8 HUMAN SUBJECTS CONSIDERATIONS

8.1 Applicable US Federal Regulations and Guidelines

Because HPTN studies are funded by the United States (US) National Institutes of Health (NIH), they must be conducted in accordance with applicable sections of the US Code of Federal Regulations (CFR).

45 CFR 46: All studies must be conducted in accordance with CFR Title 45, Part 46 (45 CFR 46) entitled "Protection of Human Subjects," which includes subparts related to:

- Review of research by Institutional Review Boards/Ethics Committees (IRBs/ECs)
- Requirements for obtaining and documenting informed consent
- Additional protections and requirements when the following types of human subjects are involved in research:
  - pregnant women
  - fetuses
  - neonates
  - children
  - prisoners

Health Insurance Portability and Accountability Act (HIPAA): All US Clinical Research Sites (CRSs) participating in HPTN studies must also comply with CFR Title 45, Parts 160 and 164 entitled "Standards for Privacy of Individually Identifiable Health Information," (also known as the "Privacy Rule") which include subparts related to:

- Standards for use and disclosure of protected health information (PHI)
- Authorizations to use and disclose PHI or waivers of authorization
- Tracking of PHI uses and disclosures

Refer to Section 8.5 for more information about HIPAA.

IND Studies: Studies conducted under an Investigational New Drug (IND) application are additionally subject to regulation by the US Food and Drug Administration (FDA) and must be conducted (at the CTU/CRS, LOC, SDMC and LC) in accordance with:

- 21 CFR 11: Electronic Records, Electronic Signatures
- 21 CFR 50: Protection of Human Subjects
- 21 CFR 54: Financial Disclosure by Clinical Investigators
- 21 CFR 56: Institutional Review Boards
- 21 CFR 312: Investigational New Drug Application
- 21 CFR 314: Applications for FDA Approval to Market a New Drug

FDA Form 1572: The Clinical Trials Unit (CTU) Principal Investigator (PI) must designate an Investigator of Record (IoR) for each HPTN study conducted at each CRS (see Section 3.4.1.3 for a full description of IoR responsibilities). The IoR is responsible for all aspects of study implementation at a CRS.

The IoR is required to sign either an FDA Form 1572 (for IND studies – 21 CFR 312) or a Division of AIDS (DAIDS) Investigator of Record Form (for DAIDS sponsored non-IND studies) to formally document his/her agreement to conduct the study in accordance with the study protocol and applicable US regulations. The forms are completed and submitted to the DAIDS Regulatory Support Center (RSC) as part of the site-specific protocol registration process described in Section 10.10.

Current versions of both forms, as well as form completion instructions are available on the RSC website; additional guidance is available in the DAIDS Policy: DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual Appendix: Source Documentation Requirements.

In addition to the above, HPTN studies must be conducted in accordance with:

- Other applicable US regulations and guidelines and/or NIH policies
- In-country national, regional, or local regulations, guidelines, and/or policies applicable to human subject research in general and/or the conduct of study procedures in particular

8.2 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Consolidated Guidance for Good Clinical Practice

DAIDS requires that all HPTN studies be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). (Use drop down menu in webpage.)

8.3 Protection of Human Subjects Training

In accordance with DAIDS policy, all key CRS protocol staff must complete Human Subjects Protection (HSP) training prior to activation for clinical research and every three years thereafter (institutional requirements may vary and more frequent training may be required). "Key" CRS staff include any individual who is named on the Form FDA 1572 or DAIDS Investigator of Record Form and CTU/CRS personnel who have more than minimal involvement with the conduct of the research (i.e., performing study evaluations or providing interventions) or more than minimal contact with research participants or confidential study data, records or specimens. Further information related to this training requirement is provided in Section 11.1. The Office of Clinical Site Oversight (OCSO) assumes primary responsibility for the verification of training. Additionally, all LOC, SDMC, and LC staff who are involved in research activities as defined by internal Standard Operating Procedures (SOPs) or institutional requirements, are required to complete this training every three years (see Section 11).

8.4 IRB/EC Review and Approval

Consistent with the regulations and guidance referred to in Sections 8.1 and 8.2, all HPTN studies must be reviewed and approved by IRBs/ECs responsible for oversight of research involving human subjects conducted at a CTU/CRS, as applicable. A responsible IRB/EC registered with the US Office for Human Research Protections (OHRP) under a Federal Wide Assurance (FWA) must oversee HPTN research conducted at each CRS. OSCO will verify the FWA registration. In many cases, more than one IRB/EC are involved, for example, if a CRS is funded through a US institution with one or more CRSs in other countries. In such cases all responsible IRBs/ECs must review and approve all required study-related documentation (as described further below). HPTN studies must be reviewed and approved by all responsible IRBs/ECs prior to the initiation of study implementation. Thereafter, studies must undergo continuing review and be approved at least annually.

By law, all US sites participating an HPTN study that is conducted at more than one US site must use the single IRB (sIRB) contracted by the HPTN. Any site that cannot cede oversight to the sIRB for a study will not be able to participate in that study. Non-US-based sites are not subject to the use of the sIRB.

The IRBs responsible for oversight of HPTN research must meet the requirements of 45 CFR 46 and 21 CFR 56 (as applicable) and must be associated with an institution/organization that has received an FWA from the OHRP, which formalizes the institution's commitment to protect human subjects. Additional information related to assurances is available on the OHRP website. US research regulations and the ICH/GCP specify the documents that CRSs are required to submit to their IRBs/ECs when obtaining initial and continuing review of research involving human subjects. Some IRBs/ECs may require additional documentation in support of their reviews (e.g., copies of case report forms [CRFs]); if so, CRS staff must comply with all IRB/EC requirements.

CRS staff must maintain documentation of all submissions to and all approvals from all responsible IRBs/ECs — and any other IRB/EC correspondence — in their HPTN Essential Document Files. In addition, as part of its protocol registration process, DAIDS requires submission of certain IRB/EC approval documentation and other required documents to the RSC through a direct upload using the DAIDS Protocol Registration System (DPRS). The Leadership and Operations Center (LOC) clinical research manager (CRM) may review the documentation and provide assistance with the registration process as needed. Further information on the protocol registration process and requirements for submitting IRB/EC approval documentation to the RSC are provided in Section 10.10 of this manual as well as on the RSC website. DAIDS requires all IRB/EC approval documentation to be labeled with the full protocol title, DAIDS ES and/or Network protocol ID number, protocol version number, and/or protocol version date.

Although not required, study CRSs are encouraged to request that IRBs/ECs note the effective and expiration dates of all approvals.

Required IRB/EC Submissions for Initial Review and Approval

(prior to study initiation)

Protocol version 1.0 (or first implementation version of the protocol, if not version 1.0)*
Informed consent forms*: — Screening — Enrollment — Specimen Storage Note: HPTN informed consent forms typically contain information on participant incentive amounts and schedule; however, incentives may be approved through submission of separate materials.
Investigator's Brochure(s)** or Package Inserts**
Other safety-related information (if applicable)
Current Investigator of Record Curriculum Vitae
Participant recruitment materials developed prior to study initiation
Other written information for study participants developed prior to study
Other documentation required/requested by the IRB/EC (e.g., CRFs, SOPs)

**Based on US regulations and ICH/GCP guidance, written approval is required for these documents. Additional approvals may be required by responsible IRBs/ECs. If so, the required approvals must be obtained and filed.*

***Required for study with investigational products.*

Note: All documents must be submitted to all IRBs/ECs responsible for oversight of study implementation at the CRS, both locally-based and US-based, if applicable. CRSs must communicate with IRBs/ECs to ascertain what documentation is required.

Documentation of all submissions and approvals from all responsible IRBs/ECs must be maintained in the HPTN Essential Document Files at the CRS.

8.4.1 Continuing Review

The OHRP requires that all federally-funded research be subject to continuing review by an IRB/EC at intervals appropriate to the degree of risk, but not less than once per year.

The IoR is responsible for ensuring timely submission of continuing review requests to IRBs/ECs so that no lapse in approval occurs for an ongoing study. The CTU PI is responsible for ensuring that the IoR fulfills this responsibility.

An IRB/EC must review research at convened meetings at which the majority of the members are present, including at least one member whose primary concerns are in non-scientific areas.

In certain circumstances, an IRB/EC may use expedited review procedures for conducting continuing review when the initial review was approved by a convened IRB/EC. These circumstances are as follows:

- Where the research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects
- Where no subjects have been enrolled and no additional risks have been identified
- Where the remaining research activities are limited to data analysis

Continuing review of research may also be conducted under expedited review procedures if the research is not conducted under an IND and the IRB/EC has determined and documented at a convened meeting that the research involves no greater than minimal risk.

For more information on the use of expedited review procedures for continuing review, see Federal Register at 63 FR 60364-60367.

In conducting continuing review all IRB/EC members as determined by their local guidelines should receive a protocol summary and a status report of the research including:

- The number of participants accrued
- A summary of adverse events and any unanticipated problems involving risks to participants or others and any withdrawal of participants from the research
- A summary of any relevant recent literature, interim findings, and amendments (submission of the clarification memos is not required but is strongly encouraged)
- Any relevant multi-center trial reports
- Any other relevant information, especially information about associated risks
- A copy of current informed consent forms and any newly proposed informed consent forms, if applicable

In addition, at least one member of the IRB/EC should also receive a complete protocol including amendments previously approved by the IRB/EC.

When reviewing research under expedited procedures, the IRB/EC Chair (or other IRB/EC designated member) should review the complete protocol in addition to all the above-mentioned documentation.

CRS staff members are required to submit IRB/EC continuing review approval letters directly to the DAIDS Protocol Registration Office (PRO) through the DPRS. Instructions are provided on the RSC website.

8.5 Informed Consent Process

Informed consent must be obtained from participants prior to undertaking research procedures.

Informed consent is a process by which an individual voluntarily expresses willingness to participate in research after having been informed of all aspects of the research that are relevant to his or her decision. Informed consent is rooted in the ethical principle of respect for persons and is a fundamental component of conducting ethically sound research involving human subjects. It is not merely a form or a signature, but a process that involves information exchange, assessment of comprehension, and assurance of voluntariness on the part of both the potential study participant and the study staff member who obtains informed consent from the participant. Details regarding the informed consent process to be undertaken in each HPTN study are provided in each study-

specific procedures (SSP) manual. In addition, each HPTN CRS must develop an SOP for obtaining informed consent from potential study participants as a condition for study activation (see also Section 10); CRSs are encouraged to seek IRB/EC review and approval of these procedures. Section 4 of the HIV Prevention Trials Network (HPTN) Ethics Guidance for Research (revised February 2020) also provides points to consider in the development and implementation of the informed consent process.

CRS staff may also seek input from the local Community Advisory Board (CAB) early in the consent development process. CABs may provide input on appropriate translation and incentives within the informed consent forms, or any other documents that the CRS develops to use during the consent process.

In some studies, informed consent for both screening procedures and enrollment or "on study" procedures may be undertaken in one step, whereas in other studies a two-step process is employed, such that participants first consent to be screened for the study and subsequently consent to enrollment in the study after having been found to be eligible during the screening process.

In addition to informed consent for screening and enrollment, DAIDS requires that HPTN study participants undergo a specific informed consent process for special testing or interviews that may occur during the study such as the storage and possible future research testing of biological specimens if specimens are to be stored and used post-study or genomics testing or other testing of genes. Study participants may decide not to consent to any of these types of testing, but still participate in an HPTN study. The informed consent will have sections dedicated to the description of these tests and a separate line for the participants to provide their initials on the signature page of the consent to state their agreement to allow these tests. Alternatively, the protocol may have a separate consent altogether to cover this additional material. Additional consents may be needed for participants regarded as part of a special population (adolescents, for example). Therefore, HPTN studies may have three or more different types of informed consent.

Because informed consent is considered an ongoing process, key elements of informed consent should be reviewed at all study follow-up visits.

In addition to the above, when an informed consent form is revised, or new information is found that may influence a participant's decision to remain in the study, study participants may need to be re-consented. The decision regarding the need for re-consent should be made in consultation with the protocol team and local IRB.

For studies conducted at US CRSs, additional authorization to use or disclose protected health information may be required if the CRS is regarded as a "covered entity" under HIPAA, and therefore subject to the Privacy Rule. This additional authorization may be included as part of the study informed consent form or may be a separate document. Authorization to use or disclose Protected Health Information must be approved by a responsible Privacy Board for the covered entity. The Department of Health and Human Services (DHHS) Office for Civil Rights (OCR) has developed tools to help entities determine whether they are covered entities and subject to the HIPAA.

NIAID developed Data Management and Sharing Guidelines, which clarifies that the rights and privacy of human subjects will be protected at all times and restricts how data is shared within HIPAA guidelines. DAIDS will continue to review informed consent forms for compliance with the Common Rule and US FDA regulations and DAIDS requirements, but not for Privacy Rule compliance.

US regulations (21 CFR 50 and 45 CFR 46) specify the elements of informed consent that must be conveyed to research participants through the informed consent process. The DAIDS Protocol Registration Manual includes detailed instructions on obtaining site protocol registration, including the content and formatting of ICFs that must be submitted.

8.6 Documentation of Informed Consent

US regulations (21 CFR 50 and 45 CFR 46) require that informed consent be documented by the use of a written informed consent form approved by the responsible IRBs/ECs and signed and dated by the participant or the participant's legally authorized representative at the time of consent, unless waived per the specifications of 45 CFR 46 Subpart A. The DAIDS SCORE Manual for Informed Consent of Participants provides extensive detailed information to guide CRS staff in meeting this requirement, as well as several suggestions for documenting the informed consent process apart from the informed consent form. CRS SOPs for obtaining informed consent should specify standard informed consent practices to be followed by all CRS staff involved in conducting the informed consent process with potential study participants.

In general, all signature and date blocks included on informed consent forms must be completed (see Section 8.7.1 for information on completing signature and date blocks for illiterate participants). Signatures and dates must be entered in ink, and date blocks must be completed by each signatory; CRS staff may not enter the date for participant signatures.

Legal names should be used. Fabricated/falsified names should not be used. Initials may not be used in place of a participant's full surname, and it is strongly recommended that initials not be used in place of a participant's full first name. However, if a participant commonly signs his or her name using an initial for the first name, the initial may be used, provided this practice is acceptable per the policies of the CRS institution(s). Also, character symbols (e.g., Chinese characters) are acceptable in countries that use them. Additional documentation considerations applicable for special populations are discussed below.

8.7 Special Populations

8.7.1 Additional Considerations for Illiterate Participants

US regulations as well as the ICH/GCP guidance specify additional protections that must be in place when obtaining informed consent from illiterate participants. In particular, a witness who is literate in the language in which the informed consent discussion is conducted must be present during the entire informed consent process undertaken with illiterate participants. The ICH/GCP guidance identifies an impartial witness as a person who is independent of the study and cannot be unfairly influenced by people involved with the study. This witness need not be totally unaffiliated with the study. It may be possible, for example, to designate a 'subject advocate' who would be available at each CRS. The witness will sign and date the informed consent form to attest that the information in the consent form was accurately explained to, and apparently understood by, the participant, and that informed consent was given freely by the participant. CRS SOPs for obtaining informed consent should specify procedures to be followed when obtaining informed consent from illiterate persons and should define who may serve as the witness to the informed consent process.

Additional considerations for documenting the informed consent process for illiterate participants are as follows:

- The study staff member who completed the informed consent process with the participant should document the participant's illiteracy in his or her study chart.
- The study staff member who completed the informed consent process with the participant should enter the participant's name below the "participant's printed name" block on the informed consent form, together with a signed and dated note documenting the name of the person who made the entry and the date of the entry. The "participant signature date" should be completed in this same manner.
- The participant should make his or her mark (e.g., thumbprint) in the "participant's signature" block.

It is highly recommended that informed consent procedures, including procedures for consenting illiterate participants, be submitted for review and approval by the responsible IRBs/ECs prior to study initiation. CRSs may also seek input from community representatives before finalizing procedures and SOPs. As part of these procedures, CRSs should specify how literacy is determined.

8.7.2 Additional Considerations for Research Involving Fetuses, Pregnant Women, and Underage Participants

Some HPTN studies involve pregnant women or women who may become pregnant, *in utero* fetuses, infants, and children who are not of legal age to independently consent to research.

US Department of Health and Human Services (DHHS) regulations for the protection of human subjects (45 CFR 46 Subpart B) specify additional considerations for research involving fetuses and pregnant women. Subpart D specifies additional considerations for research involving children. These considerations outline additional duties of IRBs/ECs in connection with research involving these vulnerable populations and requirements regarding the relative risks and benefits to research participants in these populations.

For research projects including children or adolescents, DAIDS requires documentation of the IRB/EC designation of a risk/benefit category from 45 CFR 46.404 and IRB/EC approval for involvement of children based on the determinations specified in that category. The documentation may be in the IRB approval letter or in other official correspondence from the IRB to the investigator. This requirement applies to the initial and continuing reviews of research protocols and to any subsequent reviews of amendments or Letters of Amendment involving potential study risks or benefits. Protocol registration will not be approved if this documentation is not received.

Obtaining and documenting consent for participation of infants and children may involve obtaining consent from a legally authorized representative or guardian in absence of a parent. DHHS regulations at 45 CFR 46.102(C) define a legally authorized representative as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. Thus, under 45 CFR 46.102(C), the determination of who may be a legally authorized representative is a matter of state or local law. Therefore, it is highly recommended that informed consent procedures, including defining the minimum age for independent consent and defining and ascertaining legal guardianship, be submitted for review and approval by the responsible IRBs/ECs prior to initiation of HPTN studies involving infants and children.

Additionally, CRSs are required by DAIDS to establish an SOP outlining the process specific to enrolling minors. Please refer to the SCORE Manual Clinical Research Site Requirements for Enrolling Minors into DAIDS Clinical Research (nih.gov).

8.7.3 Additional Considerations for Prisoners

The HPTN does not plan to implement any studies that recruit, screen, or enroll participants from a prison setting. However, it is possible that persons enrolled in HPTN studies could become incarcerated during follow-up. 45 CFR 46, Subpart C specifies additional considerations for protection of prisoners as subjects in biomedical and behavioral research including enhanced IRB/EC review requirements and a requirement to obtain approval for prisoner participation from the Secretary of the US DHHS. HPTN CRSs will comply with the specifications of 45 CFR 46 prior to involving prisoners in any HPTN research activity.

8.8 Storage of Informed Consent Forms

HPTN CRSs must maintain, in a confidential and secure manner, the complete, original, signed and dated informed consent forms of all persons who screen for and/or enroll in HPTN studies, in accordance with the specifications of the study protocol (in particular the protocol sections on Confidentiality and Investigator's Records) and the SSP manual (see also Section 8.9).

8.9 Confidentiality

CRS staff will make every effort to maintain the confidentiality of study participants and information that can be linked to them; however, absolute confidentiality cannot be guaranteed.

Authorized representatives of the following organizations are granted access to participant study records as needed to assess the quality of study conduct:

- NIH
- Pharmaceutical co-sponsors
- Clinical Site Monitor
- HPTN LOC, SDMC, and LC
- Responsible IRBs/ECs
- US FDA
- Other regulatory authorities

In addition to efforts undertaken by CRS staff to ensure confidentiality, eligible research studies that are funded by NIH are automatically issued a Certificate of Confidentiality (CoC) under the NIH Policy for Issuing Certificates of Confidentiality that protects CRSs from being compelled to disclose study-related information by any US federal, state or local civil, criminal, administrative, legislative act or other proceedings. The provisions of the CoC, as well as its limitations (e.g., in cases of reportable harm to self or others), will be included in the informed consent form and will be explained to participants during the informed consent process for each study to which the certificate applies (see Section 7.3).

CoCs are issued to recipients for applicable research regardless of the country where the investigator or the protected information resides. However, CoCs may not be effective for data held in foreign countries.

8.10 Participant Costs for Study Participation

Unless otherwise specified in the study protocol, HPTN study procedures are performed at no cost to study participants.

8.11 Participant Reimbursement for Study Participation

Pending IRB/EC approval, participants may be reimbursed for their time and effort when taking part in HPTN studies, and/or be reimbursed for costs associated with travel to study visits, time away from work, childcare, etc. Guidance should be sought from local community representatives on appropriate site-specific reimbursement types, amounts, and schedules prior to final IRB/EC approval.

8.12 Access to HIV-related Care

8.12.1 HIV Counseling and Testing

Most HPTN studies involve HIV testing. All such testing will be provided in the context of HIV pre-test, risk reduction, and post-test counseling. See also Section 10 of the HIV Prevention Trials Network (HPTN) Ethics Guidance for Research (revised February 2020) for a discussion of standard of care and treatment for those who are enrolled in research and those who are screened out.

In accordance with NIH policies, participants must receive their HIV test results in order to enroll in HPTN studies.

8.12.2 Provision of Care in HPTN Studies

The provision of care for all participants in the study will be addressed by the study team in the study protocol and will generally be deferred to the investigators at the CRS and the local standards of care. The protocol should include reference to the provision of care for HIV negative participants who seroconvert during the study, but may also include those that are identified as HIV positive during screening, etc.

In most studies, the study IoR at each CRS will work to identify funding sources for HIV-related care (e.g., access to, or provision of, antiretroviral therapy [ART] or ART-related care) for enrolled participants after the discontinuation of the study's financial support by the NIH. Individual CRSs will provide to the NIH a written plan for provision of ART or HIV-related care after the study ends. The plans will focus on participants in whom ART and HIV-related care would be considered required according to local standards of care and accepted guidelines (e.g., World Health Organization [WHO], US Public Health Service Commissioned Corps [USPHS] for US CRSs).

An example is provided as follows:

- HIV-infected individuals identified through screening for all parts of the study who do not meet eligibility criteria or who do not wish to enroll in the study will be referred to local HIV care services or other agencies that provide care or access to treatment. They will also be referred for possible enrollment into other available HIV treatment clinical trials.
- For participants who become infected with HIV during any part of the study, the CRS will make every effort possible to provide HIV-related care to those individuals as resources will allow. When appropriate, participants will be referred to local HIV care services, non-governmental organizations (NGOs), or other agencies that provide care or access to treatment. They will also be referred for possible enrollment into other available HIV treatment clinical trials.

For any participants identified as being both HIV-infected and pregnant, every effort will be made to facilitate access to antiretroviral prophylaxis and/or other interventions to reduce the probability of HIV transmission to the participant's fetus or infant.

Further information and guidelines on HIV prevention, treatment, and care may be found on the World Health Organization website.

8.13 Communicable Disease Reporting Requirements

HPTN study staff will comply with all applicable local requirements to report communicable diseases identified among HPTN study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.