF set, such that a form set reflecting all required site input can be finalized prior to conduct of study-specific training.

Following the visit, the LOC, LC and SDMC staff member will generate a visit report and distributes it to the site investigators, DAIDS, and the other Network entities, as appropriate. The LOC CRM, LC representative and SDMC CDM will work with the site staff to address any issues raised by the visit(s) and documented in the visit report(s).

10.3.3 Study-specific Training Visit

LOC, SDMC, and LC staff members collaborate with site staff to plan and implement study-specific training. This training is described in Section 11.4.

10.4 Site-specific Study Activation Notification

When a site has completed all study activation requirements (see Table 10-1), the LOC CRM will send the completed activation checklist to the DAIDS Medical Officer (or DAIDS Branch Chief) for approval for study activation. After approval from DAIDS, 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).

10.5 CRF/eCRF Development

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

- Development of CRF 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. Scientific expertise (e.g., behavioral scientists, clinicians) is sought externally, as appropriate
- CRF content is gathered or developed, as needed
- The SDMC will convene a conference call or in-person meeting of a subset of the protocol team in order to obtain the team's input on CRF content. The subset should include representatives from the LOC, LC, DAIDS, investigators, community representatives, and other site staff as appropriate. The draft form set and relevant study materials (e.g., Schedule of Forms) are comprehensively reviewed during the call or meeting. Approved changes are incorporated into the CRFs/eCRFs and other study materials. The SDMC, LOC, and LC determine if CRFs and related study materials should be part of any planned operational "walkthrough" during a pre-study operations visit
- As needed, finalized CRF content is translated by the study sites or contractor (ideally before any planned operational walkthrough or pre-study operations visit). The translation process is initiated and coordinated by the SDMC. Back-translations, especially for behavioral questionnaires, will be reviewed by the SDMC and LOC for approval
- Study-specific training is conducted (see Section 11.4)
- After study-specific training is conducted (see Section 11.4) final CRFs or EDC set-up are distributed by the SDMC to study sites prior to or upon activation (see Section 12.3.2)

10.6 Additional Data Capture Methods

Some types of studies may require methods of data collection in addition to, or instead of, EDC or CRFs. For example, questions about a study participant's sexual behavior or drug use may best be collected using a computerized questionnaire methodology such as an "[Audio]-Computer Assisted Self-Interview" ([A]CASI). The protocol team and SDMC 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 CRF/eCRFs.

10.7 Study-specific Procedures (SSP) Manual

10.7.1 SSP Manual Development

In addition to study protocols, an SSP manual is prepared as an instructional and reference resource to guide conduct of HPTN studies at each site. SSP manuals contain links to applicable DAIDS policies and manuals (such as 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 CRF development beginning when a protocol is nearly finalized. The LOC CRM is responsible for assembling the manual in close cooperation with the SDMC and LC, as well as other key protocol team members. All manuals follow a common template table of contents that is tailored to the needs of each study.

The LOC CRM is responsible for coordinating the development of the SSP manual; however, other protocol team members are assigned authorship and review responsibilities for certain sections. For example:

- The SDMC CDM is responsible for sections of 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 sections of the manual related to laboratory processing, testing, etc.
- The DAIDS Medical Officer and other clinically-trained team members often are required to develop and/or carefully review sections of the manual related to clinical procedures
- The DAIDS PAB protocol pharmacist is responsible for sections of the manual related to investigational product management by the site pharmacist. The PAB protocol pharmacist also provides significant input on other sections of the SSP Manual related to participant study product use

Regardless of primary authorship assignments, the LOC CRM is responsible for coordinating the development of all sections, reviewing all sections, and incorporating all sections into the manual. As the manual is developed, the LOC CRM will forward it for review by other team members as needed, collect comments, and incorporate these into revised draft versions of each section. Input may also be sought from site staff prior to finalization of the manual, both by requesting review and comment on draft versions of the document and through conduct of the pre-study operations visits described in Section 10.3.2.

After incorporating all team and site input as needed, the LOC CRM will issue the first final implementation version of the SSP Manual, labeled with version 1.0 and the version date. This electronic copy of the manual will also be posted on the HPTN website's collaboration portal once final. Release of version 1.0 of the SSP Manual typically closely follows conduct of study-specific training and usually precedes study activation at the first participating site.

10.7.2 SSP Manual Amendment

If a need for additions or modifications to the SSP Manual is identified after distribution of the first final implementation version, the LOC CRM will draft or obtain the new text and obtain review and comment from protocol team members as needed/applicable. The LOC CRM also will update an SSP Manual version control log to document the change. After review comments are incorporated, the new text and the version control log will be considered final and ready for distribution. Electronic file(s) containing the revised sections and version control log will be posted on the HPTN website's collaboration portal. The LOC CRM will inform the study team and site staff that the electronic file(s) containing the revised section(s) (with new version number and version date) and version control log have been posted on the HPTN website's collaboration portal and instruct the site staff to add the revised section(s) to the SSP Manual filed with the site's administrative and regulatory documents for the study and to replace the existing sections with the new sections in all other working copies of the SSP Manual.

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.

10.8 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, and filing requirements are specified in the DAIDS policy: Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS funded and/or Sponsored Clinical Trials. 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. Guidance is provided in the DAIDS policy on essential documents.

10.9 IRB/EC Approval

Section 8.4 of this manual details the study-related documents that must be submitted to and approved by all IRBs/ECs responsible for oversight of research involving human subjects at each study site. All required approvals by all responsible IRBs/ECs must be obtained and documented prior to study initiation.

The DAIDS-approved version of the study protocol will be provided by the LOC CRM to each site for submission to the IRBs/ECs. If specific IRB/EC requirements make it difficult to adhere to the procedures described in the following sections, site staff must notify the LOC CRM.

10.9.1 Site-specific Informed Consent Forms: English Version

The protocol will include sample informed consent forms as appendices. Site staff will adapt the sample informed consent forms appended to the protocol to reflect local procedures and IRB/EC requirements, site-specific information (e.g., amount of participant reimbursement in local currency), and local contact information. As outlined in the DAIDS Protocol Registration Manual, the site-specific informed consent forms must be labeled with the exact protocol number and title listed on the cover page of the protocol, the protocol version number, and protocol version date. Pages must be numbered 1 of x, 2 of x, 3 of x, etc., with “x” representing the total number of pages in the individual informed consent form. Version control conventions (e.g., labeling all forms with both the protocol version number and date and the informed consent form version number and date) must be implemented at each site to avoid confusion and inadvertent use of an outdated form. Each informed consent form also should be labeled (e.g., English Language Informed Consent; Back-translation of Local Language Screening Consent, etc.). Figure 10-1 presents examples of the recommended label format for all informed consent forms. Note that a site may elect to submit one version of the consent form to the IRB/EC first (e.g., English site-specific version), before finalizing the others (translation, back-translation) for submission; however, all versions must be provided to the IRBs/ECs.

Figure 10-1 Examples of Informed Consent Footers

Site–specific English consent

HPTN 0XX	page 1 of X English Language Enrollment Consent
Protocol Version 1.0	Informed Consent Version 1.0
Dated 10 October 2015	Dated 12 March 2016

Local Language Consent

HPTN 0XX Consent Protocol Version 1.0 Dated 10 October 2015	page 1 of X Chinese Language Enrolment Informed Consent Version 1.0 Dated 12 March 2016

Back-translation of Local Language Consent

HPTN 0XX Consent Protocol Version 1.0 Dated 10 October 2015	page 1 of X Back translation of Chinese Enrollment Informed Consent Version 1.0 Dated 12 March 2016

Site staff are allowed to add information to their site-specific informed consent forms in order to help explain study concepts to participants or to comply with IRB/EC requirements. However, if site staff delete or make any substantive change to the risk or alternative treatment information presented in the sample informed consent forms, written justification must be provided for the deletion or change. The justification must be approved by the site IRBs/ECs, and documentation of IRB/EC approval must be submitted for review and approval by the DAIDS Protocol Registration Office (PRO) at the RSC. Similarly, if non-US laws or regulations result in the deletion or substantive change to any of the required information in the sample forms, written justification must be submitted to the DAIDS PRO for review and approval. Refer to the DAIDS Protocol Registration Policy and Procedure Manual for further details.

Site staff may submit their locally adapted English informed consent forms to the LOC CRM before submission to all responsible IRBs/ECs and before the forms are translated and back-translated (if back-translations are required).

10.9.2 Site-specific Informed Consent Forms: Translations

Site staff will translate the informed consent forms into all applicable local languages (note that the DAIDS RSC will create Spanish translations of the sample informed consent if requested by the LOC, but cannot do so for other languages) and, if applicable, arrange for an independent back-translation of each informed consent form. Back-translations are *NOT* required if a clinical research site (CRS) has an English site-specific informed consent.

If informed consent discussions will only be conducted in Spanish, site-specific Spanish language informed consent forms must be submitted to the PRO. No back-translations are required by DAIDS.

Note: CRSs are required to complete the DAIDS Protocol Registration Translation Confirmation Document (which can be found on the RSC website) for any protocol registration documents in Spanish.

If informed consent discussions will be conducted in English and another local language, including Spanish, the site-specific English and local language informed consent forms must be submitted to the PRO. No back-translations are required by DAIDS.

If informed consent discussions will be conducted only in a local language other than English or Spanish, site-specific local language informed consent forms must be submitted to the PRO. Back-translations of the site-specific local language informed consent forms (into English) also must be submitted to the PRO.

10.9.3 Submission to IRBs/ECs

Site staff will submit the protocol, site-specific informed consent forms, and other required documents (see Section 8.4) to all responsible IRBs/ECs. The cover letter provided to the IRBs/ECs with the required documents should include:

- DAIDS ES and/or Network protocol ID number
- Full protocol title
- Protocol version number from the final version of the protocol approved by DAIDS and/or the final version date of the protocol document approved by DAIDS
- List (title and date) of all documents submitted, including informed consent forms

Note: For sites with multiple responsible IRBs/ECs, it is likely that all IRBs/ECs will provide comments on the submitted study documents. It is the responsibility of the IoR to incorporate all such comments into a single final version of the study informed consent forms and obtain approval of this final version from all responsible IRBs/ECs. This may require multiple submissions to the responsible IRBs/ECs.

10.9.4 Obtain IRBs/ECs Approval Documentation

In order to link the IRB/EC approval letter(s) to the current DAIDS-approved version of the protocol, documentation from each IRB/EC of approval must reference the following:

- N-CRMS and/or Network protocol ID number
- Full protocol title
- Protocol version number and/or date
- The approved informed consent forms, version number and date
- Risk/benefit category if research involves pregnant women, children or adolescents (see Section 8.5.6 for more information)
- Effective date of IRB/EC approval
- Signature of the IRB/EC Chair or designee
- Title of the person signing for the IRB/EC

It is recommended, but not required, that the expiration date of the approval also be included. If the approval documentation is provided in a language other than English, the document must also be translated into English.

10.10 Site-specific Protocol Registration

After obtaining approval from all responsible IRBs/ECs, HPTN study sites must complete protocol registration procedures with the DAIDS PRO. Complete details of the site-specific protocol registration are included in the DAIDS Protocol Registration Manual. Protocol registration is completed for each HPTN study on a site-by-site basis. The registration submission is done by the site directly to the PRO via the NIAID Clinical Research Management System (CRMS). The purpose of these procedures is for DAIDS to confirm regulatory compliance and completeness of site informed consent forms and IRB/EC approval documentation prior to study initiation. If a site encounters problems when submitting protocol registration materials through the DPRS, a CRS can submit protocol registration materials via email to the DAIDS Electronic Protocol Registration (EPR) mailbox at EPR@tech-res.com. The DAIDS Protocol Registration Checklist must accompany EVERY submission made to the DAIDS PRO through the EPR mailbox.

Upon obtaining all required IRB/EC approvals, site staff will submit the following documents to the PRO:

- A copy of the signed and dated FDA Form 1572 or DAIDS Investigator of Record Form (the original must remain at the site)

- Signed and dated current CV of the IoR, in English (current within two years)
- Documentation of approval from all relevant IRBs/ECs and RE, if applicable, of the study protocol, informed consent forms, and other required material such as recruitment material. This documentation must reference the protocol number, title, version number, and date as it appears on the cover page of the protocol. If the approval documentation provided by the IRB/EC is in a language other than English, both the non-English version and a translation into English must be submitted
- Copy of the approved site-specific informed consent forms (English and any local language); the approved informed consent forms must include the protocol number, title, version number, and date as they appear on the cover page of the protocol
- Back-translations of the local language site-specific informed consent forms (if applicable) See Figure 10-1
- A local language DAIDS Protocol Registration Translation Confirmation Document. Only one Translation Confirmation Document that attests to the accuracy of the translation of each language for all of the protocol registration documents is required with each protocol registration submission

PRO staff will review all materials including a careful review of the site-specific informed consent document(s) if applicable (see Section 10.2.3). Sites will receive an Initial Registration Notification from the PRO that indicates whether or not the registration was completed successfully. The site must place a copy of all final protocol registration notifications from the PRO in the site's regulatory files.

PRO staff try to complete their reviews of submitted materials within 10 working days of receipt; however, more time may be required if there are multiple informed consent forms to be reviewed. If modifications to the informed consent forms are required, the site will need to address these and submit revisions to their IRB/EC for approval. The site will provide any further documentation or resubmissions to the PRO.

10.11 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* provided to HPTN study investigators and pharmacists by the DAIDS PAB. All sites conducting studies with drugs or other investigational 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 return. The manual also details the responsibilities of the Pharmacist of Record. The pharmacist at each CRS 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 SSP manual and/or in a separate study-specific pharmacy procedures document developed by the DAIDS PAB in conjunction with the LOC and other team members as necessary.

Questions regarding the management of study products should be directed to the DAIDS PAB protocol pharmacist.

10.12 Pharmacy Establishment Plans

A Pharmacy Establishment Plan is required for each site conducting an HPTN study involving investigational 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 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 DAIDS PAB will provide an initial response to the Pharmacist of Record within 10 to 12 working days; revisions and review will continue until PAB has approved the Plan.

The Pharmacist of Record is encouraged to work with study investigators and other local staff members to complete the DAIDS Standard Pharmacy Establishment Plan. For sites conducting multiple studies using different types of products with different storage and dispensing requirements (e.g., topical microbicides and systemic antiretrovirals), DAIDS PAB may require that a separate Pharmacy Establishment Plan be completed for each study.

Questions regarding the completion and review of Pharmacy Establishment Plans should be directed to the DAIDS PAB.

10.13 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, 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.

To avoid repetitive cycles of translation, translations are completed after the English versions are finalized. Translated informed consent forms and CRFs must be back-translated into English by a translator not involved in the original translation, as described in Section 10.5. Other materials also may require back-translations at the discretion of the Protocol Chair(s), statistician, LC representative, LOC CRM, or SDMC CDM.