

Section 1. Introduction

1.1 Overview of Section 1

This section specifies the sources of procedural information available to HPTN 052 study site staff, the responsibilities of the site Investigator, and the process by which each site will be approved to implement HPTN 052.

1.2 Sources 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, the specifications of the protocol take precedence. Please alert one of the HPTN Coordinating and Operations Center (CORE) Clinical Research Managers (CRM) of any such inconsistencies.

In instances where there is an urgent need for a change to the SSP, and when a full revision of the SSP is not imminent, the CORE may distribute an email containing a “Notification of Interim Change” to the current version of the SSP. The “Notification of Interim Change” will also be posted on the HPTN 052 website. These interim changes will be considered an official part of the SSP and should be considered official by the monitoring agent.

For questions related to HIV/AIDS clinical care and the administration and toxicity management of antiretroviral therapy (ART), queries should be sent to the HPTN 052 Clinical Management Committee (HPTN 052 CMC) using the email alias 052CMC@hptn.org.

All other questions should be sent to the HPTN 052 management team at the email alias 052MGMT@hptn.org and the proper person will respond. Please note that the management team consists of the CRMs from the CORE, the project managers from SCHARP, and representatives from the HPTN Network Laboratory (NL).

Note: Only email addresses included in the electronic HPTN directory at www.hptn.org will be able to send email communications to the 052CMC@HPTN.org and the 052MGMT@hptn.org email aliases. Please contact one of the CORE CRMs if you need to be added to the electronic HPTN directory.

CORE Clinical Research Managers (CRMs): **Marybeth McCauley**
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mmccauley@fhi.org

Theresa Gamble
919-544-7040 Ext: 11350
tgamble@fhi.org

Jackie Talley
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SCHARP Project Manager: **Leslie Cottle**
206-667-7405
leslie@scharp.org

HPTN 052 Clinical Management Committee: **052CMC@hptn.org**

HPTN 052 Management Team:
(CORE/SCHARP/HPTN NL): **052MGMT@hptn.org**

Network Laboratory (NL) Representative: **Estelle Piwowar-Manning**
410-614-6736
epiwowa@jhmi.edu

LDMS **ldmshelp@fstrf.org**

Contact information for all other HPTN 052 team members can be found in the electronic HPTN directory at www.hptn.org.

To make comments or suggestions for the SSP, please send email to:
052SSP@fhi.org.

1.3 Investigator Responsibilities

HPTN 052 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 CORE or found online at www.gpoaccess.gov/cfr/index.html and <http://www.ich.org/cache/compo/276-254-1.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

<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Regulatory.htm>

and

<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/ClinicalSite.htm>, respectively.

HPTN 052 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 052 is required to sign a Form FDA 1572, as well as 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.

IoRs may delegate work involved in conducting the study to other study staff members; however, delegation does not relieve the IoR 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 Guidances: Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors* available at <http://www.fda.gov/oc/ohrt/irbs/default.htm>.

1.4 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). Thereafter, sites must complete Protocol Registration with the DAIDS RCC, and Study Activation procedures with the HPTN CORE. The remainder of this section outlines the steps required to complete these procedures. These procedures are also described in the HPTN Manual of Operations (MOP). HPTN 052 study procedures may not be conducted prior to completing all of these steps and receiving of a site-specific study activation notice from the HPTN CORE. Note that study activation is not complete and the study may not begin at your site until DAIDS has granted final approval.

1.4.1 Protocol Distribution

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

1.4.2 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 CRM prior to translation into local languages.

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

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

1.4.4 IRB/EC Review

After incorporating review comments received from the CORE CRM, site staff will submit the study protocol, site-specific informed consent forms, the current curriculum vitae (CV) of the Investigator of Record, Investigators Brochures and Package Inserts, and any other study-related materials for review by all responsible local and US-based IRBs/ECs. Any participant information sheets, promotional materials, or advertisements used during the study must be reviewed and approved by all responsible IRBs/ECs prior to use.

In the event that either the US and/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. If a local language consent form is being used, the final English back-translation must reflect the approved informed consent forms that will be used at the site.

An overview of IRB/EC submissions required before and during HPTN 052 is included in Table 1-1.

Table 1-1: IRB/EC Submissions Required Prior to Study Initiation and During Study Conduct

Document	Prior to Study Initiation		During Study Conduct	
	Source	Approval Required*	Source	Approval Required*
Protocol	HPTN CORE	yes	NA	NA
Protocol amendments (including letters of amendment) and any other changes increasing risk to participants and/or affecting significantly the conduct of the study.	NA	NA	HPTN CORE	yes
Protocol clarification memos (submission encouraged but not required by DAIDS)	NA	NA	HPTN CORE	no
Protocol departures/deviations/violations (per IRB/EC requirements and/or as directed by DAIDS)	NA	NA	Site	no
Informed consent forms (local language(s) and back translations, if applicable). Screening (index/partner); Enrollment (index); Enrollment (partner); Specimen Storage (index and partner); Pregnancy (index)	Site	yes	NA	NA
Amended informed consent forms (local language(s) and back translations, if applicable)	NA	NA	Site	yes
Current CV for Investigator of Record	Site	no	NA	NA
Revisions to current CV for Investigator of Record (if Investigator of Record changes during study)	NA	NA	Site	no
Participant recruitment materials (posters, flyers, advertisements, etc.)	Site	yes	NA	NA
Updated/additional participant recruitment materials (posters, flyers, advertisements, etc.)	NA	NA	Site	yes
Other written information for study participants	Site	yes	NA	NA
Updated/additional written information for study participants	NA	NA	Site	yes
Other documentation required or requested by the IRB/EC	Site	no	Site	no
Study status reports/updates (at least annually) This approval documents continuing review.**	NA	NA	Site	yes
New information that may affect adversely the safety of study participants or the conduct of the study	NA	NA	DAIDS through the HPTN CORE	no
Final study report/closure report	NA	NA	Site	no

DAIDS; Division of AIDS; EC, ethics committee; HPTN CORE; HIV prevention trials network coordinating and operations center; IRB, institutional review board; NA, not applicable.

* 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/policy/index.html#continuing>.

Note: 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

1.4.5 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://rcc.tech-res.com/forms.htm>.) and the HPTN MOP (located at <http://www.hptn.org/index.htm>.)

Upon obtaining approval from all responsible IRBs/ECs, site staff will submit the following documents to the Protocol Registration Office (PRO) at the RCC. These documents may be sent electronically to protocol@tech-res.com. Site staff will also submit a copy of the submission documents to the CORE CRM.

- Signed and dated FDA Form 1572 (original)
- 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.

- 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 attests to the accuracy of the translation in writing for each back-translated document.

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 and a copy should be submitted to the CORE CRM.

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

1.4.6 Study Activation

The HPTN has specified certain requirements that must be met in order to activate HPTN study operations. The activation requirements for HPTN 052 are defined in Table 2 of the HPTN MOP (www.hptn.org) and are listed below. If there is an inconsistency between the items in this SSP and the HPTN MOP for site activation, contact an HPTN CORE CRM for clarification.

- OCSO site approval (Refer to Table 1 of the HPTN MOP for Minimum Requirements for OCSO Site approval)
- Pharmacy approval from PAB of site readiness
- Data Management approval from the Statistical and Data Management Center (SDMC) of site readiness
- Laboratory approval from Network Laboratory (NL) of site readiness
- Study Specific SOPs reviewed by CORE (See Table 1-2)
- Other Required Activities:
 - Local regulatory authority approval of the study protocol, e.g., Ministry of Health, drug controller/regulatory agency (if applicable, in addition to IRB/EC approval)
 - Protocol registration approval from the Regulatory Compliance Center (RCC) Protocol Registration Office, based on the following:
 - approvals of the study protocol from all responsible Institutional Review Boards/Ethics Committees (IRBs/ECs)
 - IRB/EC-approved informed consent forms (including local language versions, back-translations and Local Language Informed Consent Verification Statements where applicable)
 - signed Food and Drug Administration (FDA) Form 1572 or DAIDS Investigator of Record Agreement
 - Curriculum vitae (CV) of the Investigator of Record (IOR)
 - Ensure human subjects protection (HSP) training for key study staff is current
 - Ensure Good Clinical Practice (GCP) training for key study staff is current
 - Study staff signature sheet, roster, and delegation of duties
 - CVs available on site for key study staff
 - Completion of study-specific training; DAIDS approval of resolution of findings/actions identified during training
 - Resolution of any other action items identified in any other site preparation activities
 - Final DAIDS Branch Chief approval for study activation

Table 1-2: Required SOPs for HPTN 052

Category	SOP	
Pharmacy	Investigational product storage, dispensing, and accountability	
Data Management	On-site data management including QA/QC procedures	
Specimen Processing	Sample storage	
	Specimen processing (included specifically below)	
Laboratory	Establishment and maintenance of normal ranges	
	Laboratory equipment maintenance	
	Local specimen handling and “chain of custody” related to study endpoints	
	Local laboratory backup arrangements	
	LDMS reconciliation	
	Critical value reporting	
	Biohazard safety and containment and occupational safety,	
	Lab data management and storage	
	Specimen transport (local and international)	
	Explicit SOP for each lab assay	
	Sodium	Complete blood count (including hemoglobin and platelets)
	Potassium	Syphilis serology
	Chloride	Hepatitis B
	Phosphate	Lipase
	Bicarbonate	Creatinine kinase (CK)
	Creatinine	Total bilirubin
	Albumin	Alkaline phosphatase
	Candida	AST
	Bacterial vaginosis	ALT
	CD4	HIV EIA antibody test/Western blot/IFA
	HIV RNA PCR	Urine pregnancy test
	Neisseria gonorrhea PCR	Chlamydia/trachomatis PCR
<i>Trichomonas vaginalis</i>		
Clinical Management	Medical management of HIV/AIDS (includes prophylaxis and treatment other than ART)	
	ART management	
	Handling medical emergencies	
	Reference for maternal care	
	Safety monitoring for clinical study participants	
	Explicit SOP for each clinical procedure (includes specimen handling)	
	Blood	Genital ulcer swabs
	Urine	Male and female genital secretions
	Chest X-ray	
	Administrative	Source documentation

Category	SOP	
and Regulatory	Essential documents	Communication with HPTN
	Community Advisory Board input	AE / EAE reporting
	General operating procedures	Informed consent process
	Power failure	Staff training and certification
	Staff roles, responsibilities and qualifications	Participant confidentiality
	Study file management	Audits and inspections (including review and follow-up to monitoring report findings)
	SOP development and review	
Counseling	HIV Voluntary Counseling and Testing	
	Couples counseling	
	Adherence counseling	
Study-Specific	Recruitment	
	Participant eligibility determination	
	Retention	

The required elements of the SOPs listed in Table 1-2 may be grouped together in single SOPs (*e.g.*, there may be one SOP for counseling containing VCT, couples, and adherence counseling information) or split among several SOPs (*e.g.*, information about staff training may be added to each SOP.)

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

1.4.7 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.

- Protocol amendment registration approval from DAIDS/RCC based on the following:
 - Approvals from all responsible IRBs/ECs for the protocol and site-specific ICFs
 - IRB/EC-approved informed consent forms (including local language and back translation where applicable)

- Sites should review, and if necessary revise, their FDA Form 1572, CV for the IoR, their FHI Study Site Form, the CRF Source Documentation Table, and all study-related SOPs.
- The IoR must sign the “Investigator of Record Signature Page” included in the protocol amendment
- All study drugs required by the revised protocol must be on site
- Completion of study-specific training for (remote or on site) the latest version of the protocol
- The current CRFs and randomization envelopes must be on site, and, if required, old randomization envelopes must be returned to SCHARP
- 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

1.5 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. 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 EAEs 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 Office of Human Research Protection (OHRP) website:
<http://www.hhs.gov/ohrp/policy/index.html#continuing>.