

Section 1. Introduction

This section specifies the sources of procedural information available to HPTN 046 study site staff, the responsibilities of the Investigator of Record (IoR), and the process by which each site will be approved to begin implementation of HPTN 046. Also included is information on required submissions to Institutional Review Boards (IRBs) and/or Ethics Committees (ECs).

1.1 Sources of Procedural Information

All study procedures must be conducted in accordance with the study protocol (see Section 2) and this 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 Specialists of any such inconsistencies.

Study site staff are encouraged to contact the CORE Protocol Specialists with all questions related to interpretation and proper implementation of the protocol. Site staff should contact the Statistical and Data Management Center (SDMC) Project Manager 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 network lab specimens. Site staff should send all queries for CORE, SDMC or NL to the e-mail address named Site Queries, which is specified below and includes representatives from all entities above. Questions regarding pharmacy issues should be directed to the protocol pharmacist at the DAIDS Pharmacy Affairs Branch. Questions regarding open-label NVP/study drug dosing resumption or discontinuation following occurrence of toxicities as outlined in Appendix IV of the study protocol and Section 11 of this Study Specific Procedures (SSP) manual should be directed to the Protocol Safety Review Team.

Note: To ensure a rapid and consistent response, both the CORE Protocol Specialists and the SDMC Project Manager should be copied on all queries from site staff to central network and sponsor personnel.

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Contact information for all other HPTN 046 team members can be found in the team roster included in the study protocol and electronic HPTN directory at www.hptn.org.

1.2 Investigator Responsibilities

HPTN 046 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 these regulations and guidelines are referenced in the HPTN Manual of Operations (MOP) which is available at <http://www.hptn.org/>.

The U.S. National Institutes of Health (NIH) Division of AIDS (DAIDS) Standard Operating Procedures (SOPs) for Essential Documents and Source Documentation are useful tools for interpreting and operationalizing these regulations and guidelines. The SOPs are provided in Appendices A and B, respectively.

HPTN 046 also must be conducted in accordance with all other US and 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 046 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 study-specific procedures 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 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, 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.

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 IRBs/ECs. Thereafter, sites must complete Protocol Registration procedures with the DAIDS Regulatory Compliance Center (RCC) (the HPTN CORE Protocol Specialist may assist with this process) and study activation procedures with DAIDS and the HPTN CORE, SDMC, and NL. Detailed information on the requirements of these pre-implementation steps can be found in the HPTN MOP. On a site-by-site basis, the HPTN CORE will issue a Site-Specific Study Activation Notice when all requirements have been met. The remainder of this section outlines the steps required to complete these procedures. HPTN 046 study screening and enrollment may not be conducted prior to completion of all of these steps and receipt of an Activation Notice from the CORE.

1.3.1 Protocol Distribution

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

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

Site staff will adapt the sample informed consent forms appended to the study protocol to reflect local procedures and IRB/EC requirements and forward the forms for review by the CORE Protocol Specialist prior to IRB/EC submission.

It is recommended that site staff submit the English language version of the consent forms to the CORE Protocol Specialist prior to translation into local languages so that the Protocol Specialist can provide any comments before translation. The Protocol Specialist will provide review comments to site staff as quickly as possible.

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

After incorporating review comments from the CORE Protocol Specialist, 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. The Protocol Specialist will provide review comments to site staff as quickly as possible.

1.3.4 IRB/EC Review

After incorporating review comments received from the CORE Protocol Specialist, site staff will submit the study protocol including sample informed consents, site-specific informed consent forms, and back-translations for review by all responsible — local and US-based — IRBs/ECs. Site staff should also submit the current curriculum vitae (CV) of the Investigator of Record and any other study-related materials required by the IRBs/ECs.

Tables 1-1 and 1-2, located at the end of this section, list all IRB/EC submission, review, and approval requirements pertinent to HPTN 046. Any participant information sheets, promotional materials, advertisements, flyers, etc. used during the study must be reviewed and approved by all responsible IRBs/ECs prior to use. Documentation of these approvals is not required for the Protocol Registration and Study Activation processes described below.

It is likely that both the US and local IRBs/ECs will provide comments on the submitted study documents. It is the responsibility of the investigator 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.

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, available at <http://rcc.tech-res.com>.

Upon obtaining approval from all responsible IRBs/ECs, site staff will submit the following documents to the DAIDS RCC Protocol Registration Office:

- Signed 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, informed consent forms, and other required materials

Note: Documentation of IRB/EC approval must reference the exact protocol number, title, and version number as listed on the cover page of the protocol, the date of IRB/EC approval, and the IRB/EC chair or designee's signature and title. 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.

- Designation of a risk/benefit category from 45 CFR 46.404-407 and approval for involvement of children based on determinations specified in that category from all responsible IRBs/ECs

Note: This documentation may be in the IRB/EC approval letter or in other official correspondence from the IRB/EC to the investigator.

- A copy of the approved site-specific informed consent forms

Note: The approved informed consent forms must include the exact protocol number, title, and version number, 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 footer of all back-translations should identify the document as the “English back-translation.” Sites are required to submit a Local Language Informed Consent Verification Statement signed by the back-translator for each local language consent form submitted. This document can be found at rcc.tech-res.com and http://www.hptn.org/research_studies/hptn046.asp

The CORE Protocol Specialist may review these materials prior to submitting to the RCC, notify the site of any significant deficiencies in the documents and provide instructions for required corrections as quickly as possible.

DAIDS RCC Protocol Registration Office staff will communicate their review findings to the Investigator of Record, the study coordinator and the CORE Protocol Specialist by email. The CORE Protocol Specialist will coordinate any required responses or re-submissions.

Note: After registration, any changes to the site-specific informed consent forms must be approved by all applicable IRBs/ECs prior to use. A copy of these should be forwarded to the CORE Protocol Specialist for submission to the DAIDS RCC for their records.

1.3.6 Site-Specific Study Activation

The HPTN has specified certain requirements that must be met in order to activate HPTN study studies. The activation requirements for HPTN 046 are as follows:

- Current Federal Wide Assurance number (FWA) on file with OHRP for the study site institution(s)/IRBs
- Completion of US FDA 30-day review period and safe to proceed notice
- Completion of human subjects training for all “key” study staff (as defined by US National Institutes of Health policy)

- 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 PRO, based on the following:
 - US and in-country IRB/EC approvals and approved informed consent forms (local language and back-translation)
 - Designation of a risk/benefit category from 45 CFR 46.404-407 and approval for involvement of children based on determinations specified in that category from all responsible IRBs/ECs
 - FDA Form 1572, signed and dated
 - CV of the Investigator of Record, signed and dated
- Other local government or regulatory authority approval of the study protocol, if applicable
- Pharmacy Establishment Plan approved by DAIDS Pharmaceutical Affairs Branch
- SOP for investigational product management and accountability and approval from the DAIDS Pharmaceutical Affairs Branch
- All applicable import approvals for study products (local drug authority approval)
- All applicable export approvals for study products
- Study staff signature sheet, roster, and delegation of duties (See Appendix C)
- 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 Network Lab approval of local lab readiness, including approval/confirmation of:
 - Proficiency in performing protocol-required testing
 - QC/QA procedures
 - SOP for establishing/maintaining normal ranges or other appropriate validation for protocol-specified tests
 - Documentation of normal ranges or other appropriate validation
 - SOP for local specimen handling and maintenance of “chain of custody” related to testing for the primary study endpoint (HIV)
 - Local laboratory back-up arrangements
 - LDMS set up and connected to the Network Lab
 - IATA specimen shipping certification (for study staff members directly involved in specimen shipping)
- Site SOP for communication with responsible IRBs/ECs (See list of required IRB submissions in Tables 1-1 and 1-2 at the end of this section)
- Site SOP for obtaining informed consent from potential study participants

- SOP for mother and infant enrollment eligibility determination
- SOP for infant randomization eligibility determination
- SOP for source documentation
- SOP for infant safety monitoring and Adverse Event (AE)/Expedited Adverse Event (EAE) reporting
- Participant accrual plan
- Participant retention plan
- Documentation of local HIV counseling procedures
- Site plan for the provision of the local standard of care antiretroviral regimen for the prevention of mother to child transmission
- Site plan for the provision of medical and psychosocial care to HIV-infected mothers and infants as outlined in Section 9.3 of the HPTN 046 protocol
- Conduct of and DAIDS approved site response to Clinical Site Monitoring Group (CSMG) study-specific initiation visit
- Completion of study-specific training (on-site comprehensive study training, SAE reporting training, rash management training, source documentation training)
- Completion of World Health Organization (WHO) Infant Feeding Counseling Training for all counselors providing general breastfeeding and safe alternatives counseling
- Resolution of action items identified in study-specific training and/or other site preparation/initiation activities (e.g. CSMG site initiation visits) including documentation that all study staff have reviewed the final study-specific procedures manual
- Final approval of DAIDS Prevention Sciences Branch Chief for activation, based on request from the CORE Protocol Specialist following completion of all activation requirements as specified above

When all activation requirements above have been met for a site, the CORE Protocol Specialist 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.

Table 1-1: IRB/EC Submissions Required Prior to Study Initiation for HPTN 046

Required Document	Written Approval Required*
HPTN 046 Protocol Version 3.0, dated 26 September 2007	Yes
Informed consent forms (local language(s) and back-translation(s), if applicable): - Study Enrollment V 3.0 - Study Enrollment V 3.0 for participants enrolled under Version 2.0 (if applicable) - Specimen Storage V 3.0 <i>Note: 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.</i>	Yes
Investigator of Record current CV	No
Viramune® (nevirapine) Package Insert	No
Investigator's Brochure and any updates issued by DAIDS prior to study initiation	No
Safety Reports, Safety Memos and other safety distributions issued by DAIDS after the site is registered to the protocol, even if prior to study initiation	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 submissions do not need approval by the IRB/EC per se (as indicated above) but rather are provided for their information; however, acknowledgement of receipt should be obtained from the IRB/EC for all submissions, if possible. Submissions cover letters should always list the title and date of all attachments.

** IRB/EC approval of recruitment materials and written materials to be provided to study volunteers must be obtained prior to use but is not actually required prior to study initiation.

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>.

Table 1-2: IRB/EC Submissions Required During Study Conduct for HPTN 046

Required Document	Written Approval Required*
Study status reports/updates (at least annually) for renewal of protocol and informed consent form approval	Yes
Protocol clarification memos (submission encouraged but not required by DAIDS)	No
Reports of AEs, SAEs and/or events meeting the criteria for expedited reporting to DAIDS (according to individual IRB requirements)	No
Viramune (nevirapine) Package Insert Updates	No
Investigator's Brochure Updates	No
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 affecting significantly the conduct of the study	Yes
New information that may affect adversely the safety of study participants or the conduct of the study	No
Amended informed consent forms (local language(s) and back-translation(s), if applicable) <i>Note: 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.</i>	Yes
Protocol departures/deviations/violations (per IRB/EC requirements and/or as directed by DAIDS)	No
Investigator of Record current CV (if Investigator of Record changes during study)	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
Other documentation required/requested by the IRB/EC	If required by IRB/EC
Notification that all participant follow-up has been concluded/completed at the site	No
Final study report/closure report	No

* Some required submissions do not need approval by the IRB/EC per se (as indicated above); however, acknowledgement of receipt should be obtained from the IRB/EC for all submissions, if possible. Submissions cover letters should always list the title and date of all attachments.

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

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>