Section 1. Introduction

1.1 Overview of Section 1

This section contains specifics of study conduct and describes sources of procedural information for the HPTN 084 protocol version 4.0 and version 5.0 (the Open Label Extension [OLE] components of the study). Information in this section is intended for study site staff and outlines responsibilities of the site Investigators.

1.2 Source of Procedural Information

All study procedures must be conducted in accordance with the study protocol currently approved for implementation by the site's local Institutional Review Board (IRB)/Ethic Committee (EC), etc., as is appropriate (either version 4.0 or version 5.0 of the 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 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: 084mgmt@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 Project Managers	Jennifer Farrior Tel: +1 919-321-3517 jfarrior@fhi360.org Scott Mitchell Rose Tel. +1 919 768-2067 (Mobile) srose@fhi360.org
HPTN LOC Clinical Trials Assistant	Jill Stanton Tel: +1 919-321-3413 jistanton@fhi360.org
HPTN LOC Community Program Managers	Rhonda White Tel: +1 919-321-3598 RWhite@fhi360.org
HPTN SDMC Clinical Data Manager	Stephanie Orme Tel: +1 206-667-7109 Email: sbeigelo@scharp.org
HPTN LC Representatives	Estelle Piwowar-Manning Tel: +1 410-614-6736 Email: epiwowa@jhmi.edu Yaw Agyei Tel: +1 410-614-6736 Tel: 27-813766180 Email: yagyei1@jhmi.edu
Laboratory Data Management System (LDMS)	Tel: +1 716-834-0900, Ext. 7311 Email: ldmshelp@fstrf.org
DAIDS Protocol Pharmacist	Katie Shin Tel: +1 240-627-3047 Email: KaShin@niaid.nih.gov

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

1.3 Sites Participating in HPTN 084

Clinical Research Sites (CRSs) that are participating in HPTN 084 OLE are listed in Table 1-2.

Table 1-2 Participating HPTN 084 OLE Sites in Alphabetical Order				
	CRS ID	**CRS Name**	**City**	**Country**
1	31798	Baylor Uganda CRS	Kampala	Uganda
2	30301	Blantyre CRS	Blantyre	Malawi
3	31445	Botha's Hill CRS	Botha's Hill	South Africa
4	31790	Desmond Tutu TB Centre - Stellenbosch University CRS	Cape Town	South Africa
5	30346	Emavundleni CRS	Cape Town	South Africa
6	12701	Gaborone CRS	Gaborone	Botswana
7	31635	Isipingo CRS	Durban	South Africa
8	31460	Kisumu CRS	Kisumu	Kenya
9	12001	Malawi CRS	Lilongwe	Malawi
10	30293	MU-JHU Research Collaboration CRS	Kampala	Uganda
11	30313	Milton Park CRS	Harare	Zimbabwe
12	30294	Seke South CRS	Chitungwiza	Zimbabwe
13	31610	Soweto HPTN CRS	Soweto	South Africa
14	30314	Spilhaus CRS	Harare	Zimbabwe
15	30303	St Mary's CRS	Chitungwiza	Zimbabwe
16	31994	Eswatini Prevention Center	Mbabane	Eswatini
17	30924	UVRI-IAVI	Entebbe	Uganda
18	31663	Verulam CRS	Verulam	South Africa
19	31966	Ward 21	Johannesburg	South Africa
20	30320	Zengeza CRS	Chitungwiza	Zimbabwe

1.4 Investigator Responsibilities

HPTN 084 must be conducted in accordance with the US Code of Federal Regulations (CFR) and the International Council on Harmonization (ICH) Consolidated Guidelines 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. DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual describes operational requirements for Clinical Research Sites (CRSs) implementing DAIDS-sponsored clinical research within the DAIDS Clinical Trials Networks and can be downloaded from https://www.niaid.nih.gov/research/daids-score-manual

HPTN 084 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 responsible for the conduct of the clinical trial at the CRS. The IoR is the signatory for the FDA Form 1572. (Note: Since the HPTN 084 OLE components are amendments to the original, double-blinded HPTN 084 component, a new Form 1572 is not required.) 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/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 under either the v4.0 or v5.0 protocol amendments, each study site must obtain approval to conduct the amendment from all responsible US and local IRB/ ECs and any other appropriate local regulatory bodies. Sites must complete Protocol Registration with the DAIDS Regulatory Support Center (RSC) according to the timeline requirements in the Protocol Registration Manual.

Note: Before sites could implement the v3.0 protocol amendment, a Site-Specific Activation Notice from the HPTN LOC was required. However, no activation notices are being issued for Protocol Amendment V5.0 (OLE2). Sites may implement v5.0 once all approvals are in place.

1.5.1 Protocol Distribution

The HPTN 084 OLE Project Managers (PMs) or Clinical Trials Assistant (CTA) will distribute approved protocol amendments 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 (either v4.0 or 5.0, as is appropriate) to reflect local procedures and IRB/EC requirements. If the site wishes to, it may forward the site-specific ICFs to the HPTN LOC Project Managers (PMs) for review prior to submission to local review bodies. The HPTN LOC PMs are not required to review the site-ICFs for subsequent Letters of Amendment (LOA)or Clarification Memos (CMs); however, the PMs are available for assistance.

Note: The ICF for original, double-blinded portion of the study are irrelevant to the open-label protocol amendments. Sites should implement the ICFs associated with the amendments.

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

For the protocol amendments of v4.0 and v5.0, site staff will translate the ICFs into all applicable local languages. Sites are not required to submit the translated forms, back-translations of the forms, and a certificate of translation for review to the HPTN LOC. Please note back-translations are not required if local language is Spanish. 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

Site staff will submit the study protocol, site-specific ICFs, and any other study-related materials as applicable for protocol amendments for review by all responsible local and US-based IRBs/ECs (as is appropriate to the site). 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 and its amendments are 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 2016) and any subsequent updates	RSC	no
Truvada® (TDF/FTC) Package Insert (December 2016) and subsequent updates	RSC	no
Intralipid® 20% Fat Emulsion Package Insert (April 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

Document	Source	IRB/EC Approval Required*
Data and Safety Monitoring Board (DSMB) summaries	LOC	no
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 for HPTN 084 Amendments

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 may be sent electronically to protocol@tech-res.com.

- Signed and dated protocol signature page

- 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.

1.6 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 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

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/