Section 1. Introduction

1.1 Overview of Section 1

This section has specifics on study conduct including the sources of procedural information available to HPTN 074 study site staff, the responsibilities of the site Investigators, and the process by which each site will be approved to implement HPTN 074.

1.2 Source of Procedural Information

All study procedures must be conducted in accordance with the study protocol and this study specific procedures (SSP) manual. In the event that this manual is inconsistent with the protocol, the specifications of the protocol take precedence. Please alert the HPTN Leadership and Operations Center (LOC) of any such inconsistencies.

In instances where there is an urgent need for a change to the SSP manual, and when a full revision of the SSP is not imminent, the LOC may distribute an email containing a "Notification of Interim Change" to the current version of the SSP manual. These interim changes will be considered an official part of the SSP manual, and should be considered official by any monitoring agents.

Site staff are encouraged to contact the HPTN LOC with all questions related to interpretation and proper implementation of the protocol. Site staff should contact the Statistical Center for HIV/AIDS Research and Prevention (SCHARP) with questions related to data collection. Site staff should contact the HPTN Laboratory Center (LC) with questions related to the collection, processing, and storage of local and central lab specimens.

LOC Staff:

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SDMC Staff:

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Laboratory Center (LC) Staff:	Estelle Piwowar-Manning Tel: 410-614-6736 Email: epiwowa@jhmi.edu Paul Richardson Tel: 410-502-0435 Email: pricha18@jhmi.edu
Laboratory Data Management System (LDMS):	Tel: 716-834-0900 ext 7311 Email: ldmshelp@fstrf.org

Contact information for all other HPTN 074 team members can be found in the electronic HPTN directory at www.hptn.org.

1.3 Investigator Responsibilities

HPTN 074 must be conducted in accordance with the US Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Consolidated Guideline for Good Clinical Practice (GCP) and DAIDS regulations. Copies of the regulations governing the conduct of this study (45 CFR 46 and 21 CFR 11, 50, 54, 56, and 312) and the ICH guideline can be requested from the LOC or found online at www.gpoaccess.gov/cfr/index.html and http://www.ich.org/cache/compo/276-254-1.html, respectively. The DAIDS Policy for Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-RA-03.00) and the DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-CL-04.00), which are useful for interpreting and operationalizing these regulations and guidelines, can be downloaded from: http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Regulatory.htm and http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/ClinicalSite.htm, respectively.

HPTN 074 also must be conducted in accordance with all local regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular.

The Investigator of Record (IoR) at each site is the person responsible for the conduct of the clinical trial at the clinical research site. This person is the signatory for the Investigator of Record Agreement, which must be signed prior to site activation. The IoR is also required to sign the protocol signature page, to formally indicate his/her agreement to conduct the study in accordance with the protocol; this SSP manual; all applicable US and in country regulations, policies, and guidelines; and HPTN policies. The IoR must also sign a signature page for any letters of amendment (LoAs) during the study.

Investigators may delegate work involved in conducting the study to other study staff members; however, delegation does not relieve the Investigator of his/her ultimate responsibility for all study procedures performed and all study data collected. Additional guidance can be found in the US Food and Drug Administration's Information Sheet Guidances: Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors available at http://www.fda.gov/oc/ohrt/irbs/default.htm.

1.4 Study Activation Process

Prior to undertaking any study procedures, each study site must obtain approval to conduct the study from all responsible US and local Institution Review Board/Ethics Committee (IRBs/ECs). Thereafter, sites must complete Protocol Registration with the DAIDS RSC, as well as Study Activation procedures with the HPTN LOC. These procedures are also described in the HPTN Manual of Operations (MOP). OCSO has separate procedures for the establishment of new sites to any DAIDS network. Those procedures are detailed in OCSO policies and procedures and will be communicated to sites separately from this SSP Manual.

HPTN 074 study procedures may not be conducted prior to completing all of these steps and receipt of a site specific study activation notice from the HPTN LOC.

1.4.1 Protocol Distribution

The LOC Clinical Research Managers (CRMs) will distribute the final implementation version of the protocol and any relevant updates to the study site.

1.4.2 Development and LOC Review of Site-Specific Informed Consent Forms (ICFs): English Language Version

Site staff will adapt the sample informed consent forms appended to the study protocol by including site-specific information, such as PI name and phone number. If there are local procedures and IRB/EC requirements, these should be included in the English adaptations. The LOC offers to review the consents prior to translation into local language and prior to submitting the ICF(s) to the IRB/ECs.

1.4.3 Development and LOC Review of Site-Specific ICFs

Sites should translate the ICFs into the local language(s). Therefore, participants in HPTN 074 will take part in the consent discussion and ICF document in their native language. For quality assurance purposes, sites should also back-translate the local language consents into English. Ideally this should be completed by another person who has not seen the original English consents. **Sites will also need to complete a Translation Confirmation Document for each language (found here http://rsc.tech-res.com/protocolregistration/) at the time of protocol registration.**

1.4.4 IRB/EC Review

After incorporating review comments received from the LOC CRM, site staff will submit the study protocol, site-specific informed consent forms, the current curriculum vitae (CV) of the Investigator of Record (IoR), and any other relevant study-related materials for review by all responsible IRBs/ECs. Any participant information sheets, instruments such as questionnaires and interview guides, promotional materials, partner referral cards, advertisements, or other supporting documents used during the study must be reviewed and approved by all responsible IRBs/ECs prior to use.

In the event that any of the IRBs/ECs request changes to the submitted ICFs, it is the responsibility of the IoR to incorporate all such comments into a single final version of the study ICFs, and to obtain approval of this final version from all responsible IRBs/ECs. This may require multiple submissions to the responsible IRBs/ECs. If a local language consent form is being used, the final English back-translation must reflect the approved informed consent forms that will be used at the site.

An overview of IRB/EC submissions required before and during HPTN 074 is included in Table 1-1. Further guidance on IRB/EC activities can be found from the US Office for Human Research Protection (OHRP) at http://www.hhs.gov/ohrp/policy/index.html#continuing.

Table 1-1: IRB/EC Submissions Required Prior to Study Initiation and During Study Conduct

Document	IRB/EC Approval Required?*		Source of Document: HPTN LOC or CRS
	Prior to Study Initiation	During Study Conduct	
Protocol, Version 1.0 and versions following Version 1.0	yes	yes	HPTN LOC
Protocol amendments (including letters of amendment) and any other changes increasing risk to participants and/or affecting significantly the conduct of the study.	Yes (if applicable)	yes	HPTN LOC
Protocol clarification memos (submission to IRB/EC encouraged but not required by DAIDS).	No (if applicable)	no	HPTN LOC
Protocol departures/deviations/violations (per IRB/EC requirements and/or as directed by DAIDS).	NA	Local regulations apply	CRS
Informed consent forms, (English and all translations). 1) Screening Consent 2) Enrollment Consent for Index 3) Enrollment Consent for Network Injection Partners 4) Qualitative Key Informant Consent	yes	yes	CRS
Current CV/Biosketch for IoR(s)	Local regulations apply	Local regulations apply	CRS
Participant recruitment materials (posters, flyers, advertisements, etc.)	yes	yes	CRS
Other written information for study participants	yes	yes	CRS
Other documentation required or requested by the IRB/EC	Local regulations apply	Local regulations apply	CRS
Study status reports/updates (at least annually); this approval documents continuing review.**	NA	yes	CRS
New information that may affect adversely the safety of study participants or the conduct of the study	NA	no	DAIDS through the HPTN LOC
Final study report/closure report	NA	Local regulations apply	CRS

Acronyms: DAIDS, Division of AIDS; EC, ethics committee; HPTN LOC, HIV Prevention Trials Network Leadership and Operations Center; CRS, Clinical Research Site; IoR, Investigator of Record; IRB, institutional review board; NA, not applicable.

* Based on US regulations and GCP guidelines. Local regulatory authorities and/or responsible IRBs/ECs may require additional approvals. If so, the required approvals must be obtained and filed.

** Guidance from the US Office for Human Research Protections (OHRP) on continuing review can be found at: http://www.hhs.gov/ohrp/policy/index.html#continuing.

Note: All documents must be submitted to all IRBs/ECs responsible for oversight of study implementation at the performance site. Documentation of all submissions to and approvals from all responsible IRBs/ECs must be maintained in the Essential Document files at the local performance site.

1.4.5 Protocol Registration

Note: *Additional details on the protocol registration process can be found in the Division of AIDS (DAIDS) Protocol Registration Policy and Procedure Manual*

(located at *http://rsc.tech-res.com*) and the HPTN MOP (located at *www.hptn.org/network_information/policies_procedures.htm.)*.

Upon obtaining approval from all responsible IRBs/ECs, site staff will submit the following documents to the Protocol Registration Office (PRO) at the RSC. These documents will be submitted through the DAIDS Protocol Registration System (DPRS). Site staff will also submit a copy of the submission documents to the LOC CRM. The required documents are also listed on the RSC Submission Checklist, which can be accessed using the link above.

- Copy of DAIDS IoR Form signed and dated by IoR
- Current, signed, and dated CV/Biosketch of the IoR, in English
- Documentation of approval from all responsible IRBs/ECs of the study protocol and the ICFs
- A copy of the approved site-specific English ICFs
- Translated local language site-specific informed consent forms
- DAIDS Protocol Registration Translation Confirmation Document

Note: Documentation of IRB/EC approval must reference the exact protocol number, title, version number, and date as listed on the cover page of the protocol. *If the IRB/EC approval documentation is provided by the IRB/EC in a language other than English, the document must be translated into English, and both the local language version and the English language version must be submitted.*

Note: The approved informed consent forms must include the exact protocol number, title, version number, and date as listed on the cover page of the protocol. *Pages should be numbered 1 of x, 2 of x, etc.*

The site may have additional site-specific documents to be included with the protocol registration package (*e.g.*, additional information requested by DAIDS). These documents should be submitted to the RSC and a copy should be submitted to the LOC CRM. DAIDS regulatory staff will communicate their review findings to site staff members, who will coordinate any required re-submissions.

1.4.6 Study Activation

The HPTN has specified certain requirements that must be met in order to activate HPTN study operations. The activation requirements for HPTN 074 are defined in Section 10 of the HPTN MOP (http://www.hptn.org/network_information/policies_procedures.htm) and are listed below. If there is an inconsistency between the items in this SSP and the HPTN MOP for site activation, contact an HPTN LOC CRM for clarification.

- Verify OCSO site approval

- US Federal Wide Assurance (FWA) number on file with OHRP for the study site institution(s)
- IRB/EC approval of the current study protocol, and any other site-specific approvals, if applicable
- Approved current site-specific informed consent forms (including translation into local languages)
- Signed IoR Agreement
- Signed IoR Protocol Signature Page
- Signed and dated CV/Biosketch of the IoR and Co-Investigator
- Completion of human subjects protection (HSP) training within the last three years for all "key" study staff, as defined by US NIH policy—(key personnel include all individuals named on the IoR Agreement and research staff who have more than minimal contact with research participants, study data, or specimens)
- Completion of good clinical practices (GCP) training within the last three years for all "key" study staff, as defined by US NIH policy-(key personnel include all individuals named on the IoR Agreement and research staff who have more than minimal contact with research participants, study data, or specimens)
- Completion of good clinical laboratory practices training for the appropriate laboratory staff
- DAIDS RSC Protocol Registration
- CRF Source Documentation Table(s) (signed and dated by IoR)
- Study staff signature sheet, roster, and delegation of duties
- SCHARP approval of site readiness for data management, based on:
  - Installation of required data relay equipment (DataFax) and/or validation of existing equipment; testing of equipment
  - Internet access with connections for data relay devices (DataFax)
  - Availability of CRFs and other SDMC-provided materials onsite
  - Data Management and other study-specific SOPs (please see Table 1-2 list below)
- HPTN LC approval of local lab readiness, based on:
  - Proficiency in performing protocol-required tests
  - Documentation of appropriate validation
  - Local laboratory back-up arrangements
    - 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)
  - LDMS set up including computer, printer, and scanner, and appropriate LDMS training, and connection to FSTRF
  - IATA specimen shipping certification (for at least one study staff member)
  - Laboratory SOPs (please see Table 1-2 below), including QA/QC procedures and Chain of Custody SOP
  - Freezer storage capacity

  - 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
- The presence on site of the Standard Operating Procedures (SOPs) listed in Table 1-2 (below)
- Completion of study-specific training for all study staff including fieldworkers, navigators, counselors, qualitative interviewers, and other involved staff
- Resolution of any other findings/action items identified during site preparation activities, PPDor lab audits
- Final approval from DAIDS
- Site Activation Notice per LOC (FHI 360) procedures

Table 1-2: Required SOPs for HPTN 074

Data Management	On-site data management including storage, QA/QC procedures, data entry, data query, and correction
	Randomization
Laboratory	Specimen management and chain of custody
	Lab data management and storage (LDMS SOP)
	Demonstrated proficiency for CD4 Testing (UK NEQAS - IQA)
	Demonstrated VQA proficiency for Viral Load Testing
	HIV testing
	Viral Load Testing
	CD4 Testing
	Blood Sample Collection
	Dried Urine Preparation and Storage
	Plasma Preparation and Storage
	Urine Collection
	Frozen Urine Storage
Administrative and Regulatory	IRB Communication
	Essential documents
	Confirmation received from IoR that current CVs for key staff available on site
	Staff Training and certification documentation
	Audits and Inspections (including review and follow-up of monitor report findings)
	Staff Safety Plan
	Staff Roles and Responsibilities
	Safety and Social Harms Monitoring
	SOP Development and Version Control
Study-Specific	HIV/STI pre-test and Counseling and Testing, risk reduction counseling
	Referral for substance use treatment
	Communication with responsible IRB/EC (may be site-specific SOP)
	Community Involvement Plan
	Participant Eligibility Determination (including source documentation of eligibility)
	Recruitment
	Follow-up and Retention (may be written as SOP or plan)
	Staff training on protocol and procedures
	Source Documentation (including CRFs as Source Documentation Table)
	Social Network List
	Informed Consent Process
	Qualitative Research
	Intervention SOP

The required elements of the SOPs listed in Table 1-2 may be grouped together in single SOPs (e.g., one SOP to include source documentation and essential documents) or split among several SOPs (e.g., information about staff training may be added to each SOP). The site may use pre-existing SOPs, if appropriate.

Once all study activation requirements are met at a site and have been documented, the HPTN LOC CRM/PS will issue a site-specific Study Activation Notice 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.

1.4.7 Abbreviated Study Activation for Protocol Amendments

When a full protocol amendment (version change) is implemented after study initiation, the site is not required to repeat the entire site-specific study activation process. However, a subset of these activities must be conducted in order to prepare for the changes to study conduct based on full protocol amendments. All materials must reflect the amended protocol and both the amended protocol and Informed Consents must be approved by the IRB prior to study activation, therefore prior to study implementation. The list below outlines the required activities and/or items that must be completed under a full protocol amendment. Not all items will apply for each amendment.

- Protocol amendment registration approval from DAIDS/RSC based on the following:
  - Approvals from all responsible IRBs/ECs for the amended protocol and site-specific ICFs
- The site should review, and if necessary revise, the CV for the IoR, the CRF Source Documentation Tables (if new CRFs result from the amendment), and all study-related SOPs
- The IoR must sign the "Protocol Signature Page" included in the protocol amendment
- Completion of study-specific training (remote or on site) for the latest version of the protocol, if deemed necessary
- The current (translated, if applicable) CRFs must be on site
- The site must have a current IATA specimen shipping certification for at least one study staff member
- If any of the SOPs are revised, they must be reviewed and approved by the appropriate reviewers, LC, SCHARP, or as appropriate

1.5 Continuing Review

Throughout the course of the study, the site is required to submit annual progress reports to the IRB(s)/EC(s) overseeing study conduct and receive annual approval. The submission sent to the IRB(s)/EC(s) for annual review should include the following:

- The full current protocol
- The current ICFs
- An annual report which includes:
  - The number of subjects accrued
  - A summary of SAEs and any unanticipated problems involving risks to participants
  - The number of participants who have withdrawn and any complaints about the research since the last IRB/EC review
  - A summary of any modifications or amendments since the last IRB/EC review
  - Any other relevant information, especially information about risks associated with the research
- Any additional items as required by the local IRB/EC (e.g., protocol deviations).

Additional information and guidance about continuing review can be found at the Office of Human Research Protection (OHRP) website:
http://www.hhs.gov/ohrp/policy/index.html#continuing.