Section 1. Introduction

1.1 Overview of Section 1

This section contains specifics of study conduct and includes sources of procedural information available to HPTN 084-01 study site staff, responsibilities of the site Investigators, and the process by which each site will be approved to implement HPTN 084-01.

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, follow the protocol. 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 members should use the following email alias when they have study-related questions: 084-01mgmt@hptn.org. Staff members of the HPTN LOC, HPTN Statistical and Data Management Center (SDMC), and HPTN Laboratory Center (LC) will receive the email. Emails with questions will be responded to by the most appropriate HPTN representative.

Table 1-1: HPTN Staff and Contact Information

HPTN LOC Senior Clinical Research Manager	erica hamilton Tel. +001 919-321-3493 Email: ehamilton@fhi360.org
HPTN LOC Senior Clinical Research Operations Manager	Scott Mitchell Rose Tel. +001 919-405-1447 (work) +001 919 768-2067 (cell) Email: srose@fhi360.org
HPTN LOC Clinical Trials Assistant	Amber Babinec Tel: +001 919-627-6407 Email: ABabinec@fhi360.org
HPTN LOC Community Programs	Rhonda White Tel: +001-919-321-3598 Email: rwhite@fhi360.org Molly Dyer Tel: +001 919-321-3851 Email: mdyer@fhi360.org
HPTN SDMC Representatives	Julie Ngo (Clinical Data Manager; first contact) Tel: +001 206-667-2094 Email: jhngo@scharp.org Lynda Emel Tel: +001 206-667-5803 Email: lemel@scharp.org James Hughes Phone: +001 206 616 2721 Email: jphughes@uw.edu

HPTN LC Representatives	Yaw Agyei Phone: +001 410 614 6763 Email: yagyei1@jhmi.edu Estelle M. Piwowar-Manning Phone: +001 410 614 6736 Email: epiwowa@jhmi.edu Mark Marzinke Tel: +001 443-287-7516 Email: mmarzin1@jhmi.edu Ethel Weld Tel: +001 410-502-8129 Email: eweld@jhmi.edu
Laboratory Data Management System (LDMS)	Tel: +001 716-834-0900, Ext. 7311 Email: ldmshelp@fstrf.org
DAIDS Protocol Pharmacist	Katherine Shin Tel: +001 240- 627- 3047 Email: KaShin@niaid.nih.gov

Contact information for all other HPTN 084-01 team members is found in the electronic HPTN directory at www.hptn.org.

1.3 Sites Participating in HPTN 084-01

Clinical Research Sites (CRSs) that will participate in HPTN 084-01 are listed in Table 1-2.

Table 1-2: Participating HPTN 084-01 CRSs

	DAIDS CRS ID	**CRS Name**	**City**	**State/Country**
1	31966	Ward 21 CRS	Johannesburg	South Africa
2	30314	Spilhaus CRS	Harare	Zimbabwe
3	30293	MU-JHU Research Collaboration (MUJHU CARE LTD) CRS	Kampala	Uganda

1.4 Investigator Responsibilities

HPTN 084-01 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). 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 Site Clinical Operations and Research essentials (SCORE) Policy and DAIDS SCORE Manual, 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 084-01 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, including the need for compliance with DAIDS policy on research involving minors.

The Investigator of Record (IoR) at each site is responsible for the conduct of the clinical trial at the clinical research site (CRS). The IoR is the signatory for the FDA Form 1572, which must be signed prior to site activation, 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 IRBs/ECs 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 their IRBs/ECs; and any suspension or termination of IRB approval.

IoRs may delegate the work involved in study conduct to other site staff members; however, delegation does not relieve the IoR of ultimate responsibility for all study procedures performed and all study data collected. Additional guidance can be found in the US FDA's Information Sheet Guidance: Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors available at https://www.fda.gov/media/83121/download.

1.5 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) and any other local regulatory bodies. 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 084-01 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 084-01 Clinical Research Manager (CRM) 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 (ICFs) appended to the study protocol to reflect local procedures and IRB/EC requirements and forward the forms for review by the HPTN LOC CRM prior to submission to local review bodies for the initial version of the protocol, e.g. Version 1.0. The HPTN LOC CRMs do not need to review the site-specific informed consent forms for subsequent letters of amendment or full amendments to the protocol; however, the CRM is available for assistance.

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

For the initial version of the protocol, after incorporating review comments from the HPTN LOC CRM, site staff will translate the ICFs 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/EC Review

After incorporating review comments received from the HPTN LOC CRM, site staff will submit the study protocol, site-specific ICFs, the current curriculum vitae (CV) of the IoR, and any other study related materials for review by all responsible local and US-based IRBs/ECs.. . Any participant information sheets, flip charts, promotional materials, or advertisements used during the study must be reviewed and approved by all responsible IRBs/ECs prior to site use.

In the event that either the site and/or local 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. The final English back translation of the ICFs submitted to the DAIDS RSC must accurately and entirely reflect the approved local-language ICFs that will be used at the site.

An overview of IRB/EC submissions required before and during HPTN 084-01 is included in Table 1-3.

Table 1-3: IRB/EC Submissions, Source and IRB/EC Approval Required

Document	Source	IRB/EC Approval Required*
Protocol, Version 1.0 and higher	LOC	yes
Protocol amendments (including full amendments and Letters of Amendment [LOAs])	LOC	yes
Protocol Clarification Memos (CMs)	LOC	no**
Protocol deviations	site	no**
Site specific ICFs, 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
CASI-based assessments	site	yes
Printed copies of the e-case report forms as required by the IRB/EC	site	yes, if required
Cabotegravir Investigator's Brochure (December 2019) and any subsequent updates	RSC	no
Truvada® (TDF/FTC) Package Insert (December 2016) and subsequent updates	RSC	no
Other written information for study participants and any updates	LOC/sites	yes
Study Monitoring Committee (SMC) summaries	LOC	no
Data and Safety Monitoring Board (DSMB) summaries	LOC	no

Document	Source	IRB/EC Approval Required*
Other documentation required or requested by the IRB/EC	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; IRB = institutional review board;

* 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.

** IRB/EC 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: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-continuing-review-2010/index.html

**** IRB/EC approval of the actual information is not required; local IRB/EC policies should be followed for this kind of information.

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.

1.5.5 Protocol Registration

Note: *Additional details about protocol registration is found in the Division of AIDS (DAIDS) Protocol Registration Policy and Procedure Manual (located at* https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual*) and the HPTN MOP.*

Upon obtaining approval from all responsible IRBs/ECs, site staff will submit the following documents, among requested others, 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 all responsible IRBs/ECs, and local regulatory authority if applicable, of the study protocol and the ICFs.

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.*

- A copy of the approved site-specific ICFs including local language translations, back-translations (if appropriate) 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 ICFs 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 an IRB/EC approves a ICF 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 sites. The activation requirements for HPTN 084-01 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/resources/manual-of-operations.

If there is an inconsistency between the items in this SSP manual and the HPTN MOP for study-specific site activation, contact the HPTN 084-01 CRM for clarification.

- OCSO CRS Approval (if appropriate)
- Confirmation from IoR that Human Subjects Protection training and Good Clinical Practices training for key study staff is completed and current
- Confirmation received from IoR that current CVs for key staff available on site
- Study staff signature sheet, roster, and delegation of duties

  Sites should use the DAIDS approved Delegation of Duties Log. Only one log is required. The DAIDS template and other items can be found on the DAIDS Clinical Site Implementation and Operations (CSIO) webpage: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

  - Template: Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual | NIH: National Institute of Allergy and Infectious Diseases
  - Instructions: DAIDS SCORE Manual Appendix: Guidance on Completion of Delegation of Duties Log (nih.gov)
  - Policy: Division of AIDS Clinical Research Policies and Other Information | NIH: National Institute of Allergy and Infectious Diseases
- DAIDS RSC PRO 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.

  (Note: there may be other documents required as well.)
- Completion of study-specific training
- Final DAIDS approval for study-specific site activation

Pharmacy

- All applicable import approvals for study products
- Study product is 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:

- Electronic data capture system in place and test run completed
- SOP for on-site data management (including data QC/QA procedures)

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
- Specimen management and specimen chain of custody including appropriate validations and proficiency in place
- Established local laboratory backup arrangements
- 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
- SOP for sample collection and storage
- Approved SOPs for specimen management and specimen chain of custody
- Approved SOP and established proficiency for each protocol-specified test (SOPs include QC/QA procedures for each test)

- Approved SOP for critical value reporting to study clinicians
- Network EQA requirements fulfilled
- 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):

- Study source documentation, including eCRF source
- Informed consent
- Participant safety monitoring and adverse events/serious adverse event (AE/SAE) reporting (including specific management instructions for ISRs)
- Study drug counseling SOP (for oral and CAB LA)
- Seroconversion SOP
- Communication with IRB
- Participant eligibility determination
- Community Engagement Work Plans (CEWP) (includes plans for participant accrual and retention)

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. 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 IRB/EC approval for the protocol and site specific-ICFs. The list below applies to any version after Version 1.0.

- Approvals from all responsible IRBs/ECs 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 IRB(s)/EC(s) overseeing study conduct and receive annual approval. Documentation of this approval must be submitted to the RSC. See https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual for more information.

The submission sent to the IRB(s)/EC(s) for annual review should include the following:

- The full protocol
- The current ICFs
- An annual report which includes:
    - The number of participants 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

Additional information and guidance about continuing review can be found at the OHRP website: http://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-continuing-review-2010/