1. Introduction

1.1 Overview of Section 1

This section includes specifics on study conduct including the sources of procedural information available to HPTN 094 study site staff, the responsibilities of the site Investigators, and the process by which each site will be approved to implement HPTN 094.

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. Unless instructed by the HPTN Leadership and Operations Center (LOC), if there is inconsistency between this manual and 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.

Study site staff are encouraged to contact the HPTN LOC Clinical Research Managers (CRMs) with all questions related to interpretation and proper implementation of the protocol. Questions related to community education and outreach should be directed to

the HPTN LOC Community Program Manager. Questions related to data management and data collection should be directed to the HPTN Statistical and Data Management Center (SDMC) Protocol Manager. Questions related to the collection, processing, and storage of local and central lab specimens should be directed to the HPTN Laboratory Center (LC) study representatives. Questions regarding pharmacy issues should be directed to the protocol pharmacist at the Division of AIDS (DAIDS) Pharmacy Affairs Branch (PAB). The persons to contact information for these types of questions are:

HPTN LOC Senior Clinical Research Managers	Sam Griffith Tel. 919.544.7040 ext. 11571 Email: sgriffith@fhi360.org Phil Andrew Tel. 919-544-7040 ext. 11213 Email: pandrew@fhi360.org
HPTN LOC Research Specialist	Laura Mkumba Tel. 919-544-7040 Email: lmkumba@fhi360.org
HPTN LOC Community Program Manager	Jonathan Lucas Tel: 919-544-7040, Ext. 11458 Email: jlucas@fhi360.org
HPTN SDMC Clinical Data Manager	Melissa Cummings Tel: 206-667-1232 Email: mcumming@scharp.org
HPTN Laboratory Center (LC) Representatives	Paul Richardson Tel: 410-502-0435 Email: pricha18@jhmi.edu Jessica Fogel Tel: 410-614-6498 Email: jfogel@jhmi.edu
Laboratory Data Management System (LDMS)	Tel: 716-834-0900, Ext. 7311 Email: ldmshelp@fstrf.org
DAIDS Protocol Pharmacist	Cindy Parker Tel: Email: cindy.parker@nih.gov

Contact information for all other HPTN 094 protocol team members can be found in the protocol roster in the HPTN 094 protocol.

1.3 Sites Participating in HPTN 094

Clinical Research Sites (CRSs) that will participate in HPTN 094 are:

Table 1-2
Participating HPTN 094 Sites in Alphabetical Order

	CRS ID	CRS Name	City
1	30261	Bronx Prevention Research Center CRS	Bronx, NY
2	31608	George Washington University CRS	Washington, DC
3	31473	Houston AIDS Research Team CRS	Houston, TX
4	30310	Penn Prevention CRS	Philadelphia, PA
5	31607	UCLA Vine Street CRS	Los Angeles, CA

1.4 Investigator Responsibilities

HPTN 094 must be conducted in accordance with the US Code of Federal Regulations (CFR) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Consolidated Guideline for Good Clinical Practice (GCP). 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 HPTN LOC or found online at https://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR and http://www.ich.org/home.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 https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations.

HPTN 094 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. Additionally, site investigators must promptly report to the single Institutional Review Board (sIRB) and if required, to their local IRB any changes in the study and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following: unanticipated problems involving risks to participants or others; serious or

continuing noncompliance with applicable regulations or the requirements or determinations of the sIRB; and any suspension or termination of IRB approval.

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 Guidance: Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors available at https://www.fda.gov/science-research/guidance-documents-including-information-sheets-and-notices/information-sheet-guidance-institutional-review-boards-irbs-clinical-investigators-and-sponsors.

1.5 Study Activation Process

Prior to undertaking any study procedures, each study site must obtain approval to conduct the study from the Institutional Review Board that will be responsible for this study. Thereafter, sites must complete Protocol Registration with the DAIDS Regulatory Support Center (RSC), as well as Study Activation procedures with the HPTN LOC. These procedures are also described in the HPTN Manual of Operations (MOP) available at: https://www.hptn.org/resources/manual-of-operations. HPTN 094 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.

1.5.1 Protocol Distribution

The HPTN 094 Clinical Research Manager will distribute the final implementation version of the protocol electronically to the study sites.

1.5.2 Development and HPTN LOC Review of Site-Specific Informed Consent Forms: English Language Versions

Site staff will adapt the sample informed consent forms appended to the study protocol to reflect local procedures and IRB requirements and forward the forms for review by the HPTN LOC CRM prior to submission for IRB approval.

1.5.3 Development and HPTN LOC Review of Site-Specific Informed Consent Forms: Local Language Version(s) and Back-translation(s)

After incorporating review comments from the HPTN LOC CRM, site staff will translate the informed consent forms into all applicable local languages and then submit the translated forms, back-translations of the forms, and a certificate of translation for review by the HPTN LOC. Please note back-translations are not required if local language is Spanish. The HPTN LOC CRM will provide review comments to site staff as quickly as possible. The back-translation need not be completed by a certified translator; however, it is recommended that two different individuals translate the document(s) and then review each other's work to prepare a composite. The back-translation should be completed by an individual who did not participate in the translation process.

1.5.4 IRB Review

After incorporating review comments received from HPTN LOC CRM, site staff will submit site-specific informed consent forms, the current curriculum vitae (CV) of the

IoR, and any other study-related materials for review by the sIRB. Any participant information sheets, flip charts, promotional materials, or advertisements used during the study must be reviewed and approved by the sIRB prior to use.

In the event that the sIRB requests changes to the submitted informed consent forms, it is the responsibility of the IoR to incorporate all such comments into a single final version of the study informed consent forms, and to obtain approval of this final version from the sIRB. This may require multiple submissions to the sIRB. The final English back translation of the ICFs submitted to the DAIDS RSC must accurately and entirely reflect the approved local-language informed consent forms that will be used at the site.

An overview of sIRB submissions required before and during HPTN 094 is included in Table 1-1.

Table 1-1: IRB Submissions, Source and IRB Approval Required

Document	Source	sIRB Approval Required*
Protocol, Version 1.0 and higher	LOC	yes
Protocol amendments (including full amendments and letters of amendment)	LOC	yes
Protocol clarification memos	LOC	no**
Protocol deviations	site	no**
Site specific Informed consent forms, Version 1.0 and any subsequent updates	site	yes
Current CV for IoR (and subsequent updates)	site	no
Participant recruitment materials (posters, advertisements, etc.) and any subsequent updates	site	yes
Other written information for study participants and any updates	LOC/sites	yes
Data and Safety Monitoring Board summaries	LOC	no
Other documentation required or requested by the IRB	site	yes
Study status reports/updates (at least annually) This approval documents continuing review***	site	yes
New information that may adversely affect the safety of study participants or the conduct of the study	DAIDS	no****
Final study report/closure report	site	no

DAIDS = Division of AIDS; EC = ethics committee; LOC = HIV Prevention Trials Network Leadership and Operations Center; sIRB = single institutional review board;

* Based on US regulations and GCP guidelines. The responsible IRB may require additional approvals. If so, the required approvals must be obtained and filed.

** sIRB submission is not necessarily required depending on DAIDS or local regulatory requirements.

*** 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

**** sIRB approval of the actual information is not required; sIRB policies should be followed for this kind of information.

Note: All documents must be submitted to the responsible IRB. Documentation of all submissions to and approvals from the responsible IRB must be maintained in the Essential Document files at the local performance site.

1.5.5 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/protocolregistration/*) and the HPTN MOP.*

Upon obtaining approval from the sIRB, site staff will submit the following documents to the Protocol Registration Office (PRO) at the RSC. These documents may be sent electronically to protocol@tech-res.com. Site staff will also submit a copy of the submission documents to the HPTN LOC:

- Current, signed, and dated CV of the IoR, in English

- Documentation of approval from the sIRB of the study protocol and the informed consent forms.

Note: *Documentation of sIRB approval must reference the exact protocol number, title, version number, and date as listed on the cover page of the protocol.*

- A copy of the approved site-specific informed consent forms including local language translations, back-translations and a certificate of translation (if appropriate). Please note, per the DAIDS Protocol Registration Manual, no back-translations are required by DAIDS for Spanish informed consents.

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. When the sIRB approves a single informed consent form that will be used at multiple sites, and the approved form contains blank spaces for site contact information, a memo specifying the relevant information for each site must be submitted together with the approved form.*

Some sites 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 DAIDS RSC and a copy should be submitted to HPTN LOC.

If the site deletes or makes any substantive change to basic and/or additional elements as presented in the ICFs, the IoR must provide written documentation to explain the deletions/change(s) at the time of initial protocol registration with the DAIDS RSC.

DAIDS regulatory staff will communicate their review findings to the site staff, who will coordinate any required re-submissions.

1.5.6 Study Activation

The HPTN has specified certain requirements that must be met in order to activate HPTN study operations. The activation requirements for HPTN 094 are outlined below. General HPTN study-specific site activation requirements can be found in Table 1 of Section 10 of the HPTN MOP https://www.hptn.org/sites/default/files/2019-01/Section%2010%20FINAL%20DEC2018%281%29.pdf.

If there is an inconsistency between the items in this SSP manual and the HPTN MOP for study-specific site activation, contact the HPTN 094 CRM for clarification.

- OCSO Clinical Research Site Approval
- Confirmation from IoR that Human Subjects Protection training and Good Clinical Practices training for key study staff is completed and current
- Confirmation received from Investigator that current CVs for key staff available on site
- Study staff signature sheet, roster, and delegation of duties
- DAIDS RSC Protocol Registration Office Registration, based on receipt and approval of: Approval of the study protocol from local IRB/EC, including any other local regulatory entity approval as applicable; CV of IoR; completed and signed FDA Form 1572
- Completion of study-specific training
- Final DAIDS approval for study-specific site activation

Pharmacy

- Study-supplied medication and all other study-required medications are available at the local site pharmacy
- Confirmation from the DAIDS Protocol Pharmacist that the local site pharmacy is approved to participate in the study

SDMC approval of site readiness for data management including approval/confirmation of:

- Availability of SDMC-provided study-specific materials on site (including translations, if applicable)
- Confirmation of access to web-based EDC or survey software, randomization, and associated training modules
- Confirmation of site investigator and staff access, registration, and setup of clinical database
- SDMC approval of Data Management and Randomization SOPs
- SDMC approval of site readiness for data management

HPTN Laboratory Center approval of local lab readiness, including approval/confirmation of:

- Completion of good clinical laboratory practice (GCLP) training by at least one key on-site staff member with responsibility for laboratory quality assurance
- Completion of laboratory safety training by all laboratory staff members within the last 12 months
- IATA specimen shipping certification within the last 24 months for all laboratory staff members who transport, ship, or receive infectious substances and diagnostic specimens
- Adequate freezer space available for samples and approval of storage procedures
- LDMS readiness with most current version installed
- Completion and LC approval of any required laboratory method validations
- Documentation of normal ranges for protocol-specified tests
- SOPs for protocol-required tests performed in the mobile unit
- SOP for sample collection and storage
- Approved SOPs for specimen management and specimen chain of custody, including critical value reporting to study clinicians

- LC approval of site readiness based on all of the above

Note: Not all of the items listed above are required if CLIA certified laboratories are used. This will be handled on a case-by-case basis by the HPTN LC.

Study-specific SOPs or functions confirmed to be in place at the site (and reviewed by the HPTN LOC):

- Determining eligibility
- Study source documentation, including CRF source
- Informed consent
- Participant safety monitoring and serious adverse event (SAE) reporting
- Communication with IRB
- Participant accrual plan
- Participant retention plan
- Community education/outreach plan

Once all of the above-listed requirements have been met, and associated documentation has been provided to HPTN LOC, the HPTN LOC will inform DAIDS that all requirements have been met. DAIDS will inform the HPTN LOC that the site is approved to implement the study and the HPTN LOC will provide written approval to the site to initiate study operations.

1.5.7 Abbreviated Study Activation for Protocol Amendments

When a full protocol amendment is implemented, sites are 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. The list below outlines the required activities and/or items that must be in place before a site can begin study conduct under a full protocol amendment. Not all items will apply for each amendment. Sites should submit for DAIDS protocol registration within 14 days after receiving sIRB approval for the protocol and site specific-ICFs. The list below applies to any version after Version 1.0.

- Approvals from the sIRB for the protocol and site-specific ICFs
- Sites should review, and if necessary, revise the CV for the IoR, the CRF and Eligibility Source Documentation Tables, and all study-related SOPs.
- Completion of study-specific training (remote or on site) for the latest version of the protocol, if necessary
- The site must have a current IATA specimen shipping certification for at least one study staff member
- If any of the following laboratory-related SOPs are revised, they must be reviewed and approved by the network laboratory.
    - SOP for laboratory QA/QC procedures
    - SOP for chain of custody related to testing primary study endpoints
    - SOP for local laboratory back-up arrangements

1.6 Continuing Review

Throughout the course of the study, all sites are required to submit annual progress reports to the sIRB and receive annual approval. This will occur after the study level sIRB annual approval is received. Sites will be informed when the study level approval is received. Documentation of this approval must be submitted to the RSC. See http://rsc.tech-res.com/protocolregistration/ for more information.

The submission sent by the site to the sIRB for annual review should include the following:

- 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 sIRB review

- Protocol deviations that may affect the subjects' rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data
- Subject death
- Suspension of enrollment
- Termination of the study
- A summary of any modifications or amendments since the last sIRB review
- Any other relevant information, especially information about risks associated with the research

Additional information and guidance about continuing review can be found at the Office of Human Research Protection (OHRP) website: http://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-continuing-review-2010/.