

## Section 1 Introduction

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## Section 1 Introduction

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This section specifies the sources of procedural information available to HIV Prevention and Trials Network (HPTN) 058 study site staff, the responsibilities of the Site Investigator, and the process by which each site will be approved to begin implementation of HPTN 058.

### 1.1 Sources of Procedural Information

All study procedures must be conducted in accordance with the study protocol (see Section 2) 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 Coordinating and Operations Center (CORE) Protocol Specialist (PS) and Prevention Research Specialist (PRS) to any such inconsistencies. This SSP Manual will be updated as necessary and distributed to study site staff. If procedures are changed in this manual, site staff have 30 days from the date of translation into local language and all necessary approvals of corresponding protocol updates (amendments) to implement the change.

Study site staff are encouraged to contact the CORE PS and PRS with all questions related to interpretation and proper implementation of the protocol. Site staff should contact the Statistical and Data Management Center (SDMC) Project Managers (PMs) with questions related to data collection and management. Site staff should contact the HPTN Network Lab (NL) Representatives with questions related to the collection, processing, and storage of local and NL specimens. Questions regarding pharmacy issues should be directed to the protocol pharmacist at the Division of AIDS (DAIDS) Pharmacy Affairs Branch (PAB). Questions regarding study drug dosing resumption or discontinuation following occurrence of toxicities should be directed to the Protocol Safety Review Team (PSRT).

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Protocol Pharmacist:

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Protocol Safety Review Team:

[058PSRT@hptn.org](mailto:058PSRT@hptn.org)

Laboratory Data Management System (LDMS)

[ldmshelp@fstrf.org](mailto:ldmshelp@fstrf.org)

Contact information for all other HPTN 058 team members can be found in the team roster included in the study protocol and/or the electronic HPTN directory at [www.hptn.org](http://www.hptn.org).

## 1.2 Investigator Responsibilities

HPTN 058 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) (included as Appendix A of this manual). 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 CORE or found online at [www.gpoaccess.gov/cfr/index.html](http://www.gpoaccess.gov/cfr/index.html) and <http://www.ich.org>, respectively. The *DAIDS Standard Operating Procedures (SOPs) for Essential Documents (Appendix B)* and *Source Documentation (Appendix C)*, which are useful for interpreting and operationalizing these regulations and guidelines, can be downloaded from the HPTN website. HPTN 058 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 participating in HPTN 058 is required to sign both a protocol signature page and an FDA Form 1572 to formally indicate his/her agreement to conduct the study in accordance with the protocol, this SSP manual, HPTN policies, and all applicable US and in-country regulations, policies, and guidelines. The obligations and responsibilities assumed by the IoR when signing the US FDA Form 1572 are listed on the form itself, which can be found in Section 3.4 of the HPTN MOP, and are also included below. By signing this form, the investigator obligates himself/herself and, by delegation, all study staff, to:

- Conduct the study in accordance with the relevant, current protocol and only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of study participants.
- Personally conduct or supervise the described investigation.
- Agree to inform any patients, or any persons used as controls, that the drug is being used for investigational purposes and ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and IRB review and approval in 21 CFR Part 56 are met.
- Report to the sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64.
- Read and understand the information in the investigator's brochure and package insert, including the potential risks and side effects of the drug.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records in accordance with 21 CFR 312.62 and make those records available for inspection in accordance with 21 CFR 312.68.

- Ensure that an Institutional Review Board (IRB) or Ethics Committee (EC) that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the investigation, promptly report to the IRB/EC all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR 312; 45 CFR 46 and any applicable local regulations, policies, and guidelines.

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 (FDA) *Information Sheets for Institutional Review Boards and Clinical Investigators* available at [www.fda.gov/oc/ohrt/irbs/default.htm](http://www.fda.gov/oc/ohrt/irbs/default.htm).

### **1.3 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 Institutional Review Boards/Ethics Committees (IRBs/ECs). Thereafter, sites must complete Protocol Registration procedures with the DAIDS Regulatory Compliance Center (RCC) via the CORE and study activation procedures with DAIDS and the HPTN CORE, SDMC, NL, and PAB. Documents required for submission are noted in section 1.3.5 of this SSP.

Note that even after all of these steps have been completed, that study activation is not considered final and the study may not begin (that is, no procedures including screening, may be performed) at your site until DAIDS has granted final approval and a site-specific study activation notice is received from HPTN CORE.

#### **1.3.1 Protocol Distribution**

The CORE Protocol Specialist will distribute the current version of the protocol to the study sites.

#### **1.3.2 Development and CORE Review of Site-Specific Informed Consent Forms: English Language Version**

Upon receipt of the final study protocol, site staff will adapt the sample informed consent forms appended to the protocol to reflect local procedures and IRB/EC requirements and forward the forms for review by the CORE PS and/or PRS prior to translation into local languages.

#### **1.3.3 Development and CORE Review of Site-Specific Informed Consent Forms: Local Language Version(s) and Back-translation(s)**

After incorporating review comments from the CORE PS/PRS, site staff will translate the informed consent forms into all applicable local languages, obtain an independent back-translation of the forms, and then submit the translated forms and back-translations for review by the CORE Protocol Specialist and Prevention Research Specialist. The PS/PRS will provide review comments to site staff as quickly as possible. The 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 others' work to prepare a

composite. The back-translation must be completed by an individual who did not participate in the translation process.

#### **1.3.4 IRB/EC Review**

After incorporating review comments received from the CORE PS/PRS, site staff will submit the study protocol, site-specific informed consent forms, the current curriculum vitae (CV) of the IoR, Investigator's Brochures and Package Inserts, and any other study-related materials for review by all responsible local and US-based IRBs/ECs. Any materials that will be given to or seen by participants, such as participant information sheets, promotional materials, or advertisements used during the study, must be reviewed and approved by all responsible IRBs/ECs prior to use. It is also recommended that the PS/PRS review these materials prior to submission to help sites avoid inconsistencies or errors.

In the event that either the US or local IRBs/ECs request 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 all responsible IRBs/ECs. This may require multiple submissions to the responsible IRBs/ECs. The final English back-translation must accurately and entirely reflect the approved local-language informed consent forms that will be used at the site.

An overview of IRB/EC submissions required *before* HPTN 058 begins is included in Table 1-1. Table 1-2 lists requirements that must be met *during* study implementation and *at completion* of the study.

**Table 1-1 IRB/EC Submissions Required Before Study Initiation**

<p style="text-align: center;"><b>Submit the Following Required Documents</b></p> <p>All documents must be submitted to all IRBs/ECs responsible for oversight of study implementation at the performance site — both locally-based and US-based, if applicable. 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.</p>	<p style="text-align: center;"><b>Written Approval Required*</b></p>
HPTN 058 Protocol Version 2.0, dated 16 September 2008	Yes
<p>Informed consent forms (local language(s) and back-translations):**</p> <ul style="list-style-type: none"> <li>• Screening for full study and safety phase</li> <li>• Study Enrollment for full study and safety phase</li> <li>• Specimen Storage, if future testing will be allowed at site</li> </ul>	Yes
Investigator of Record current CV signed and dated within the previous 2 years	No
Suboxone® (buprenorphine/naloxone) Package Insert (September 2006)	No
Investigator’s Brochure (May 29, 2008) and any updates issued by DAIDS prior to study initiation	N/A
Safety Reports, Safety Memos and other safety distributions issued by DAIDS after the site is registered to the protocol, even if prior to study activation (time point begins at RCC registration)	No
Participant recruitment materials (posters, flyers, advertisements, etc.) ***	Yes
Other written information for study participants***	Yes
Other documentation required/requested by the IRB/EC	If required by IRB/EC

\* Some required documents do not need approval by the IRB/EC (as indicated above) but are provided to IRB/ECs for their information; however, acknowledgement of receipt should be obtained from the IRB/EC for all submissions, if possible. Submission cover letters should always list the title and date of all attachments.

\*\* HPTN informed consent forms typically contain information on participant payment amounts and schedules. If this information is not presented in the informed consent forms, it should be submitted for IRB/EC review in a separate documentation.

\*\*\* IRB/EC approval of recruitment materials and written materials to be provided to study volunteers must be obtained prior to use with study participants.

*Note: The list of submissions above is 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.*

**Table 1-2 IRB/EC Submissions Required during Study Conduct and at Completion**

<b>Submit the Following Documents During Study Implementation</b>	<b>Written Approval Required*</b>
Study status reports/updates (at least annually) for renewal of protocol and informed consent form approval	Yes
Protocol clarification memos if requested by IRB (submission to IRBs is not required by DAIDS but IS recommended)	No
Reports of adverse events (AEs), severe adverse events (SAEs) and/or events meeting the criteria for expedited reporting to DAIDS (according to individual IRB requirements)	No
Suboxone (buprenorphine/naloxone) Package Insert Updates	No
Investigator’s Brochure Updates	N/A
IND Safety Reports, Safety Memos and other safety distributions issued by DAIDS	No
DSMB Review Summaries	No
Protocol amendments (including letters of amendment) and any other changes increasing risk to participants and/or significantly affecting the conduct of the study	Yes
New information that may adversely affect the safety of study participants or implementation of the study	No
Amended informed consent forms (local language(s) and back-translation(s), if applicable)**	Yes
Protocol events (departures/deviations/violations) (per IRB/EC requirements and/or as directed by DAIDS)	No
Investigator of Record current CV within 2 years	No
Participant recruitment materials (posters, flyers, advertisements, etc.), including any updates to materials previously approved***	Yes
Written information for study participants, including any updates to materials previously approved***	Yes
<b>Submit the Following Documents at Study Completion</b>	
Notification that all participant follow-up has been concluded/completed at the site	No
Final study report/closure report	Yes

\* Some required documents do not need approval by the IRB/EC (as indicated above) but are provided to IRB/ECs for their information; however, acknowledgement of receipt should be obtained from the IRB/EC for all submissions, if possible. Submission cover letters should always list the title and date of all attachments.

\*\* HPTN informed consent forms typically contain information on participant payment amounts and schedules. If this information is not presented in the informed consent forms, it should otherwise be submitted for IRB/EC review.

\*\*\* IRB/EC approval of recruitment materials and written materials to be provided to study volunteers must be obtained prior to use with study participants.

*Note: The list of submissions above is 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/humansubjects/guidance/contrev0107.htm>

### 1.3.5 Protocol Registration

*Note: Additional details on the protocol registration process can be found in the DAIDS Protocol Registration Policy and Procedure Manual (located at [rcc.tech-res-intl.com/forms.htm](http://rcc.tech-res-intl.com/forms.htm)) and the HPTN MOP (located at [www.hptn.org/network\\_information/policies\\_procedures.htm](http://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 RCC:

- Protocol Registration Checklist
- Original, signed and dated original FDA Form 1572
- Current, signed and dated CV of the Investigator of Record, in English
- Documentation of approval from all responsible IRBs/ECs of the study protocol and the informed consent forms.

***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 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 to the CORE.***

- A copy of the approved site-specific (local language) informed consent forms

***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 an IRB/EC 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.***

- Back-translations of the local language site-specific informed consent forms into English

***Note: The site is required to submit a Local Language Informed Consent Verification Statement document where the translator(s) and back-translator(s) attest to the accuracy of the translation in writing for each back-translated document.***

Once all documents meet the RCC review criteria, the site staff will forward them to the DAIDS RCC Protocol Registration Office for review. DAIDS regulatory staff will communicate their review findings to the Principal Investigator.

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 RCC.

Sites are encouraged to invite the CORE to review submission packages as a guide. This extra step may assist sites that are new to this process avoid any simple errors. Any error, no matter how miniscule, will cause a package to be rejected by the RCC, meaning the re-submission process must begin anew.

### **1.3.6 Study Activation**

The HPTN has specified certain requirements that must be met in order to activate HPTN study operations. The activation requirements for HPTN 058 are defined in Figure 10-1 of the HPTN MOP and are listed below.

- US Federal Wide Assurance (FWA) number on file with OHRP for the study site institution(s)/IRBs
- Completion of US FDA 30-day review period/safe to proceed notice
- Local regulatory authority approval of the study protocol, e.g., Ministry of Health, drug controller/regulatory agency (if applicable)
- Completion of human subjects training for all “key” study staff (as defined by US National Institutes of Health (NIH) policy, key personnel includes all individuals responsible for the design and conduct of the study)
- Completion of GCP training by at least one study staff member with responsibility for oversight of study implementation (e.g., Investigator, Study Coordinator, Lead Clinician, Data Manager)
- Protocol Registration approval from the DAIDS RCC Protocol Registration Office, based on the following:
  - Approvals from all responsible IRBs/ECs
  - IRB/EC-approved informed consent forms (local language and back-translation where applicable)
  - Original, signed and dated FDA Form 1572
  - Current (within 2 years), signed, and dated curriculum vitae of the Investigator of Record (in English)
- Study staff signature sheet, roster, and delegation of duties
- SDMC approval of site readiness for data management, based on the following:
  - Installation of required data transfer equipment
  - SOP for data management, including data Quality Control/Quality Assurance (QC/QA) procedures
  - Availability of SDMC-provided materials (e.g., DataFax forms) on site
- HPTN NL approval of local laboratory readiness, including approval/confirmation of:
  - QC/QA procedures
  - Documentation of normal ranges or other appropriate validation
  - Proficiency in performing protocol-required tests

SOP for establishing/maintaining normal ranges or other appropriate validation for protocol-specified tests

SOP for local specimen handling and maintenance of “chain of custody” related to testing for the primary study endpoint (HIV)

- LDMS set up and connected to the NL
- International Air Transport Association (IATA) specimen shipping certification (for at least one study staff member)
- Pharmacy Affairs Branch (PAB) approval of pharmacy readiness, including approval/confirmation of:
  - Pharmacy Establishment Plan review and approval from the DAIDS Pharmaceutical Affairs Branch (PAB)
  - SOP for investigational product management and accountability review and approval from the DAIDS Pharmaceutical Affairs Branch
  - SOP for observing participant taking study drug
  - SOP for secure storage of study drug and pharmacy-related documents
  - SOP in the case of power failure for pharmacy
  - All applicable import/export approvals for study products
  - Plan for Quality Testing
  - Documentation of Study Drug Regimens & administration
  - Completion and availability of protocol specific prescriptions
- Site SOP for communication with responsible IRBs/ECs (See list of required IRB submissions in Tables 1-1 and 1-2)
- SOP for obtaining informed consent from potential study participants
- SOP for eligibility determination
- SOP for source documentation
- SOP for safety monitoring and Adverse Event (AE) reporting
- Participant accrual plan (can be written as an SOP)
- Participant retention plan (can be written as an SOP)
- Documentation of local HIV counseling procedures
- Completion of CSMG Site Initiation Visit; DAIDS approval of resolution of initiation visit findings
- Completion of study-specific training; DAIDS approval of resolution of findings/action items identified during training.
- Resolution of any other findings/action items identified during site preparation activities
- Final DAIDS approval for study activation

Once all of the above-listed requirements have been met and associated documentation has been provided to the HPTN CORE, the PS will issue a Site-Specific Study Activation Notice. No protocol specified study activities may begin at a site until that site has received the Activation Notice, including the screening of participants.