HPTN Manual of Operations (MOP)
Summary of Changes
22 December 2023

Section	Revisions
Section 4: HPTN Science Committees, Working Groups and Protocol Teams	• Section 4.5.1: Minor edit for clarity
Section 9: Protocol Development	• Figure 9-1 and Section 9.2.2.2: Moved SDMC operational review from being simultaneous to DAIDS PSRC Review to being simultaneous to SRC Review and HPTN Leadership review • Section 9.2.1: Clarified that the RSR will be posted to the HPTN website *as applicable* • Section 9.2.1 and Section 9.2.2.3: Added that the RSR will be submitted along with the protocol at PSRC review • Section 9.2.2.1: Minor edit for clarity
Section 12: Study Implementation	• Section 12.1.5.3: Addition of language related to the decision and timing of unblinding trials that have been terminated before completion due to sponsor decision or DSMB recommendation • Section 12.5.8: Revised language to include reference to the Cross-Network Protocol Deviation Reporting Guide and Protocol Deviation electronic Case Report Form
Section 17: Ancillary Studies/Investigations	• Updated links to the Ancillary Study Application

1. OVERVIEW

1.1. Background of the HIV Prevention Trials Network

Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immune Deficiency Syndrome (AIDS), is an uncontrolled, worldwide, public health challenge associated with extensive morbidity and mortality. The severity of the global HIV epidemic has led to intense efforts in HIV prevention research, and remarkable success using antiretroviral therapy (ART) for prevention. However, much work remains to curb the epidemic; therefore, research evaluating interventions for prevention of HIV infection remains a priority of the United States (US) National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID), under whose auspices the HIV Prevention Trials Network (HPTN) was formed.

In 1993, NIAID established a clinical research network for the conduct of both US-based and non-US-based efficacy trials of vaccines and other biomedical HIV prevention interventions, the HIV Network for Prevention Trials (HIVNET). HIVNET investigators designed and implemented trials of microbicides, vaccines and interventions to prevent mother to infant HIV transmission and behavioral interventions. In 1999, in response to a request for applications by NIAID and its collaborating institutes, an HIV Prevention Leadership Group formed the next iteration of the Network, the HPTN. Since then, the HPTN has been in place over two decades with an expanding and contracting scientific agenda through its iterations. The HPTN research agenda was focused primarily on evaluation of biomedical and other prevention interventions until 2006 (HPTN I); the agenda was then re-focused on non-microbicide, non-vaccine interventions (HPTN II, 2006-2013); focus then evolved to discovery of novel agents for pre-exposure prophylaxis (PrEP) and integrated strategies (HPTN III, 2013-2020). At this stage of the epidemic, with no effective vaccine yet in sight, the current HPTN agenda (HPTN IV, 2020-2027) will focus on four components of HIV prevention: 1) long-acting antiretroviral (ARV) agents and delivery systems for PrEP; 2) multipurpose prevention technologies (MPTs) that concurrently prevent HIV and pregnancy, sexually transmitted infections (STIs) or opioid dependence; 3) broadly neutralizing antibodies (bnAbs), alone and in combination, for PrEP; and 4) integrated strategies for HIV prevention. This agenda continues to build on the HPTN's accomplishments and ongoing work and takes advantage of recent advances in HIV prevention science.

1.2. HPTN Mission

The HPTN was formed to conduct research on promising biomedical and behavioral strategies to reduce the acquisition and transmission of HIV. Since its inception, the HPTN has proactively addressed its goal of developing a state-of-the-art, collaborative, multi-site, multi-trial, multidisciplinary HIV prevention science research agenda. Research is conducted in diverse and vulnerable populations such as heterosexual cisgender men and women, men who have sex with men (MSM), transgender men and women, persons who inject drugs (PWID), and adolescents.

In response to compelling research needs in HIV prevention, the HPTN has established Science Committees (SC) that focus on populations at risk and key areas of importance to the HPTN research agenda. The HPTN also has cross-cutting Working Groups (WG) that provide the expertise required for all HPTN research efforts. In addition, the HPTN continues to make major investments of both human and financial resources to build international research structures, enhance collaborative community partnerships, and address issues in research ethics in the context of HIV prevention research.

1.3. HIV Prevention Trials Network Organization

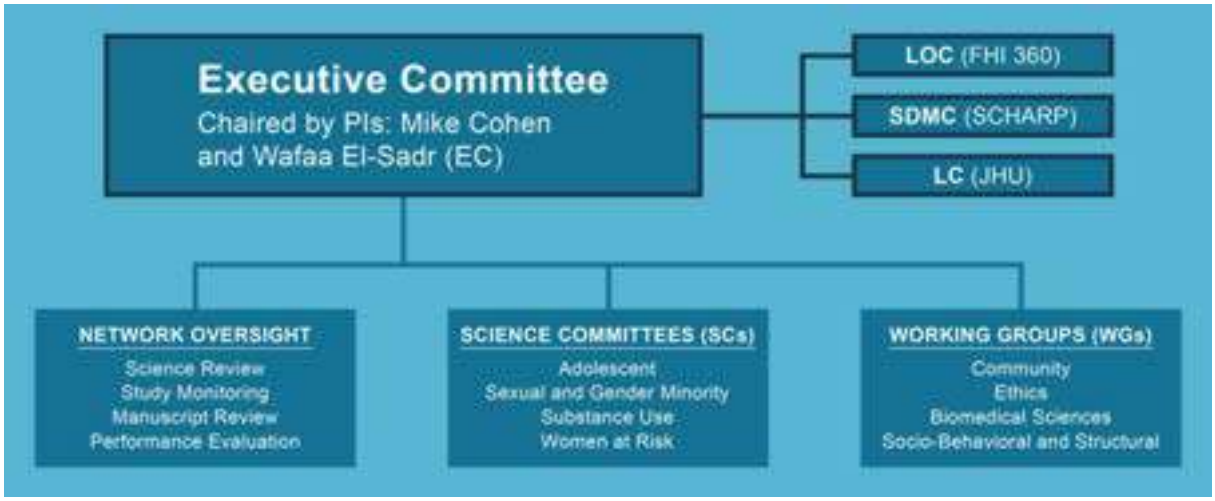
The HPTN operates under cooperative agreements with the Division of AIDS (DAIDS) of NIH/NIAID, and with support from other NIH Institutes including the National Institute of Drug Abuse (NIDA), National Institute of Mental Health (NIMH), National Institute of Child Health and Human Development (NICHD) and Office of AIDS Research (OAR). Project oversight and collaboration are provided by the staff of the Prevention Sciences Program (PSP) within DAIDS.

The HPTN is led by two Principal Investigators (PIs). The HPTN Administrative PI is responsible for ensuring the efficient development and implementation of the HPTN research agenda as well as managing the Network and coordinating activities across the Network's three Central Resources:

- Leadership and Operations Center (LOC) located at FHI 360
- Statistical and Data Management Center (SDMC) located at the Statistical Center for HIV/AIDS Research and Prevention (SCHARP)
- Laboratory Center (LC) located at Johns Hopkins University

Figure 1-1 outlines the organizational structure of the HPTN.

Figure 1-1 HPTN Organizational Structure



The HPTN's SCs and WGs contribute to the HPTN's overall research agenda through the development of research strategies in each of the Network's research areas. Concept plans based on the state of the science in each area are developed and reviewed within these committees prior to initiation of the full HPTN and NIH review processes. The SCs and WGs are the:

- Adolescents at Risk Science Committee
- Women at Risk Science Committee
- Sexual and Gender Minority Science Committee
- Substance Use Science Committee
- Socio-Behavioral and Structural Working Group
- Biomedical Sciences Working Group
- Community Working Group
- Ethics Working Group

Descriptions of all SCs and WGs are included in Sections 4.1 and 4.2.

In addition, the HPTN has four key network oversight committees to assure scientific quality:

- Science Review Committee (SRC)
- Study Monitoring Committees (SMC)
- Manuscript Review Committee (MRC)
- Performance Evaluation Committee (PEC)

These committees are described in Section 4.3.

HPTN research is conducted primarily through the DAIDS Clinical Trials Units (CTUs) with a network of clinical research sites (CRSs) throughout the world. Investigators and other representatives of these CTUs, including community representatives, participate in HPTN framework activities. Some studies in the HPTN will require the participation of populations and settings beyond the traditional DAIDS-funded sites. As needed, new sites are added to meet the HPTN's research needs. Further details of the composition and functions of the operational components of the HPTN are presented in Section 3 and throughout this document.

1.4. Governmental Organizations Involved in HPTN Research

The HPTN is sponsored by the NIH and functions in close collaboration with NIAID and the institutes and offices comprising the NIH Consortium, particularly NIDA, NIMH, NICHD and OAR. In addition, the Network must work effectively with governmental regulatory agencies including the US Food and Drug Administration (FDA), the US Office of Human Research Protection (OHRP), as well as other governmental agencies such as the US Centers for Disease Control and Prevention (CDC), Health Resources and Services Administration (HRSA), and the US President's Emergency Plan for AIDS Relief (PEPFAR), and similar agencies in other countries where HPTN research is conducted.

1.4.1. National Institute of Allergy and Infectious Diseases (NIAID)

NIAID and co-sponsors have substantial scientific and programmatic involvement in the HPTN through technical assistance, advice, and coordination. The role of the NIAID staff is to assist and facilitate, not to direct the research activities.

Further information concerning NIAID may be found on its website.

1.4.1.1. Division of AIDS (DAIDS)

The DAIDS staff (see Figure 1-2), within NIAID, are members of the HPTN study teams and governing committees. They also facilitate the communication between other partners, such as other funding agencies, pharmaceutical companies, the US FDA and other regulatory authorities, and HPTN leadership.

When a pharmaceutical collaborator provides an investigational agent to DAIDS, a Clinical Trials Agreement (CTA) is negotiated describing respective responsibilities and rights. The agreement includes, but is not limited to, Investigational New Drug (IND) application sponsorship, safety and data monitoring, and access to data. In general, terms in the CTA between DAIDS and the pharmaceutical collaborator covering data access and data sharing are shared with the HPTN Executive Committee (EC) and conform to HPTN policies. It is possible that a CTA may be between the HPTN and the collaborator (see Section 23).

DAIDS has the option to file an IND for study products evaluated in HPTN studies or defer to the pharmaceutical partner. Appropriate DAIDS staff advise the investigators on behalf of NIH on the specific regulatory requirements for IND sponsorship. In situations where DAIDS is the IND sponsor, they may also assemble, review, and submit the required regulatory documents to the US FDA.

For all HPTN protocols, a DAIDS Medical Officer (MO) is assigned. When a protocol is sponsored by a collaborating institution or research group (i.e., NIDA or NIMH), monitoring activities may be conducted by an appropriate medical representative(s).

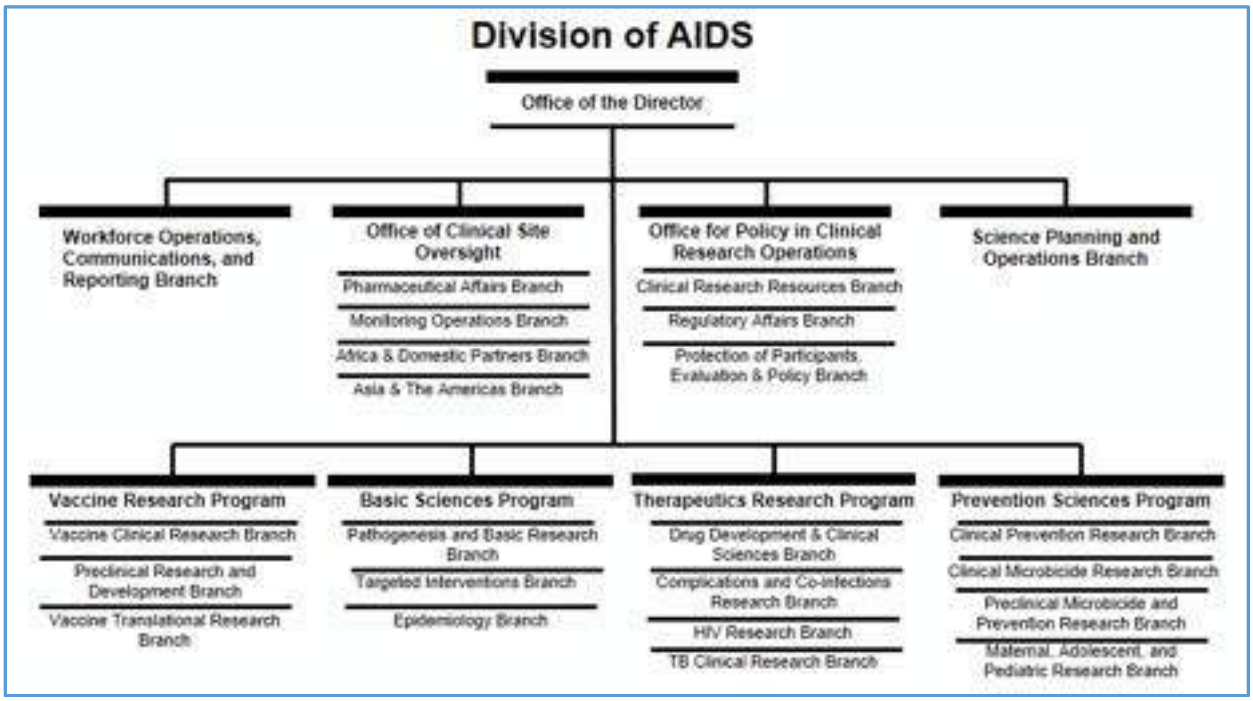
To provide consistent reporting of Serious Adverse Events (SAEs) across clinical trials groups, DAIDS established policies and procedures in the most recent version of the Manual for Expedited Reporting of Adverse Events to DAIDS. DAIDS provides ongoing regulatory training and start-up training at US and non-US sites.

DAIDS Pharmaceutical Affairs Branch (PAB) Pharmacists participate on HPTN protocol teams, develop the pharmacy section of the protocol and the Pharmacy Study-Specific Procedures (SSP) Manual for each protocol, and coordinate study product management activities. They also interact with pharmaceutical companies, HPTN protocol teams, and HPTN LOC to ensure adequate and timely supply of products.

Please refer to Section 23 for responsibilities of the HPTN Pharmacist when DAIDS is not the regulatory sponsor.

General information on DAIDS may be found on the DAIDS website.

Figure 1-2 DAIDS Organizational Structure



1.4.1.1.1. Prevention Sciences Program

The Prevention Sciences Program (PSP) within DAIDS is responsible for the HPTN. A PSP MO participates on each protocol team. During study implementation, the PSP MO monitors the safety of the intervention(s) and is provided with interim and final reports.

In some instances, the PSP members may interact directly with the CTUs regarding follow-up of specific clinical and/or regulatory issues, but will collaborate with the Office of Clinical Site Oversight (OCSO) in their interactions with sites. OCSO is responsible for oversight of clinical sites (see Section 1.4.1.1.4).

1.4.1.1.2. Office for Policy in Clinical Research Operations

The mission of the Office for Policy in Clinical Research Operations (OPCRO) is to ensure that DAIDS-sponsored clinical research:

- Complies with applicable regulations, guidance, and policies
- Develops CTAs with pharmaceutical companies
- Meets established standards of quality and integrity to protect study participants

OPCRO provides a variety of clinical trials resources to DAIDS scientists further enabling and sharpening focus on the science and HIV/AIDS research missions. OPCRO staff are responsible for quality assurance and procedural oversight of DAIDS clinical trials.

1.4.1.1.3. Regulatory Affairs Branch

The Protocol Registration Team (PRT) in the Regulatory Affairs Branch (RAB) manages the DAIDS Protocol Registration (PR) process to ensure that all sites conduct DAIDS clinical research according to all applicable regulations and DAIDS policies.

1.4.1.1.4. Office of Clinical Site Oversight

The Office of Clinical Site Oversight (OCSO) facilitates the clinical research of the DAIDS scientific programs by overseeing clinical sites associated with the NIAID-sponsored HIV/AIDS clinical trials networks. As such, it performs the following key functions:

- Oversees grants of CTUs and CRSs that participate in the HIV/AIDS clinical trials networks
- Establishes new clinical sites around the world
- Evaluates and monitors the administration, finances, and performance of existing clinical sites
- Works with other government agencies, other institutes at the NIH, and the HIV/AIDS clinical trials networks
- Verifies that optimal safeguards are employed for participant safety and that high-quality research practices are utilized
- Oversees the DAIDS clinical research standards, policies and procedures that are used by clinical sites
- Monitors enrollment of underserved populations and ensuring community representation
- Organizes and/or participates in program and regional meetings as necessary
- Oversees the clinical site monitoring group contract, reviews monitoring reports and requires site staff to respond to issues identified in the reports (see Section 15)

1.4.1.1.5. Pharmaceutical Affairs Branch

The Pharmaceutical Affairs Branch (PAB) in OCSO:

- Provide expertise on all pharmaceutical aspects of protocol development and conduct
- Coordinate and oversee the supply, packaging, blinding and distribution of study products for DAIDS-supported clinical trials
- Establish processes, provide oversight and monitor adherence to quality assurance standards and standard operating procedures for all pharmacy and product-related issues at sites

When DAIDS is not the regulatory sponsor, please refer to Section 23 for responsibilities of the HPTN Pharmacist.

1.4.1.1.6. Workforce Operations, Communications, and Reporting Branch and Science Planning and Operations Branch

The DAIDS Workforce Operations, Communications, and Reporting Branch (WOCRB) and the Science Planning and Operations Branch (SPOB) within the Office of the Director coordinate HIV media relations for DAIDS, including central support for community education on HIV. The WOCRB also conducts various training activities. For an overview, please refer to https://www.niaid.nih.gov/about/division-aids-overview.

1.4.2. DAIDS Contractors

The following typically pertains when DAIDS is the regulatory sponsor.

1.4.2.1. Regulatory Support Center

The Regulatory Support Center (RSC), under contract to DAIDS, provides regulatory support to the HPTN for all DAIDS-sponsored US and non-US clinical trials. This support consists of:

- Preparation and maintenance of INDs, including annual reports, responses to US FDA comments, and IND amendments
- Preparation of New Drug Applications (NDAs), including providing responses to US FDA comments
- Protocol and informed consent review for regulatory compliance
- Protocol registration
- Receipt and management of expedited adverse event (EAE) reports
- Preparation and submission of IND Safety Reports to the US FDA
- Preparation of CTAs
- Distribution and management of Investigator Brochures
- Distribution and management of safety information
- Tracking of regulatory records

1.4.2.2. Clinical Research Products Management Center

The Clinical Research Products Management Center (CRPMC) supports the HIV/AIDS clinical trials networks. As a contractor of DAIDS, the CRPMC centrally manages the receipt, storage, and distribution of study products for all studies for which DAIDS is the regulatory sponsor (both IND and non-IND studies). See the DAIDS SCORE Manual for further information.

1.4.2.3. Clinical Site Monitor

DAIDS contracts with a Clinical Site Monitor (CSM) to evaluate the CRSs for adherence to Good Clinical Practice (GCP), regulatory compliance, accurate protocol implementation, internal quality assurance, HIV testing and counseling, and study product accountability.

CSM staff visit CTUs and CRSs periodically to review study documentation for selected protocols, review regulatory documents, audit pharmacies, and document error resolution per assignments received from DAIDS. Further details on monitoring by the CSM are included in Section 15.

1.4.3. NIAID Committees

1.4.3.1. NIAID DAIDS Prevention Science Review Committee

The Prevention Science Review Committee (PSRC) is an internal, multidisciplinary DAIDS committee. Draft HPTN protocols must be reviewed and approved by the PSRC. Protocols are submitted for review to the DAIDS MO by the HPTN LOC on behalf of the protocol teams.

Protocols are reviewed by the full PSRC. Protocol amendments may be reviewed by the PSRC Chair, a subgroup of the Committee, or the full Committee as determined by the PSRC Chair and DAIDS MO or Program Officer.

The PSRC evaluates protocols relative to:

- The soundness of study design
- The NIAID and other co-sponsoring institutes' research agendas and other NIH clinical studies
- Participant safety
- Compliance with US federal regulations
- Study oversight and monitoring
- Feasibility of timely completion
- When appropriate, plans for interim monitoring and analysis

The PSRC Chair or a designee returns comments and recommendations to the group within 10 business days after review. If a protocol is disapproved, NIAID will not provide study products or permit expenditure of NIH funds for the proposed investigation.

The PSRC constitutes DAIDS central scientific and ethical review for HPTN protocols. PSRC members are:

- PSRC Chair
- PSP Chief or designee
- Preclinical Research Development Branch, Chief or designee
- Vaccine Clinical Research Branch, Chief or designee
- Biostatistics Research Branch representative
- PAB representative
- RAB representative
- PSRC Coordinator
- Primary reviewer(s), as determined for each protocol by the PSRC Chair

1.4.3.2. Multinational Data and Safety Monitoring Board

The NIAID DAIDS Multinational Data and Safety Monitoring Boards (MDSMB or simply DSMB) play a crucial role in ensuring the safety and welfare of participants enrolled in randomized, comparative efficacy (Phase IIb and III) trials. The "convening authority" for DSMBs is NIAID leadership who has the authority and responsibility to act upon the recommendations of the DSMBs. In unusual situations, there may be a different "convening authority".

In general, DSMBs will review safety, efficacy, and overall study conduct as specified in the protocol and/or protocol monitoring plan for each trial. Trials are assigned by DAIDS to DSMBs according to the type of trial (i.e., therapeutics, prevention, vaccine) and geographic location of performance sites.

It is a fundamental principle of blinded clinical trials monitoring that access to the accumulating endpoint data should be limited to as small a group as possible. Limiting the access to blinded results to the DSMB relieves the investigator of the burden of deciding whether it is ethical to continue to randomize participants and helps protect the study from bias in participant evaluation. For these reasons, meetings of the DSMB are closed to the public. However, protocol team members and in particular the Protocol Chair(s) and statistician(s) are typically asked to attend open portions of the DSMB meetings in person to discuss study progress and respond to DSMB questions. See Section 15.8 for additional details.

The membership of the DSMB reflects the disciplines and medical specialties necessary to interpret the data from trials conducted by the HPTN. Members are completely independent of the studies being reviewed and have no financial interest in the outcomes of the studies reviewed. Members include experts in the fields of biostatistics and medical ethics, in addition to clinicians and other scientists who are expert in the transmission of HIV and its associated disorders. *Ad hoc* members may be appointed for specific protocols as circumstances require and to ensure appropriate country representation for non-US studies. Appointments are made by NIAID. At periodic intervals during each trial, the DSMB:

- Reviews the general progress of the study and assists DAIDS and the HPTN in resolving any problems that may arise
- Examines the accumulated endpoint and safety data in order to make recommendations to DAIDS and the HPTN EC concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse effects of the interventions under study

Additional information about NIAID DAIDS DSMBs can be found on the NIAID DAIDS DSMB SOP webpage.

1.4.4. US Food and Drug Administration

In its capacity as a regulatory agency of the US federal government, the US FDA acts as a close advisor and important liaison to the NIAID in the development and monitoring of studies of investigational products. Since many of the clinical trials conducted by the HPTN are performed under an IND, the US FDA has direct responsibility for reviewing and approving protocols and amendments that guide HPTN IND trials conducted in the US and at non-US sites. In many HPTN trials, DAIDS holds the IND and thus is responsible for working directly with the US FDA. Additionally, in-country agencies may also have authority over HPTN trials performed in non-US settings.

The US FDA also receives and reviews copies of serious adverse event reports that meet the criteria of Title 21, Code of Federal Regulations (CFR) §312.56. As part of its role in new product review, the US FDA may conduct audits of HPTN studies.

1.4.5. Department of Health and Human Services

1.4.5.1. Office for Human Research Protections

The US Office for Human Research Protections (OHRP) fulfills responsibilities set forth in the Public Health Service Act, including monitoring compliance relative to Department of Health and Human Services (DHHS) regulations for the protection of human subjects in research supported by any component of the DHHS. OHRP is also responsible for establishing criteria for and negotiation of Assurances of Compliance with institutions engaged in research involving human subjects supported by the DHHS. The HPTN and its protocols operate in full compliance with the regulations and guidelines of OHRP.

1.4.5.2. US Office for Civil Rights

For studies conducted in US settings at institutions that are covered entities, compliance with the Health Insurance Portability and Accountability Act (HIPAA) must be assured. Each institution is responsible for ensuring its own compliance. For non-US institutions, each institution is responsible for determining whether it is a covered entity under HIPAA, and, if so, each covered entity is responsible for ensuring compliance with this requirement, as set forth in Title 45 CFR §160 and §164.

2 HPTN LEADERSHIP

2.1 HPTN Principal Investigators

The HPTN Principal Investigators (PIs) are the leaders of the entire Network and also serve as the PIs of the Leadership and Operations Center (LOC). The PIs are responsible for ensuring the efficient development and implementation of the HPTN research agenda as well as managing the Network and coordinating activities across the three Central Resource groups: the LOC, Laboratory Center (LC), and Statistical and Data Management Center (SDMC).

The chairmanship of the HPTN Executive Committee (EC) will be held by one PI for the first three years (administrative PI), followed by the other PI. The function of the chair is to:

- Coordinate and facilitate HPTN EC responsibilities, including development and implementation of the HPTN research agenda
- Schedule and chair regular and special meetings and conferences calls of the HPTN EC and communicate the decisions and action items to HPTN investigators
- Ensure coordination of Network activities across Central Resources and provide regular and effective communications with the Clinical Trials Unit (CTU)/Clinical Research Site (CRS) Investigators

A special election of the voting members shall be held if it becomes necessary to replace either or both of the Network PIs ahead of schedule. The rotation of the network PIs at three years will start the selection process for the new PIs. This will allow a continuum of leadership that is consistent, yet changing.

2.2 Executive Committee

The HPTN EC, under the direction of the HPTN PIs, with the assistance of the relevant institutes at the United States (US) National Institutes of Health (NIH), sets the research priorities of the HPTN and directs its scientific activities. The HPTN EC:

- Sets the overall HPTN research agenda
- Reviews Scientific Committees (SCs)/Working Groups (WGs) research plans including the review and prioritization of concepts, assess study progress and contingency planning
- Evaluates and recommends the distribution of resources among the different components of the Network
- Recommends to National Institute of Allergy and Infectious Diseases (NIAID) that funds be released for specific protocol implementation
- Approves policies and procedures of the HPTN, including the governing structure and membership of standing committees
- Reviews and approves protocol leadership
- Approves study site selection
- Establishes key standing Network committees (for example, Science Review Committee, Performance Evaluation Committee, Manuscript Review Committee)
- Reviews and resolves site-related issues as needed
- Pursues new partnerships and funding opportunities
- Ensures that community and site representatives' feedback is considered

The HPTN EC, in conjunction with NIH, determines the overall research capacity and capability for the HPTN, as well as the capacity of individual CTUs and CRSs or other sites. With members serving as liaisons to each SC/WG, the HPTN EC will ensure that the specific areas of prevention science addressed by SCs/WGs are effectively coordinated and are aligned with the priority areas. The HPTN EC will delegate the management of certain functions (e.g., protocol review, monitoring the study during implementation) to the oversight committees as described below. The structure and composition of all SCs and WGs is described in Section 4. All committees are ultimately accountable to the HPTN EC.

The HPTN EC conducts conference calls at least monthly and holds in-person (or virtual) meetings at least annually. The table below shows both voting and non-voting membership. A quorum, defined as two-thirds of the voting membership, must be present for key decisions and votes to be taken.

2.2.1 Membership

The HPTN EC membership includes representatives from the LOC, the SDMC, the LC, community, CRS and NIH. Representatives of the CRSs may rotate off the HPTN EC every two years.

When new members are solicited, all CRS nominees will submit a brief biosketch to the HPTN EC administrator or designee. Biosketches for nominees will be compiled, attached to the voting ballot and sent to HPTN EC members. HPTN EC members will be asked to vote for their top two choices, indicating first and second choice. Votes will be collated. If a nominee receives a majority vote, she/he will be elected. If not, the list will be narrowed down to the top three candidates and another vote will take place.

Voting Members	Nonvoting Members
PI (Administrative), Network	Finance Manager, LOC
PI, Network	Deputy Director, LC
Non-US Lead Investigator	Co-Director, LC
Past PI, Network	Associate Director, SDMC
Past Co-PI, Network	HPTN Investigator Representatives
PI, LC	
PI SDMC	
Director, LOC	
Community Representative	
2 Site Representatives	
2 Representatives from NIH	

2.3 HPTN Leadership Group

A subset of the HPTN EC (without the NIH representatives) and members of the Central Resource groups meet routinely to discuss operational and fiscal issues related to the ongoing studies and provide timely feedback to the study teams.

3 HPTN OPERATIONAL COMPONENTS

The following HPTN components are responsible for the operational aspects of the Network and are funded through cooperative agreements with the United States (US) National Institutes of Health (NIH):

- Leadership and Operations Center (LOC)
- Statistical and Data Management Center (SDMC)
- Laboratory Center (LC)
- Clinical Trials Units (CTUs)

3.1 Leadership and Operations Center

The HPTN LOC is responsible for the Network's scientific agenda and plays a key role in all phases of science generation and protocol development and study implementation. LOC staff are responsible for facilitating and managing the scientific agenda and research operations of the HPTN, including research plan development, concept and protocol review and approval, study conduct and publication/dissemination of results. LOC staff are also responsible for scientific, technical, logistical and administrative support and management of all Network activities.

Staff from the LOC work closely with the HPTN leadership; protocol teams; staff from the SDMC, LC, and CTUs/CRSs; Division of AIDS (DAIDS) and NIH; the SCs and WGs; and CTU/CRS community programs on all aspects of the HPTN research program, as described in Section 3.1.1. FHI 360 is the LOC for the HPTN.

3.1.1 LOC Responsibilities

The LOC's specific operational responsibilities include but are not limited to:

- Leadership and Governance
  - Convene and chair the HPTN Executive Committee (EC)
  - Serve on and provide technical, scientific, logistical and administrative support for the HPTN EC, SCs, WGs, Study Monitoring Committees (SMC), Science Review Committees (SRC), Manuscript Review Committee (MRC), and Performance Evaluation Committee (PEC)
  - Oversee the HPTN Scholars Program
  - Organize and convene Network-wide meetings, including the HPTN Annual Meeting
  - Produce regular and *ad hoc* Network reports (e.g., Study Operations Reports, Performance Evaluation Reports)
  - Review, revise and retain key Network policies and procedures
  - Maintain version control of key Network policies and procedures
- Research Management
  - Appoint an LOC Clinical Research Manager (CRM) to each protocol
  - Participate in and coordinate support for Clinical Management Committees (CMCs) and other protocol-related groups
  - Lead the study-specific site selection and activation processes in accordance with Section 20 and Section 10, respectively, of the HPTN Manual of Operations (MOP)

- Collaborate with Protocol Chair and protocol team members to lead in the development of protocols, letters of amendment, clarification memos, Study-Specific Procedures (SSP) manuals, and other study implementation materials
- Coordinate submission of protocols and modifications to the HPTN and NIH/DAIDS review groups and lead in the development of response to any review comments
- Conduct pre-study operational walk-throughs with study staff, in collaboration with the SDMC and LC, if needed
- Organize and coordinate development of materials and study-specific training, as required in collaboration with the SDMC, the LC, and CRSs
- Provide guidance and offer to review materials developed by CRSs for DAIDS protocol registration and study-specific site activation and/or study implementation, in collaboration with the SDMC and the LC
- Facilitate communication between study CRSs, the SDMC, the LC and DAIDS entities
- Coordinate study-related submissions to the HPTN single IRB and facilitate communication between CTU/CRSs and the single IRB
- Develop and maintain study eTMF as needed

- Quality Management
  - Support the establishment and implementation of reliable and efficient Quality Control (QC) and Quality Assurance (QA) processes and good documentation practices for the delivery of quality services, in compliance with applicable regulations
  - Support the development and implementation of effective monitoring and quality control systems for process performance; implementing appropriate quality and process improvements, variability reduction, and innovation; and ensuring the execution of quality study management activities

- Assistance to CTUs and CRSs with Study Conduct
  - Provide guidance to CTUs/CRSs in interpretation of study protocols and regulatory requirements, as well as in achieving protocol-specified targets for accrual and retention of study participants
  - Respond to inquiries from CTU/CRS investigators and DAIDS staff concerning procedures and implementation of HPTN studies in collaboration with the SDMC and LC
  - Assess performance of CTUs/CRSs during study implementation and report results to the EC and DAIDS through site assessment visits and regular communication with and reporting from CRSs

- Community Programs
  - Facilitate broad community involvement in all Network activities (Section 5)
  - Assist CTUs/CRSs in developing and implementing community education efforts associated with HIV prevention trials

- Communication and Information Dissemination
  - Develop and maintain the HPTN website and social media accounts, including relevant information on CTUs/CRSs and HPTN studies
  - Develop and maintain alias lists and directories for the HPTN communication system
  - Maintain databases that provide key Network information to HPTN leadership, DAIDS and committees
  - Assist protocol teams by developing study-specific branding and recruitment/retention materials
  - Collaborate with protocol teams in manuscript development and dissemination of study results
  - Coordinate HPTN dissemination of study results in collaboration with NIH and other partners
  - Disseminate key Network policies and procedures to Network members
  - Support the NIAID Clinical Research Management System by maintaining compatible databases and web services systems and ensuring that current information and documents are provided in real time
- Financial Management and Support
  - Evaluate the adequacy of financial resources provided to CTUs/CRSs, as necessary
  - Assist NIH Grants Management Branch (GMB), DAIDS Prevention Sciences Program (PSP), Office of Clinical Site Oversight (OCSO), and HPTN leadership in analysis of CTU/CRS funding requests and all other Network financial matters
  - Provide guidance to CTUs/CRSs in preparing site-specific budgets as necessary, including provision of site-specific budget templates
  - Develop an annual funding plan based on the needs of the scientific agenda implemented during the funding cycle
  - Develop, negotiate, and execute agreements with participating CRSs for study-specific activation
- Product Management and Support (in certain cases – see Section 23)

3.2 Statistical and Data Management Center

The HPTN SDMC is responsible for helping to shape the network's scientific agenda and plays a key role in all phases of science generation, protocol development and study implementation. The SDMC is responsible for all aspects of data collection, reporting, and statistical analysis for HPTN trials following the principles of Good Clinical Data Management Practices (GCDMP) as well as Good Clinical Practices (GCP). The SDMC manages the HPTN study databases and guides protocol teams on both the statistical components of study design and the collection and analyses of study data. The SDMC for the HPTN is located at the Fred Hutchinson Cancer Center (FHCC, Fred Hutch) in Seattle, Washington and is comprised of faculty statisticians in the Vaccine and Infectious Disease Division (VIDD) and the Statistical Center for HIV/AIDS Research and Prevention (SCHARP).

3.2.1 SDMC Responsibilities

The SDMC's specific operational responsibilities, by functional area, include but are not limited to:

- Leadership and Governance
  - Serve on the EC, LG, SCs, WGs, SRC, PEC, SMCs, PPG, and MRC
  - Convene and chair study SMCs
  - Provide reports to the EC, SMC, PEC and DAIDS on the status of CTU/CRS performance, including participant data management quality, accrual, retention, specimen collection, and adherence
- Scientific Leadership and Statistical Support
  - Appoint a SDMC faculty statistician to serve as lead protocol statistician for each HPTN protocol
  - Develop appropriate statistical methodologies for the conduct and analysis of HPTN trials including modelling if needed
  - Develop statistical and data management components of HPTN concept plans and protocols, including statistical analysis plans (SAP), interim monitoring plans and data management plans (DMP)
  - Provide regular reporting to the protocol team and HPTN leadership to facilitate monitoring of CRS data management quality, recruitment, retention, and adherence
  - Contribute to assessments of CRS performance regarding data management quality, enrollment, retention, and adherence to Network leadership and to the PEC
  - Develop and implement randomization and treatment allocation schemes for HPTN protocols
  - Conduct data analyses and generate open and closed reports for SMC reviews; chair and participate in SMC reviews
  - Conduct data analyses and generate open and closed reports for the Data and Safety Monitoring Board (DSMB); participate in the presentation and interpretation of those reports to the DSMB
  - Contribute to abstract, presentation and manuscript preparation
  - Provide data tables to fulfill Investigational New Drug (IND) reporting requirements
  - Provide study data and reporting to pharmaceutical partners under the terms of the Clinical Trials Agreement (CTA)
  - Provide needed information to the DAIDS Clinical Site Monitor to assist with site-monitoring visits
- Clinical Data Management
  - Design and maintain the study databases
  - Develop and implement centralized data management, QC, and validation systems
  - Collaborate with protocol team members in developing protocols, data-related SSP manuals and other study materials

- Lead the development of study electronic Case Report Forms (eCRFs) or other means of data capture (e.g., computerized questionnaires) and procedures for collecting data from CTUs/CRSs
- Conduct operational walkthroughs of CRFs and other study materials and procedures, with LOC and LC, as needed
- Conduct data collection and management training for CTU/CRS staff
- Provide support to CTU/CRS staff regarding data collection and management during study operations
- Identify problems in data collection and propose remedial changes in study procedures to CTU/CRS or protocol team
- Provide timely data management performance reports to each CTU/CRS and to the PEC
- Review CTA when study involves investigational product
- Create and post deidentified datasets approximately two years after last study visit

- Laboratory Data Management
  - Provide operational assistance to CTUs/CRSs and the LC in regard to Laboratory Data Management System (LDMS) reports of LDMS entry errors and discrepancies between LDMS and study databases
  - Provide data transfer plans for laboratory results data submitted by the LC and other central laboratories
  - Receive LC data; assure quality and matching of laboratory data to study data
  - Select specimens for QA testing by the LC
  - Work with LC to provide data and adjudication tools if an HPTN Endpoint Adjudication Committee (EAC) is convened (Section 13.14) and capture the endpoint adjudication results used in the analysis

- Information Technology Support
  - Develop and maintain hardware and software systems and related procedures for transmitting, receiving, processing, analyzing, and storing study data and meeting reporting requirements
  - Assist CTUs/CRSs with data collection and management systems
  - Provide an accrual information data feed of participant level information to the NIAID Clinical Research Management System (CRMS)

- Clinical Safety Data Management
  - Provide review of relevant laboratory and safety data for accuracy, consistency, and completeness
  - Provide QC and coding of adverse event (AE) and concomitant medications data
  - Verify completeness of expedited adverse event reporting through reconciliation of AEs reported to DAIDS as EAEs and those reported to the SDMC
  - For studies of products not approved by the FDA for any indication, the SDMC may engage one or more Independent Safety Reviewers, who, in addition to the DAIDS MO, will review monthly reports of safety data (see Section 14)

3.3 Laboratory Center

The HPTN LC is responsible for helping to shape the network's scientific agenda and plays a key role in all phases of science generation, protocol development and study implementation. The LC oversees all laboratory activities including specimen collection, testing, and reporting of results for testing performed at HPTN CRSs. The HPTN LC also performs QA/QC testing and specialized testing for HPTN protocols to advance the scientific agenda of the network. The LC evaluates and validates assays for use in HPTN protocols and develops novel assays and laboratory methods to achieve study objectives. The LC assists in the development and quality assessment of CRSs, including building laboratory expertise and capacity at non-US CRSs, primarily in resource-limited settings. The LC plays a leadership role in cross-network activities by updating, harmonizing and streamlining laboratory procedures used in other networks and groups. The LC is centralized at the Johns Hopkins University School of Medicine in Baltimore, Maryland, USA.

3.3.1 Laboratory Center Composition

The HPTN LC includes an Administrative Core, a Protocol Operations Core, five Laboratory Cores, two Working Groups, and Consultants. The Administrative Core is responsible for administrative, regulatory, and financial operations. The Quality Assurance/Quality Control (Protocol Operations Core) is responsible for coordinating laboratory-related activities in HPTN protocols and for providing support and oversight to study sites. The Laboratory Cores are supported by Clinical Laboratories, Research Laboratories, and laboratories that perform both clinical and research testing. This includes QA testing, protocol testing, testing for ancillary studies, and laboratory-based research related to HIV prevention. The Laboratory Cores also develop, evaluate, and validate assays relevant to the HPTN research agenda. The HPTN LC includes Key Personnel who oversee activities in HPTN LC laboratories, lead ancillary studies and research sub-studies, and provide laboratory expertise to the HPTN. Working groups help guide the HPTN LC in two key areas: POCT and Remote Technologies, and Early Product Development. Consultants provide additional expertise in Virology, Pharmacology, and other areas, as needed.

3.3.2 Laboratory Center Responsibilities

The responsibilities of the LC include but are not limited to:

- Serve on the HPTN EC, LG, SCs, WGs, SRC, PEC, SMC, PPG, and CMC
- Participate in management of the HPTN and establishment of the HPTN scientific agenda
- Provide laboratory-based scientific leadership and consultation to the HPTN
- Participate in development of HPTN protocols
- Review and define appropriate laboratory testing methods and materials to be used in HPTN studies
- Participate in the review of concepts, ancillary studies, and other related study proposals
- Release laboratory data from HPTN studies, after approval by HPTN Leadership, for presentation, publication, or ancillary studies. The LC will provide input about feasibility and regulatory laboratory-related issues as needed and will inform the HPTN EC if there are any issues relevant to release of laboratory data
- Release/use of specimens, after approval of HPTN Leadership, for ancillary studies or other work proposed by investigators outside of the HPTN LC, or for work beyond what is specified in the protocol.

- Provide input about laboratory-related regulatory issues related to data release and inform the HPTN EC if there are any issues relevant to release of laboratory specimens
- Provide each protocol with an HPTN LC QA/QC Coordinator (Protocol Specialist) and one or more HPTN LC investigator(s)
- Draft the laboratory sections of protocols and the Laboratory SSP Manual
- Provide training for CTU and CRS laboratories, as needed, for specimen tracking (using the Laboratory Data Management System [LDMS]), processing, testing, storage, and shipping; provide training for specialized testing, as appropriate
- Provide support to study teams as laboratory issues arise during design and implementation of protocols
- Assist when necessary with the design, implementation, and/or monitoring of QA procedures for local laboratory testing
- Report on local laboratory proficiency to the CTUs/CRSs
- Provide a study specific specimen management plan (processing, storage and retrieval guidelines) for specimens at both US and non-US CRSs; this information is often provided in the Laboratory SSP Manual
- Perform and/or coordinate the performance of protocol-specified laboratory testing in support of HPTN studies
- Use the LDMS to track the disposition of samples sent to the LC, including distribution to repository contractors or any other HPTN collaborator
- Use the LDMS and other systems to facilitate sample management and communication of test results between the LC, SDMC, and CTU/CRS investigators
- Respond to inquiries from CTU/CRS investigators, the LOC, the SDMC, or DAIDS staff related to laboratory issues
- Collaborate with other DAIDS-sponsored HIV clinical trial networks to harmonize laboratory methods and maximize the efficiency of protocol development, implementation, and analysis
- Provide guidance when necessary for specimen processing, assay performance and specimen-related result reporting for testing performed at CTU/CRS laboratories; this guidance is often provided during study training and site visits.
- Provide training and support in laboratory quality assessment, assay performance, and specimen shipping procedures at CTU/CRS laboratories; this is often provided during study training and site visits.
- Ensure regulatory compliance for LC activities as required for IND-enabling studies
- Maintain an LC Quality Management Plan for Clinical Laboratories and Research Laboratories within the LC
- Work with the LOC, SDMC and DAIDS on the provision of materials required for trial master file documents
- Provide opportunities to enhance expertise and build infrastructure through technology transfer, particularly to non-US laboratories
- Perform novel and routine immunologic, virologic, pharmacologic and other testing for HPTN protocols

- Work with DAIDS, the Office of HIV/AIDS Network Coordination (HANC), cross-network groups, and quality assessment partners to harmonize laboratory procedures across DAIDS-sponsored networks, whenever feasible and appropriate (see Section 13)
- Develop QA/QC and training tools and materials for use in US and non-US laboratories across DAIDS-sponsored networks
- Develop, standardize, or evaluate laboratory assays relevant to HIV prevention, with particular emphasis on assays that can be used in HPTN trials. These may include (but are not limited to) assays that:
    - Determine HIV infection status
    - Screen for and confirm sexually transmitted infections
    - Detect and/or quantify antiretroviral drugs
    - Measure hematologic and/or biochemical toxicities
    - Characterize HIV in study samples
    - Diagnose or characterize other related pathogens (e.g., hepatitis viruses, HSV-2)
    - Evaluate HIV incidence
    - Characterize the immune response to HIV infection
    - Detect drugs of abuse
    - Transfer LC test data to the SDMC including collaboration with SDMC on communication of testing plans, data transfer agreements, etc.
- Participate in preparation of presentations and publications that report results from HPTN studies
- Present and publish work performed at the LC, including work related to assay development/evaluation and pathogenesis-based studies

The LC staff maintains regular communication with HPTN CRSs, primarily through the CTU/CRS Principal Investigators (PIs) and laboratory managers and confirms that CRSs are able to do study-required laboratory procedures and tests prior to site activation. The LC staff also visit CRSs, as necessary, to assess laboratory facilities and procedures.

HPTN LC International QA/QC Coordinators (protocol specialists) based outside of the US. The responsibilities of these individuals include:

- Review and monitor the technical quality of all protocol test results
- Implement and monitor appropriate QA/QC functions of pre-analytical functions (specimen drawing, labeling, processing, test requisitions), analytical functions (testing), and post-analytic functions (test reporting, specimen storage, shipping) to assure validity of results and chain of custody of specimens
- Design and help implement appropriate policies and procedures to meet HPTN, FDA and CAP guidelines for protocol testing
- Train technologists in specific test procedures and QA procedures to be used in protocol testing
- Assess competency of technologists performing protocol testing
- Provide expertise in troubleshooting general laboratory problems or specific assay problems

- Train personnel in how to establish normal range values and write standard operating procedures (SOPs), then subsequently assure that SOPs and normal ranges are established
- Rarely, it may be necessary for a member of the LC to perform bench work at CRSs

3.4 Clinical Trials Units/Clinical Research Sites

HPTN research requires access to populations for study participation and the availability of experienced staff, adequate space, and equipped facilities. HPTN studies are typically conducted by staff of NIH-funded CTUs, which will include an administrative component and one or more clinical research sites (CRS). A CTU may have multiple CRSs in the US, outside the US, or both. The US National Institute of Allergy and Infectious Diseases (NIAID) provides resources to fund research infrastructure and study conduct through cooperative agreements with the primary CTU grantee through the LOC.

CRSs in certain circumstances may need to add additional locations (AL). With justification from the CTU PI and support from the Network leadership group, DAIDS will consider requests for addition of AL if 1) it does not compromise safety of study participants and integrity of the study and 2) it is cost-effective when considering transportation costs, staff time and other resources. Sufficient resources (personnel, supplies and fiscal) must be available at the CTU to provide to both the CRS and AL for appropriate conduct of any study-related procedures. Accrual at AL will be attributed to the CRS.

CTU/CRS investigators and staff participate in the development and implementation of the research agenda, including leadership, concept and protocol development, participant recruitment and retention, intervention delivery, data collection and maintenance, and results reporting and publication.

3.4.1 CTU Investigators

Active participation of CTU investigators is critical to the HPTN scientific mission. With regard to research conduct, investigators may fulfill one or more roles. These are described below.

3.4.1.1 CTU Principal Investigators

The CTU PI is the individual with legal and financial responsibility for a CTU cooperative agreement with NIAID. The institution that was awarded the cooperative agreement is considered the CTU administrative site. CTU investigators are expected to contribute to the HPTN scientific mission from initiation of study concepts through protocol development, implementation, and reporting of study findings in scientific reports, presentations, and manuscripts of studies in which their CRSs are participating. The CTU PI may delegate responsibilities to other investigators affiliated with the CTU but is expected to play a leadership role for the CTU and the Network.

Specifically, CTU PI responsibilities include but not limited to:

- Execution of the Network research agenda
- Coordination and collaboration with the Leadership Group (LG) to ensure performance monitoring and evaluation of CRSs
- Knowledge, acceptance and compliance by all CTU/CRS component parts with the policies, procedures and bylaws of the HPTN policies and procedures for the collection, recording, storage and reporting of clinical trial data, sharing of research data and research resources, the research priorities of the HPTN and performance standards established by the HPTN

- Ensuring that the CTU/CRS has investigators and appropriately qualified staff with demonstrated expertise in conducting HIV/AIDS multi-center clinical trials
- Ensuring implementation of clearly defined organizational and communication plans and SOPs to ensure close supervision and oversight of the day-to-day activities of the CRS (and protocol-specific (PS) sites, if applicable)
- The receipt and appropriate administration of core funding to establish and maintain a minimal level of clinical research activities
- The receipt and appropriate administration of protocol funding provided by either NIAID or the HPTN. The CTU/CRS PIs will ensure that timely and accurate financial reports for all CTU/CRS component parts are provided to the NIAID and the HPTN. This information must be part of the annual progress report, or as requested, to NIAID and sent to the LOC
- Ensuring compliance with all Federal regulations for human subjects, investigational agents and devices, and NIH and NIAID policies and procedures. HPTN-sponsored clinical research cannot be initiated at any CRS without prior approval by NIAID. All CRS(s) are also required to complete Protocol Registration for all clinical protocols in accordance with current NIAID policy and procedures prior to study initiation
- Ensuring compliance with the NIAID and HPTN standards
- Developing and implementing strategies at each CRS (and PS sites, if applicable) for the recruitment, screening, enrollment, retention and long-term follow-up of study participants appropriate to the conduct of the proposed research
- Ensuring that the CTU/CRS develops, implements, and oversees a comprehensive Quality Management Plan for all parts of the CTU/CRS in order to continually assess the quality of the research records and activities to ensure compliance with all Federal regulations, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, and NIH policies regarding participant safety, data completeness, accuracy, and quality assurance
- Ensuring cooperation with the NIAID Clinical Site Monitoring/Auditing representatives, and any other NIAID authorized groups. The purpose will include but not be limited to the review of research records and activities to verify compliance with protocol requirements, all applicable US Federal regulations, ICH GCP guidelines, and NIH policies on participant safety, data completeness and accuracy, and quality control. All performance problems identified through clinical monitoring must be evaluated in a timely manner and a plan for resolution developed, implemented, and documented, with emphasis on ensuring that the issue should not recur
- Implementation of a plan to achieve meaningful community partnership in CTU/CRS activities. This must include one or more CABs to represent the local population(s) impacted by HIV/AIDS. The CTU/CRS must have procedures to ensure the community is engaged in the research process; provide financial and technical assistance from appropriately trained, culturally sensitive and experienced staff to support CAB activities and training; foster a partnership between researchers and the community, including the sharing of research results with the community, and develop ways to assess these efforts
- Compliance with all adverse event reporting requirements designated by the NIAID and the HPTN, including, but not limited to the established policies and procedures delineated in the Manual for Expedited Reporting of Adverse Events to DAIDS

- Ensuring that the CTU/CRS provides information requested by NIAID or the HPTN in a timely manner. In addition to clinical trial data, routine and *ad hoc* reports may be required. These reports may include, but are not limited to, participant recruitment and retention rates, summary demographic profiles of study participants, timeliness and completeness of all data, completeness and quality of laboratory data, and administrative and financial reports
- Ensuring effective leadership, clear lines of authority, strong communication pathways, and appropriate oversight for all parts of the CTU/CRS

The CTU PI may or may not also serve as the Investigator of Record (IoR) (see Section 3.4.1.3) for HPTN studies.

At the discretion of the CTU PI, some of these responsibilities may be delegated to or shared with other investigators affiliated with the CTU.

3.4.1.2 CRS PI or CRS Leader

The terms "Site PI", "in-country PI" or "Site Leader" are often used — sometimes interchangeably — for investigators present at HPTN CRSs (although the official terms are CRS PI and Site PI). For some CTUs that have a US-based administrative site and CRSs in another country, an onsite counterpart to the CTU PI will have general oversight responsibility at the CRS; this investigator is referred to as the Site PI, in-country PI or Site Leader. These terms are also often used to refer to the onsite lead investigator or IoR for a specific study.

3.4.1.3 Investigator of Record

The IoR is the investigator who is responsible for the conduct of a study at a CRS. The IoR signs the FDA Form 1572 (for studies conducted under an Investigational New Drug application (IND)) or DAIDS Investigator of Record Form (for non-IND studies), as well as the protocol-specific Investigator Signature Page form, and thereby obligates the IoR, and by delegation, all study staff, to conduct the study in accordance with the responsibilities enumerated on the forms and in the list below. An IoR must be onsite. The FDA Form 1572 and the DAIDS Investigator of Record Form, as well as instructions for completing these forms, can be found on the RSC website.

The IoR for an HPTN research study must also:

- Ensure an adequate and well-trained study staff are in place prior to the initiation of an HPTN study
- Organize materials for protocol registration and activation including, signed FDA 1572/IoR Forms, financial disclosures for studies under IND, IRB/EC and other applicable regulatory approvals of protocols and informed consent forms, Delegation of Duties log, Curriculum Vitae (CVs) of CRS staff, finalization of DAIDS and study-specific site SOPs for CRSs, etc.
- Implement study protocols, including the enrollment and follow-up of participants; timely data collection, submission, and cleaning; and local data management
- Conduct the trial in accordance with ICH GCP guidelines, DAIDS procedures, and relevant local and international regulatory requirements
- Delegate the responsibilities of study product management to a licensed/registered Pharmacist of Record (PoR) and provide oversight of the site pharmacy and study product related activities of the protocol per DAIDS requirements
- Report safety information as required by the protocol, GCP/ ICH, DAIDS and responsible IRBs/ECs

- Serve on publication writing teams and take a leadership role in the conceptualization and preparation of manuscripts
- Maintain documentation, during and following a study, according to GCP standards and DAIDS requirements
- Comply with HPTN Conflict of Interest policy for IND studies and the HANC policy for non-IND studies (see Section 8)

3.4.2 CTU or CRS Staff

Specific staffing for each CTU/CRS may vary according to the location and structure of the CTU, number of affiliated CRSs, number and type of studies conducted, and local requirements. Some CTU/CRS staff members may have more general CRS functions, while other staff members have study-specific responsibilities. However, CTU/CRS staff generally includes but is not limited to:

- PI
- In-country or Site Investigator of Record (IoR) (as required and designated by the PI)
- Sub-investigators
- Coordinator (Site, Study, Clinic, as appropriate)
- Administrative/financial staff
- Community program staff
- Site QA/QC staff
- Data Manager
- Laboratory Manager and staff
- Laboratory QA/QC staff
- Research clinicians
- Pharmacists
- Recruitment and retention workers (often outreach workers)

Additional staff may include interviewers, counselors, outreach workers, laboratory technicians, data management staff and computer technicians. Each CRS must have a clear staffing plan for the CRS and each study. The CRS must have SOPs for all key aspects of CRS operations, including clinical, pharmacy and laboratory components (see Section 10 for a list of required SOPs) before activation. Duties and responsibilities for studies must be clearly articulated, delegated, and documented, as specified in the DAIDS SCORE Manual: Clinical Research Site Personnel Qualifications, Training and Responsibilities and Essential Documents**.**

3.4.2.1 CRS Staff Responsibilities

The following are general responsibilities that, collectively, staff of each CRS must fulfill. Satisfactory completion of these responsibilities will be reviewed by DAIDS OCSO and the LOC.

OCSO Requirements:

- Conduct studies according to local and US federal regulations regarding the conduct of research using human subjects, including but not limited to Title 45 CFR §46, §160, and §164 (where applicable), Title 21 CFR §312, ICH GCP, and relevant local regulatory requirements

- Ensure that all required staff have participated in an appropriate research ethics training and GCP training in accordance with NIH and DAIDS policies
- Organize materials for protocol registration and activation including, signed FDA 1572/IoR Forms, IRB/EC approvals of protocols and informed consent forms, CVs of CRS staff, finalization of DAIDS and study-specific site SOPs for CRSs
- Participate in a CRS QA program, DAIDS Clinical Site Monitor site visits and audits as required by the HPTN and DAIDS
- Respond to DAIDS Clinical Site Monitor reports in a timely manner
- Establish and support a CAB/CAG, or other approved process of community consultation, that advises the CRS regarding conduct of HPTN studies
- Assess the need for HIV prevention education; educate local communities in HIV prevention research

HPTN Requirements:

- Adhere to protocol and SSP-specified schedules and procedures, HPTN policies and procedures, and this HPTN MOP
- Submit research protocol and protocol amendments to, and receive approval from all appropriate IRBs/ECs and other applicable regulatory authorities, where necessary; comply with all IRB/EC periodic review requirements; promptly submit any safety reports to the IRB/EC; maintain files of outgoing and incoming correspondence with IRB/EC; and obtain and file current rosters for these committees
- Recruit and enroll eligible participants into HPTN-supported trials, and obtain and document written informed consent
- For studies with investigational products, administer the study products according to the prescribed regimen; provide medical monitoring, collection of specimens, and prompt reporting of adverse events and referral for inter-current events
- Maintain confidentiality of all participant records
- Collect and manage all participant data, including completion of CRFs in the order and manner specified in the SSP manual; review data; transmit to the SDMC central database in a timely manner; respond (within two weeks of original notification) to data queries from the SDMC
- Store study products according to protocol requirements; maintain complete and accurate inventory and accountability records
- Collect, process, label, inventory, ship, and transfer clinical specimens, and perform laboratory assays as specified in protocols. Data and specimens not specified in an approved study protocol may not be collected from study participants without prior review by the protocol team or its designees, written approval from the DAIDS Medical Officer, approval of the local IRB/EC, and written informed consent from the participant
- Attend scheduled meetings and conference calls
- Participate in HPTN committees, teams, and working groups
- Establish and support a CAB/CAG, or other approved process of community consultation, that advises the CRS regarding conduct of HPTN studies
- Facilitate community representative participation on protocol teams, SCs, WGs, and other HPTN organizational components
- Assess the need for HIV prevention education; educate local communities in HIV prevention research

4 HPTN SCIENCE COMMITTEES, WORKING GROUPS AND PROTOCOL TEAMS

Science Committees and Working Groups

The HPTN Executive Committee (EC) has provided general guidelines for the composition of HPTN science committees and working groups. Details are left to the individual groups, and membership of all groups should reflect the diversity of the Network, including representatives from Central Resources Network operational components, Clinical Trials Units (CTUs)/Clinical Research Sites (CRSs), and community representatives as well as scientists and researchers.

4.1 Science Committees

The Science Committees (SCs) contribute to the development of and guide the scientific agenda of the HPTN. The SCs are:

- Adolescents at Risk
- Women at Risk
- Sexual and Gender Minority
- Substance Use

Each SC is at minimum responsible for:

- Assessing research priorities considering new ideas and research opportunities
- Identifying gaps in current HPTN research agenda
- Ensuring inclusion and coordination of assessments utilized in HPTN studies that relate to the focus area or population for the scientific committee
- Reviewing relevant research concepts submitted to the HPTN
- Seeking collaboration across the scientific committees to advance the HPTN research agenda
- Assisting in dissemination of information regarding the HPTN Scientific Research Agenda

The SCs integrate scientific expertise into the development of the research agenda established by the committees through the inclusion of leaders in their respective fields (some who may not be affiliated with the HPTN) as group members.

The SC chair and co-chair attend HPTN EC meetings at least annually (and periodic conference calls as deemed appropriate by the committee) to report on activities of the committees and to discuss research priorities.

Membership

Each SC has a chair and co-chair, appointed by the HPTN EC Chair. The HPTN EC determines the composition of the committee within guidelines established by the HPTN EC. It is recommended that the SC committees have no more than 10 voting members, inclusive of the chairs. Non-voting membership in the SC includes liaisons to the Central Resources, Community Working Group (CWG), Ethics Working Group (EWG), and DAIDS.

4.2 Working Groups

HPTN working groups (WG) are cross-cutting groups that provide expertise to the Network as described below.

4.2.1 Community Working Group and Community Working Group Steering Committee

4.2.1.1 Community Working Group

The purpose of the HPTN Community Working Group (CWG) is to ensure that the principles of community involvement are the foundation of all community engagement activities at each clinical research site (CRS) and to facilitate community participation throughout the research process (concept development, study implementation, results dissemination, and post-trial access to interventions that are found to be effective).

Members of the Network CWG participate in quarterly calls, in-person (or virtual) meetings and workshops. Protocol-specific CWGs are established for many HPTN studies and are comprised of CWG members from the CRSs conducting the study. Protocol-specific CWG calls take place on a routine basis. Participation in protocol team and other network committee conference calls and meetings occur as appropriate.

The goals of the Network CWG are to:

- Assure that research conducted within the HPTN is done in partnership with trial site communities and integrates community perspectives
- Enhance community representatives of the research process so that more meaningful community participation and engagement can occur
- Increase HPTN researchers understanding and appreciation of the social context of participants in HIV prevention research
- Provide input in the science generation process

The goals of a protocol-specific CWG are to:

- Provide input into protocol development, adapting sample consent forms for local use and developing other study-related materials
- Participate in protocol-specific training and regional workshops
- Help to inform strategies for recruitment and retention, especially for populations deemed harder-to-reach
- Assist in monitoring any emerging issues in the community
- Facilitate the accurate and culturally appropriate dissemination of study results to the community

To meet these goals, the Network CWG and protocol-specific CWGs work to:

- Integrate participation of CWG members who represent diverse study communities and their advocates into WGs, SCs, and protocol teams
- Promote understanding of community needs and issues among HPTN researchers and other Network members
- Provide leadership to CTU/CRS community engagement staff in addressing issues that cut across the culturally diverse populations, communities, and technical areas of the HPTN
- Support collaboration and partnership at the CTU/CRS, SC, WG, and Network levels
- Advise and advocate for Network efforts in research, evaluation, and training addressing community participation at all levels of HPTN research

Membership

The CWG Chair and Co-Chair are selected by the CWG and appointed by the HPTN EC Chair and serves a minimum three-year term, renewable at the discretion of the HPTN EC Chair. The CRS Leader or designee appoints a Community Educator (CE) to serve on the CWG and the local Community Advisory Board (CAB) will elect the CAB member to serve on the CWG. CWG members who serve on internal and external research teams and working group are selected by the CWG and appointed by the CWG Chair and Co-Chair. The CWG Chair, CWG Co-Chair and LOC community engagement program staff determine the composition of the CWG within guidelines established by the HPTN EC. This includes members both internal and external to the HPTN.

Standing membership in the HPTN CWG includes:

- Voting Member
- CWG Chair and Co-Chair (one each, US and non-US)
- From each HPTN CRS
    - 1 CAB Member
    - 1 CE
- Non-Voting Members
    - HPTN LOC Community Engagement Program and other staff
    - HPTN Principal Investigators
    - Division of AIDS (NIAID/NIH) Representative
    - *Ad-hoc* External Scientific Advisor and Advocacy Representatives

Membership in a protocol-specific CWG includes:

- Voting Members
    - HPTN CWG Chair and Co-Chair
    - Representative from each CRS
    - 1 CAB Member
    - 1 CE
- Non-Voting Members
    - HPTN LOC Community Engagement Program and other staff

4.2.1.2 Community Working Group Steering Committee

The HPTN CWG Steering Committee provides guidance and support to the HPTN CWG and advises HPTN Leadership on matters concerning community engagement in all aspects of the HPTN research agenda. The HPTN CWG Steering Committee serves as a conduit of information between the HPTN CWG, HPTN leadership and other HPTN working groups.

The HPTN CWG Steering Committee goals are to:

- Inform, facilitate and guide the development of a community-centered, relevant, effective and ethical research agenda
- Proactively identify challenges related to community engagement and/or research implementation to ensure the ethical and scientific rigor of HPTN research
- Inform the HPTN EC of the CWG's decisions, concerns and activities
- Advise the HPTN EC on strategies to address community related challenges and issues of concern
- Develop mechanisms for sharing experiences, lessons learned and best practices for community engagement in HPTN research

The membership of the CWG Steering Committee consists of the following:

- Voting Members
  - CWG Chair and Co-Chair
  - HPTN Performance and Evaluation Committee CWG Representative
  - HPTN Ethics Working Group CWG Representative
  - HPTN Science Review Committee CWG Representative
  - HPTN HANC Community Partners CWG Representatives
  - HPTN Science Committees CWG Representatives
- Non-Voting Members
  - HPTN LOC Community Engagement Program and other staff
  - Division of AIDS (NIAID/NIH) Representative

HPTN CWG Steering Committee members participate in routine conference calls and periodic face-to-face meetings.

4.2.2 Ethics Working Group

The goals of the EWG are to contribute to HPTN research by raising awareness of and engaging Network members in dialogue about ethical issues in HIV prevention research and to facilitate decision-making around ethical issues during the research process. The EWG membership represents a broad scope of ethical, scientific, research, and community expertise — internal and external to the HPTN and from all regions of the world.

The EWG's scope of work includes:

- Ensuring ethical input into and review of HPTN concepts and protocols by serving as non-voting members of the Science Review Committee (SRC), and ad hoc resources to protocol teams and SCs as determined by HPTN Leadership
- Developing and maintaining an ethics guidance document for the conduct of HPTN studies and for publication

The EWG developed guidelines to enhance HIV prevention research studies, HPTN Ethics Guidance for Research, which is posted on the HPTN website.

Membership

The Chair and the co-chair are appointed by the EC Chair. The EWG membership includes representatives from diverse fields and geographic regions, ethicists, social scientists, HPTN investigators, community representatives, and staff members from the LOC, SDMC, LC, National Institute of Allergy and Infectious Diseases (NIAID) and other collaborating National Institutes of Health (NIH) institutes.

The full EWG typically convenes via conference call at least quarterly and holds an in-person meeting at least annually. Subgroups of the EWG meet more frequently on an *ad hoc* basis.

4.2.3 Socio-Behavioral and Structural Working Group

The charge of the Socio-Behavioral and Structural Working Group (SBSWG) is to promote scholarly discussion within protocol teams or SCs regarding the best approach for the behavioral measurement of interventions in line with the populations that the Network serves.

SBSWG's scope of work includes:

- Provide expertise in intervention acceptability
- Discuss appropriateness of measures to include in a protocol, such as use of respondent driven sampling, financial incentives, peer navigation, etc.
- Review concepts that have socio-behavioral and/ or structurally applicable elements

Membership

The Chair and the co-chair are appointed by the EC Chair. The SBSWG membership includes representatives from diverse fields within behavioral research and may include HPTN investigators, community representatives, and staff members from the LOC, SDMC, LC, NIAID, and other collaborating NIH institutes.

The full SBSWG typically convenes via conference call at least quarterly. Subgroups of the SBSWG may meet more frequently on an *ad hoc* basis.

4.2.4 Biomedical Sciences Working Group

The Biomedical Sciences Working Group (BWG) is established to provide expertise on emerging HIV prevention modalities and technologies. Including antiretrovirals (ART) for prevention multipurpose technologies (MPTs) and broadly neutralizing antibodies (bnAbs). The BWG works directly with protocol teams and Science Committees to provide input the best serves the diverse populations of the HPTN.

Membership

The Chair and the co-chair are appointed by the EC Chair. The BWG membership includes representatives from diverse fields who understand the evolution of HIV medical/pharmaceutical prevention modalities and new technologies in delivery systems for HIV prevention (injection, IV therapy, implants, etc.). The BWG may also include HPTN investigators, community representatives, and staff members from the LOC, SDMC, LC, NIAID and other collaborating NIH institutes.

The full BWG typically convenes via conference call at least quarterly. Subgroups of the BWG may meet more frequently on an *ad hoc* basis.

4.3 HPTN Oversight and Operations Committees

The HPTN EC Chair recommends, and the HPTN EC approves, chair(s) and membership of the HPTN committees. Committee members serve for the duration of the cooperative agreement, and chairs serve three-year terms unless otherwise specified. Terms of committee chairs may be extended with the approval of the HPTN EC Chair. In addition to the HPTN EC, SCs, and WGs, four key Network oversight and operations committees include:

- Science Review Committee (SRC)
- Study Monitoring Committees (SMC)
- Manuscript Review Committee (MRC)
- Performance Evaluation Committee (PEC)

4.3.1 Science Review Committee

The SRC ensures that study protocols are scientifically rigorous, accurate, consistent, complete and standardized to the extent possible relative to other HPTN protocols. The SRC will also review the protocol for operational feasibility, focusing on key issues such as site participation, infrastructure and capacity, relevance to the community and any ethical concerns.

Membership

The SRC membership for each protocol is composed of appointed and *ad hoc* members and includes representatives of relevant disciplines including prevention science, biostatistics, ethics, and clinical trial operations. The CTU/CRS investigators, EWG and community are also represented. Membership of the SRC, as proposed by the protocol team, is approved by the SRC Chair and is comprised of individuals who are not directly involved with the protocol.

Voting Members/ SRC conference call participants:

- SRC Chair (the HPTN Principal Investigator [PI] acts as designee in case of conflict of interest)
- SDMC Statistician (PI or designee)
- NIH Representative
- Ad hoc Scientific Reviewer (one or more voluntary experts knowledgeable in the research area)

Contributing Reviewers/from:

- SDMC Operations
- LOC
- LC
- CTU/CRS Investigator
- Site Coordinator
- CWG
- EWG

Note: the SRC may be observed by HPTN leadership.

The SRC convenes as needed. The SRC reviews are conducted via conference call with the voting members and the LOC CRM for the study.

As noted above, voting members are not directly involved with the protocol under discussion. If a voting member does have a conflict of interest with the protocol under consideration (e.g., is a protocol team member), a designee votes in the member's place.

Ad hoc members may include:

- Representatives (ex officio) from NIH institutes
- One or two research area experts external to the HPTN

Once an SRC is constituted for a protocol review, every attempt is made to maintain the same composition should the protocol need to be resubmitted for review.

A written review is provided to the team within 5 working days following the review. Refer to Section 9.2.2.1 for more details.

4.3.1.1 HVTN/HPTN Joint Science Review Committee

For concepts or protocols jointly led between the HVTN and the HPTN, the HVTN/HPTN Joint Science Review Committee (JSRC) ensures that the concepts or protocols have scientific merit, high public health impact, are scientifically rigorous, accurate, consistent, and standardized to the extent possible relative to other joint network protocols. As much as feasible, the majority of the protocol text for joint protocols are derived from the HVTN/HPTN mAb template for cross-protocol consistency and comparability.

Membership

The JSRC membership is a standing committee including representatives from both networks based on the positions below. Currently, the HPTN and the HVTN Laboratory Scientists who are voting members of the committee serve as the JSRC co-chairs.

JSRC Voting Members

- HPTN and HVTN Network PIs
- HPTN and HVTN Laboratory Scientists
- HPTN and HVTN Statisticians
- HPTN and HVTN Clinical Scientists
- HPTN and HVTN Community Representatives
- NIH Representatives

JSRC Observers

- Network LOC Directors
- NIH/DAIDS Medical Officers
- Protocol Operation Teams (Protocol Team Leads, Clinical Research Managers/Clinical Trials Managers, Clinical Trials Assistants)

Additional observers should be added as needed per protocol.

The JSRC convenes as needed and reviews are conducted via conference call with the voting members and observers.

4.3.2 Study Monitoring Committees

The SMC is delegated by the EC to provide a review of the conduct of all HPTN studies. Active HPTN studies are typically reviewed by a SMC approximately every six months during implementation, including prior to Data and Safety Monitoring Board (DSMB) reviews, if applicable (see Section 15.8). The SDMC PI in collaboration with HPTN leadership will determine the need for and frequency of SMC reviews for each study. Observational and feasibility studies that are not being reviewed by the DSMB and others that may be determined by HPTN leadership to not require this frequency of review will have a modified review frequency and process. Studies that may take less than a year to complete might not be reviewed by the SMC at the discretion of the EC.

The SMC reviews study conduct, such as enrollment and retention, quality/adherence to the implementation of the intervention, quality/adherence to the completeness and timeliness of data; safety, endpoint rates (only in aggregate, in closed session) and, as applicable, aggregate or by arm safety data (adverse events, abnormal laboratory results, product holds and discontinuations) in a closed session. Safety data and endpoint rates may be reviewed on the same time schedule as the scheduled SMC review of study conduct or may be more frequent, depending on the type of study (e.g., phase I/II studies of products not yet approved by the United States Food and Drug Administration (FDA)) and may be conducted by a subset of the SMC. The frequency of review of safety data by the SMC will be determined by the Protocol Chair, DAIDS MO, and SMC chair.

Membership

The PI, or designee, of each of the Central Resource components of the Network, the LOC, SDMC, and LC, as well as the DAIDS PSP Chief are members of this committee.

The voting members are not directly involved with the protocol under discussion. If a voting member has a conflict of interest with the protocol under consideration (e.g., is a protocol team member), a designee participates in the member's place. Deliberations in the closed SMC reviews remain confidential. SMC open reports are shared with the protocol team and other relevant bodies. The LOC works with the SDMC, LC, NIH Medical Officer(s) and protocol chair(s) to determine the composition of the SMC for each protocol.

Members:

- SMC Chair (a SDMC Senior Statistician)
- LOC Representative (PI or Designee)
- LC Representative
- SDMC Statistician
- One or two *ad hoc* members (expert from within or outside of the HPTN knowledgeable in the research field) not connected to the study and with no conflict of interest. If the SMC will review safety data, at least one *ad hoc* member must be a physician.
- PSP Chief or Designee

Observers:

- DAIDS Medical Officer
- DAIDS PAB Pharmacist
- LC Deputy Director or Designee
- LC QA/QC Coordinator
- SDMC Associate Director and/or Senior Clinical Data Manager (SCDM)
- SDMC CDM

- LOC Director
- LOC CRM and CTA
- LOC HPTN Network Pharmacist, as applicable
- Representative(s) from other collaborating NIH institutes
- Representatives from study partner organizations

A schedule of routine SMC reviews (based on the phase and need of the study) may be established in advance to maximize availability of voting members for initial and subsequent reviews. However, members may appoint designees from their organizations, as needed, to ensure a quorum for each review. A SMC quorum is defined as the SMC Chair and at least three (3) other members A SMC review call can only be scheduled if this minimum requirement is met. In exceptional situations, the SMC Chair may convene a call without the required quorum, or request that a review be carried out in their absence and identify a designee to serve as Chair in their stead.

Once a SMC is constituted for a study, every attempt is made to maintain the same membership throughout the study. Each study will develop a charter that outlines the membership and responsibilities as outlined above, specific to that study.

4.3.3 Manuscript Review Committee

The primary responsibility of the MRC is to ensure that abstracts, presentations, and manuscripts that contain data or statistically related content from HPTN studies are developed, reviewed and endorsed, according to the HPTN Publications Policy (Section 21) prior to submission for publication. Reviews are conducted mainly via email with written feedback provided to the submitting author(s).

Membership

Members of the MRC include:

- MRC chair(s)
- SDMC PI
- LOC representative
- Science reviewers
- LC representative

Further details of the MRC review process are found in the HPTN Publications Policy (Section 21).

4.3.4 Performance Evaluation Committee

The PEC is responsible for overseeing a continuous, comprehensive evaluation of clinical research sites conducting HPTN studies (see Section 19 for more information about the Network evaluation).

The primary purpose of the evaluation is to provide data to determine if the sites are contributing effectively to the protocols that they have undertaken and to elicit corrective action, if necessary, so that all sites are functioning at peak performance level.

Membership

The membership of the PEC includes:

- PEC Chair
- SDMC Associate Director
- LC representative
- LOC representative
- LOC Evaluation Coordinator
- CTU/CRS PI
- CTU/CRS Study Coordinator
- LOC Community Program representative
- DAIDS/PSP representatives
- Community representative

An LOC staff member serves as an Evaluation Coordinator and is responsible for compilation, production, and distribution of evaluation results as well as facilitation of the work of the PEC.

The PEC convenes routinely by conference call. A quantitative evaluation report is produced after May 31 each year and is submitted to the EC for review and action to NIAID prior to July 1.

4.4 Policy and Procedures Group

The Policies and Procedures Group (PPG), with membership from the LOC, SDMC, LC and DAIDS, is an operations committee tasked with developing and maintaining the HPTN Manual of Operations (MOP). The MOP is typically reviewed on an annual basis and revised, as necessary.

4.5 Protocol Teams

Protocol teams assume primary responsibility for scientific and operational leadership in the development, implementation, and day-to-day oversight of HPTN studies and dissemination of their results.

4.5.1 Membership

The Protocol Chair identifies protocol team members (except for those positions assigned by the LOC, SDMC, LC, and NIH). Membership of each protocol team will vary according to the protocol, but membership should include:

- Protocol Chair
- PI or a designated investigator from each participating CTU/CRS
- Community representative(s) (sites)
- LOC Community Engagement Program representative(s)
- LOC CRM
- SDMC lead statistician
- SDMC lead CDM
- LC QA/QC Coordinator (protocol specialist)

- LC Investigator
- DAIDS Medical and/or Program Officer
- DAIDS PAB Pharmacist (if applicable)
- NIAID collaborating institute representative (if applicable)
- LOC HPTN Network Pharmacist (if applicable, see Section 23)
- Pharmaceutical or industry representative (if applicable)

Additional members, as required for a specific protocol, may include a pharmacologist, virologist, behavioral scientist, immunologist, EWG representative, etc.

4.5.2 Protocol Chair Selection

Scientific priorities are decided by the HPTN EC. Concepts addressing these priorities are either generated centrally by the HPTN leadership or by investigators and scientific committees (see Section 9.1.1). For the concepts developed centrally, the protocol chair for approved concepts is selected by soliciting nominations for this leadership position. For the concepts developed by investigators or by the scientific committees, the concept teams can nominate the chair. Nomination and selection as a chair does not imply that the affiliated site (if any) will be selected for the study. Final approval as protocol chair is made by the HPTN EC.

4.5.3 Protocol Chair Responsibilities

The Protocol Chair will provide scientific leadership during the development, implementation, and reporting of the study and will assume responsibility for completion of protocol team responsibilities within the projected budget and timeline. In some instances, studies will identify a co-chair to whom the chair may delegate some specific areas of responsibility, but the ultimate responsibility for execution of the study and final decision-making authority rests with the designated chair.

Because of the time commitments necessary to successfully implement and oversee a protocol, **investigators cannot simultaneously chair or co-chair more than two HPTN studies**.

Protocol Chairs will need to familiarize themselves with the HPTN processes and adhere to them. All new protocol chairs must attend a protocol chair training to orient them to Network processes. An agreement outlining responsibilities will be provided to Protocol Chair(s), who will be required to sign it. First time Protocol Chairs/co-Chairs will be subject to specific training in Network processes and Chair/co-Chair responsibilities as outlined in Section 11.

Protocol team business is planned and managed by the Protocol Chair, in consultation and with the support of the LOC CRM and other core team members. Specifics of protocol team management vary according to the type of study (Phase I, II, III, research area, etc.), the number and location of sites involved, and individual leadership and management approaches.

In addition to duties as a protocol team member, the Protocol Chair and Co-Chair(s) are responsible for:

- Providing overall leadership to ensure that the protocol adheres to the projected budget and is completed by the projected timeline
- Working with the Central Resource partners, to provide detailed projections to the HPTN Leadership of the resources required to conduct the study, including site- specific study costs as well as costs associated with study drug and any potential outside contractors or vendors, where applicable

- Facilitating final decision making within the protocol team to achieve agreement on scientific or operational issues brought before it, including reviewing and approval of secondary and exploratory objectives; if agreement cannot be reached, referring the issue to the SC for consideration
- Participating as a member of the Clinical Management Committee
- Together with the lead protocol statistician, reporting on the status of the study at open sessions of the DSMB
- Coordinating the establishment and dissolution of working groups as necessary to achieve efficiency in the development, implementation, and reporting of the study
- Overseeing the establishment of writing teams during manuscript preparation (designates writing team members, reviews schedules, monitors progress, helps prioritize analysis, communicates publication plans, responds to the MRC review, and advocates for additional resources as required)
- Ensuring review and approval of all manuscripts, abstracts and presentations related to study endpoints.
- Providing status updates to HPTN leadership, as needed

The Protocol Chair(s) will act as a liaison between the team and the:

- SC, EC, and its standing committees with responsibilities for protocol oversight (SRC, SMC, MRC, and PEC)
- LOC and DAIDS to facilitate development, review, approval, and implementation of the protocol in accordance with all applicable clinical trials requirements with available resources
- LC in the development of the protocol design and its implementation, particularly regarding assay evaluation, protocol training and testing as needed, development and review of study-specific laboratory procedures, and establishment of quality assurance guidelines
- SDMC in the design, development, implementation, and reporting of the study

In addition, the protocol chair and team have the responsibilities outlined in the next section.

4.5.4 Protocol Team Responsibilities

The LOC CRM provides technical and operational support throughout the process. Although individual protocol team members have different roles in fulfilling specific protocol team responsibilities (see table below), all members are expected to provide scientific, operational, or site-specific input, as appropriate, to protocol team activities. Protocol team responsibilities include:

Roles of Key Protocol Team Members	
Team Member	**Primary Roles and Responsibilities**
Protocol Chair (see Section 4.4.3 for further details of chair responsibilities)	• Provide leadership in development of the protocol including judicious inclusion of secondary and tertiary objectives • Ensure that the protocol adheres to the projected budget and is completed by the projected timeline • Lead protocol team meetings and calls • Lead protocol development with LOC representative • Establish subcommittees and working groups of protocol team to complete specific activities, as needed • Monitor study implementation across sites • Participate in SMC and DSMB meetings, if applicable • Develop plan for and lead writing of manuscripts and dissemination of study results
Site Investigators (see Section 3.4.1.3 for further details of investigator responsibilities)	• Provide site-informed input into protocol development • Provide detailed site estimates of costs for study implementation • Submit protocol and other required study documents to Institution Review Boards/Ethics Committees (IRB/ECs) and relevant regulatory authorities, if necessary • Review and comment on all SSP manuals and data collection forms • Manage study implementation at sites • Participate in manuscript development
Community Representative(s)	• Provide perspective of community and potential participants; facilitate communication with site CAB: - during development of protocol and informed consent - during study conduct, bringing community concerns and issues to the attention of the protocol team - during manuscript development • Work with protocol team and CABs to develop and implement plans for dissemination of study results to the community, as needed

Roles of Key Protocol Team Members	
Team Member	**Primary Roles and Responsibilities**
LOC CRM (see Section 3.1.1 for further details of LOC responsibilities)	• With Protocol Chair, provide scientific and operational input to the protocol, coordinate and lead development of protocol • Organize protocol team conference calls and meetings and document key decisions after protocol is approved by HPTN SRC • Review study budget with sites and LOC financial staff • Submit protocol for required HPTN and DAIDS reviews (SRC, PSRC, Regulatory, Medical Officer) and manage response/revision process • Develop and produce SSP manuals with input from SDMC, LC and other team members • Provide onsite study-specific training with SDMC and LC counterparts and coordinate development of training plan and materials to provide onsite training, as needed • Provide technical assistance and oversight to CTUs/CRSs during study conduct, enabling the sites to respond to problems and issues that arise during implementation of studies and dissemination of findings • Track site progress on activation requirements and review-related Standard Operating Procedures (SOPs) • Assess the performance of CTUs/CRSs and report results, in conjunction with the SDMC, to the PEC, EC, and DAIDS • Summarize SRC and SMC reviews and distribute as appropriate • Collaborate with DAIDS Pharmaceutical Affairs Branch (PAB) and the pharmaceutical companies to meet study product supply needs • Collaborate with SDMC to develop Case Report Forms (CRFs) and test them in the field before implementation • Collaborate with LC to enable CTUs/CRSs to meet proficiency
SDMC Lead Statistician (see Section 3.2.1 for further details of SDMC responsibilities)	• Provide design, statistical and scientific input during protocol development and throughout the conduct of the study • Develop statistical components of the protocol • Develop Statistical Analysis Plan (SAP) • Develop randomization and treatment allocation scheme, if needed • Conduct data analyses and generate SMC and DSMB reports • Provide ongoing support for statistical questions • Participate in manuscript preparation

Roles of Key Protocol Team Members	
Team Member	**Primary Roles and Responsibilities**
SDMC Lead CDM	• Collaborate in development of protocol • Lead and collaborate in development and production of the data-related SSP manual • Lead the development of data collection instruments (e.g., CRFs, computer-based questionnaires) and instructions • Collaborate with CRM on review of site SOPs related to data management and randomization prior to activation • Collaborate with CRM and DAIDS PAB Pharmacist on study product distribution as it relates to randomization and data collection • Conduct data management and data collection instrument (e.g., CRF) training at sites • Develop plan for and provide regular reports to protocol team and CTUs/CRSs (enrollment, retention, adherence, specimen storage, data management quality) • Coordinate development and production of SMC and DSMB reports • Provide support for data collection and management • Collaborate with CRM to provide support for operational matters that may influence study data • Assess the data management quality of CTUs/CRSs and report results to protocol team • Conduct data management site visits as needed • Collaborate with LC on quality assurance testing of specimens • Facilitate closeout of data collection and cleaning

Roles of Key Protocol Team Members	
Team Member	**Primary Roles and Responsibilities**
LC QA/QC Coordinator (protocol specialist) (see Section 3.3.2 for further details of LC responsibilities)	• Provide laboratory input during protocol development • Define appropriate laboratory testing methods and materials to support study protocols • Lead and collaborate in development and production of the Laboratory SSP Manual • Provide training for CTU/CRS laboratories in protocol-specified laboratory tests, as needed • Coordinate and perform (as applicable) protocol-specified laboratory testing • Monitor technical quality of protocol test results; provide assistance to local laboratories, as needed • Provide laboratory expertise in eCRF development • Provide support to the study team as laboratory issues arise during implementation of the protocol • Ensure regulatory compliance for LC activities related for IND-enabling studies
LC Investigator	• Provide scientific input during protocol development, including drafting laboratory related study objectives and the design of sub-studies, as applicable • Provide input on laboratory-related issues of the protocol and direct development of the laboratory section of the protocol • Define appropriate laboratory testing methods and materials and sub-studies, as necessary • Monitor technical quality of specialized protocol test results • Provide assistance to local laboratories, as needed, for specialized tests
DAIDS Medical Officer	• Participate fully in protocol team discussions and decisions • Facilitate communication between protocol team and DAIDS groups and staff • Provide timely Medical Officer review • Provide oversight of safety monitoring

Roles of Key Protocol Team Members	
Team Member	**Primary Roles and Responsibilities**
DAIDS PAB Pharmacist (For HPTN Pharmacist role see Section 23)	• Provide expertise on all pharmaceutical and study product-related aspects of protocol development and conduct • Develop the study product/pharmacy section of the protocol and Pharmacy Study-Specific Procedure (SSP) Manual for each study • Coordinate and oversee the supply, management, and distribution of study products for DAIDS-sponsored studies • Collaborate with pharmaceutical companies and other external partners to ensure study product supply • Conduct protocol-specific training for CRS and pharmacy staff • Provide support to the protocol team and sites on protocol-specific pharmacy-related issues

4.5.5 Relationship of HPTN Executive Committee and Protocol Team

The HPTN EC monitors each HPTN protocol team with regards to protocol development, implementation, analysis, and reporting. This oversight is accomplished through the SC, the SMC, the PEC, and the MRC by a mixture of formal review of key documents produced by the protocol teams (study protocol, protocol summaries, open reports to the DSMB, and primary and secondary manuscripts) as well as review of reports prepared by the SC, the SDMC, the PEC, and the LOC.

In addition to oversight provided by the SMC or DSMB and the standing and *ad hoc* committees, routine EC oversight includes:

- Evaluation of study progress in relation to key implementation benchmarks established by the PEC and information from the protocol teams and SDMC (e.g., timeliness of enrollment and follow-up targets, routine reports to the DSMB, and progress in data analysis and reporting). The HPTN EC identifies and communicates recommended actions on delayed protocols and unexpected problems in protocol implementation
- Assistance to DAIDS in determining the need for additional resources, for example, because of unexpected costs associated with planned study procedures or in order to support ancillary studies endorsed by the protocol teams
- Adjudication of conflicts that cannot be resolved within the protocol teams and/or the relevant SC. If all reasonable attempts to adjudicate conflicts or address problems with the protocol team and the SC fail, the HPTN EC may direct that the protocol team membership or its leadership be modified

4.5.6 Conflict Resolution

Conflicts within the HPTN are handled by referring the issue in dispute to the next level of the HPTN organizational structure.

4.5.6.1 Conflicts within Protocol Teams

- If a conflict arises within a protocol team and cannot be resolved between the members involved, the issue is referred to the Protocol Chair
- If the issue cannot be resolved, it is referred to HPTN Leadership

4.5.6.2 Conflicts between HPTN Investigators and HPTN Committees

If an HPTN investigator is not satisfied with a decision of an HPTN committee (SRC, SMC) or a finding of the PEC, and the issue cannot be resolved through discussion and negotiation with the chair of that committee, the investigator or the committee chair may refer the issue to the HPTN EC.

5 COMMUNITY ENGAGEMENT IN THE HPTN

Clinical trials of HIV prevention interventions are most likely to succeed when all stakeholders — study participants, researchers, government, non-governmental organizations, service providers, community leaders, advocates and the study communities regard the trials as relevant and the process as collaborative. An aware, knowledgeable, and engaged community throughout the research process and beyond is imperative for successful scientific and ethical conduct of HPTN trials.

Community, in relation to HPTN research, is defined as the group of people who will participate in, are likely to be affected by, or have an influence on the conduct of the research. The community may include the particular group or population from which study participants are chosen. It may also include the broader geographic community in which the study will be conducted, as well as national and international activists who have an interest in the proposed research. Local traditional or governmental leaders, professionals, or volunteers who work with HIV prevention or research programs may also be key community representatives. Community members play an integral role in advising on research conducted in their community and disseminating research findings back to the community in a manner that is relevant and meaningful.

5.1 Overview

Community engagement on behalf of the HPTN is facilitated at many operational levels, including through Clinical Trials Units (CTU) and CTU-affiliated Clinical Research Sites (CRS), protocol teams, the Community Working Group (CWG), HPTN Science Committees, and the HPTN Leadership and Operations Center (LOC). The HPTN fosters a culture that supports partnerships between the community and researchers as a study is being designed, throughout its implementation, and leading up to and including dissemination of study results. CRS researchers work with and rely on the CRS Community Advisory Boards (CABs) to represent the participant community and raise issues and concerns regarding and affecting the research and the community. In addition, the inclusion of at least one representative of the CWG and/or HPTN Leadership and Operations Center (LOC) Community Engagement Program staff on key HPTN committees, working groups and on each protocol team ensures that a community voice and perspective are considered in all deliberations. At the HPTN leadership level, one of the two CWG Co-Chairs serves as a voting member of the Executive Committee (EC), and both Co-Chairs participate in EC conference calls and meetings.

In terms of community engagement, the HPTN is committed to:

- Conducting ethical research of the highest scientific quality that is supported and informed by input from local communities
- Supporting local community education and building community partnerships at HPTN CRSs, including through the provision of regular and ongoing scientific updates
- Supporting activities and infrastructure to build and sustain the community-research partnership
- Developing leadership, through the CWG, to advise the HPTN on cross-cutting community issues
- Providing technical assistance and support to HPTN and CRS community activities through the LOC Community Engagement Program staff
- Responding to concerns and misconceptions arising from study participants and communities, as needed

5.2 HPTN Community Engagement Program

Local and HPTN-wide community engagement efforts include strategies both to increase researchers' and staff members' knowledge of community engagement and to foster strong researcher-community partnerships. These partnerships support community-relevant research; appropriate plans for recruitment, retention, study product adherence; and the dissemination of study findings to the community. The HPTN LOC Community Engagement Program staff oversee HPTN's community engagement activities. Local engagement is typically done by the clinical research sites with community partners who operate on a local level.

The HPTN LOC Community Engagement Program is also responsible for overseeing stakeholder engagement, often in collaboration with CTU/CRS community program staff, HPTN LOC Communications Program, study leadership and civil society/advocacy group representatives. Whenever community consultations for a specific protocol are undertaken, it is crucial that study leadership is involved with the planning and implementation. It may be necessary to partner with a national stakeholder to conduct a consultation if they already have rapport established with stakeholders that we need to engage.

The Community Engagement Program staff or CWG may engage national stakeholders whose reach goes beyond their local community. Examples include the National Minority AIDS Counsel or the Black AIDS Institute.

Specifically, the HPTN LOC Community Engagement Program staff are responsible for the following:

- Ensuring a HPTN LOC Community Program Manager and a CWG representative are assigned to each protocol team
- Facilitating appropriate community input into the scientific agenda and the research process at the Network level
- Building capacity for local communities to provide input into research at HPTN study sites
- Facilitating the development of CRS Community Engagement Work Plans (CEWP)
- Developing mechanisms for sharing experiences, lessons learned and best practices in community involvement in research
- Facilitating training for community staff, CAB members and CWG focused on relevant topics and particular needs for capacity building
- Participating in and facilitating the HPTN CWG, protocol-specific CWGs, and HPTN CWG Steering Committee
- Working with the HPTN Communications Team to ensure that community representatives are adequately prepared prior to the launch of new studies, study milestones (e.g., Data and Safety Monitoring Board reviews) and study results, to help them manage expectations and communicate study outcomes at the community level

5.2.1 Ethics Training for Community Representatives

The FHI 360 Research Ethics Training Curriculum for Community Representatives was designed to educate community representatives about their roles and responsibilities and inform community representatives, members of research teams, CABs, and research ethics committees, about the general principles of research ethics. It also reviews the need for ethics committees, their importance, and the roles and responsibilities of community representatives in

the research process. The curriculum includes easy-to-use materials, such as slides, case studies, activities, facilitator notes, as well as an ethics training certificate.

Community education staff, community advisors and partners are encouraged to complete this training.

5.3 CTU/CRS Community Programs and Community Advisory Boards

It is the responsibility of the CTU principal investigator (PI) to ensure sufficient funds are in the CTU annual budget to support a community engagement program at each of the CTU's affiliated CRSs to facilitate the engagement of community representatives in the design, development, implementation and dissemination of results for HPTN studies. In this regard, HPTN Leadership expects that each CRS has a dedicated community education staff to coordinate a CRS community engagement program. The CTU PI and CRS Leader will ensure that the CRS community engagement program will include the following:

- Solicitation of input from community educators/liaisons on funding needs to implement CAB-related activities on an annual basis
- Support from the CTU/CRS core budget for adequate community-education staff and funding for a CTU/CRS community engagement program to support study-related community engagement plans
- Development and submission of an annual CTU/CRS CEWP
- Participation on routine conference calls with the HPTN LOC Community Engagement Program staff to provide updates on the status of the goals of the CEWP and the objectives of community engagement program activities
- Support for developing or enhancing CTU/CRS community advisory structures to be capable of working autonomously to determine their priorities, methods of organization and activities
- Development of a community advisory structure consistent with the research agenda and target priority population. In some instances, it may be prudent for CTUs/CRSs to establish priority population-specific CABs

The HPTN LOC Community Engagement Program staff work closely with the CRS community staff to:

- Develop a local CEWP that includes community assessment, community education, support from CABs and other mechanisms for community input
- Assist the CTUs/CRSs in community orientation and training, facilitation of community input into protocol development and implementation of the clinical trial
- Provide oversight, operational management and technical assistance in the development and dissemination of educational materials; the development of collaborative partnerships; and the ongoing education of trial participants, researchers and affected communities
- Provide guidance on developing community engagement program budgets
- Advocate for appropriate resources for community engagement activities and support for participation in local and network-level capacity-building initiatives

5.3.1 CRS Community Advisory Boards

A CAB is a mechanism through which a research site obtains community input into the research process; although, a CRS may refer to this structure by any locally chosen name or establish an alternative structure. CAB members work with study staff to lay the foundation for a viable research program by representing and speaking for the community. The CAB members support the site in developing appropriate plans for recruitment and retention and they advise on the dissemination of study findings to the community. They also provide feedback on draft protocols to study teams and offer advice in the development of informed consent forms, participant support materials and programs.

CTU/CRS staff will report on their CAB's activities to the HPTN LOC Community Engagement Program staff through updates provided on routine conference calls, discussions during community site-assessment visits and periodic one-on-one calls with site community educators.

To ensure their autonomy and to reduce possible conflicts of interest, CAB members are not paid site staff members; rather, CAB members are volunteers from the CRS community. They must adhere to CAB by-laws and governance regarding roles, responsibilities, and meeting attendance. They are expected to participate meaningfully so that issues requiring community dialogue can receive appropriate attention. CAB members and community partners involved in review of protocols and related documents should sign a statement of confidentiality to ensure the confidentiality of proprietary information and to protect fellow CAB members and study participants from HIV-related stigma.

The CTUs/CRSs are expected to support CAB representatives' participation in virtual and face-to-face HPTN meetings, conference calls, protocol-specific training, and regional community workshops. CTUs/CRSs should reimburse CAB members for legitimate costs associated with participating in the advisory process, such as for airtime, transportation, childcare, and meals at a level deemed appropriate by the individual CTU/CRS. This reimbursement should not be construed as payment. CTU/CRS staff should be readily available to participate in CAB meetings, as needed, as well as HPTN LOC Clinical Research Managers, Protocol Chair(s), protocol team members, and staff from the HPTN Statistical and Data Management Center or Laboratory Center should also avail themselves when at a site for training, assessment visits or any other HPTN-related business.

5.4 HPTN Community Working Group

The HPTN CWG is a group of site-based community representatives (both community education staff and CAB members) and advocates who provide consultation on and input into HPTN's efforts to ensure community engagement in its research agenda at the site and leadership levels. Its members conduct community preparedness and engagement activities to ensure the successful conduct of HPTN's studies. Protocol-specific CWGs are established for many of HPTN's studies and are comprised of CWG members from the CTUs/CRSs that are conducting the particular study.

5.4.1 Protocol-Specific Community Working Groups

Protocol-specific CWGs are created for larger studies (for example, Phase II, Phase III and open-label extension trials) with multiple study sites. They are responsible for enhancing protocol-specific community strategies and identifying possible study implementation challenges. Protocol-specific CWGs also assist in the development of study-specific educational tool kits and communication plans for disseminating information intended to keep community members informed of protocol updates, site-specific community involvement activities and to facilitate community preparedness and ongoing engagement activities and ensure the successful conduct of studies through partnerships.

5.4.2 HPTN Community Working Group Steering Committee

The HPTN CWG Steering Committee is comprised of a small subset of representatives from the HPTN CWG. The group provides guidance and support to the HPTN CWG and advises HPTN Leadership on matters concerning community engagement in all aspects of HPTN's research agenda. The HPTN CWG Steering Committee serves as a conduit of information between the HPTN CWG and HPTN Leadership and other HPTN working groups and scientific committees. See Sections 4.2.1.1 and 4.2.1.2 of this manual for further information on the CWG and steering committee's mission, goals, membership and structure.

5.5 Community Engagement in the Research Process

5.5.1 Concept/Protocol Development

The HPTN PI and co-PI ensure HPTN's commitment to community engagement in the concept/protocol development stage and throughout all aspects of the research process. Likewise, CTU/CRS Community Education Program staff, CAB members and the protocol-specific CWGs have primary or shared responsibility to:

- Attempt to fill gaps in the community's knowledge and/or expertise
- Provide real-life experiences when engaging the community
- Provide input about community/study participants' concerns, beliefs and norms
- Consider the input of scientists when developing concept plans and protocols
- Advise the site research team in the development of informed consent forms and other study-related materials, such as fact sheets and backgrounders
- Provide input on the language in the sample informed consent forms via written comments and/or participation in conference calls regarding the development of the forms
- Participate in developing and implementing strategies for recruiting and retaining study participants and facilitating adherence to study products
- Suggest strategies to address ethical and operational aspects of study conduct
- Serve as a resource to the community educator and the research team
- Share information, questions and concerns with others, i.e., local CAB members, the HPTN LOC Community Engagement Program staff and the CWG
- Function as a conduit of information between the site and potential research communities, such as CABs, nongovernmental organizations or social organizations
- When concerns arise, have discussions with local community representatives, community representatives from the other sites involved in the trial, the CRS leader and the HPTN LOC Community Engagement Program staff; among others, and ensure a complete feedback loop for information flow
- Provide protocol-development updates to fellow community representatives at the site or Network level
- Provide timely written feedback concerning concepts and protocols via an online questionnaire or email to the HPTN LOC Community Engagement Program staff

CAB members as representatives of their communities, and members of the CWG, should have the opportunity to provide input before trial-related terms are defined and translated into local languages and formats to ensure they are understandable. It is therefore important for the community to review the various versions of the protocol during its development and implementation. At a minimum, they should provide input into:

- The development of the informed consent processes and documents to enable prospective participants to provide voluntary informed consent
- Procedures for assessing individual comprehension of study-related information
- Incentives and reimbursements offered as part of participation in the study
- Study accrual, retention and product adherence strategies

It is the responsibility of the HPTN CWG Co-Chairs to:

- Submit concepts to the HPTN CWG and include the deadline and instructions for providing feedback
- Consider the HPTN CWG's feedback about concepts in preparation for submitting recommendations to the HPTN Leadership

It is the responsibility of the Site Investigators, study-specific Investigator of Record, community educators/CAB coordinators and other site staff in partnering with the CAB to:

- Include the CAB in concept and protocol team conversations and communications regarding protocol development to the greatest extent possible (for example, facilitate inclusion on conference calls or email exchanges)
- Meet regularly with the CAB to discuss and obtain feedback on concepts and protocols throughout the development process
- Conduct virtual or face-to-face CAB meetings immediately upon site selection to provide a clear explanation of the draft protocol with emphasis on the following protocol sections:
    - Background
    - Schema
    - Inclusion criteria
    - Exclusion criteria
    - Study procedures (including collection of lab specimens)
    - Informed consent forms

It is the responsibility of the HPTN LOC Community Engagement Program staff to:

- Participate in protocol team calls and meetings to clarify the community engagement program process and answer any questions
- Review written community feedback about the protocol and convene conference calls or exchange email (as necessary or possible) to further address questions, concerns and suggested changes to the concept or protocol prior to attending virtual or face-to-face Protocol Development Meetings
- Be available to site staff and community representatives to answer questions and provide technical assistance to support community participation in concept and protocol development
- Record CWG participation on study-specific CWG conference calls

It is the responsibility of the Protocol Development Team to:

- Consider input from the HPTN Steering Committee, and from the HPTN CWG, and CABs as provided by the HPTN LOC Community Engagement Program staff, site investigators, and Protocol CWG representative when developing concept plans and throughout the protocol development process
- As needed, join protocol-specific CWG, steering committee or Network CWG calls or meetings to explain the background of the concept, share information (such as peer-reviewed journal manuscripts relevant to the concept), respond to questions and address concerns

5.5.2 Study Implementation

The protocol-specific CWG is actively engaged in study implementation, as described in Section 5.4.1. Much of its work is operationalized through the CEWPs (described in more detail below). The CEWP outlines community education strategies to raise awareness and increase knowledge of general HIV prevention research and HPTN's clinical trials. It also facilitates an assessment of community education needs and enables study teams to implement educational and community entry strategies in support of study implementation.

5.5.2.1 Community Engagement Work Plans and Routine Calls and Meetings

Developing sustained relationships with community members is the responsibility of each CTU PI and CRS leader, as well as the CTU/CRS research and community program staff. CTU/CRS community engagement teams develop and implement a site/study-specific CEWP to ensure broad community support for and participation in the HPTN research agenda. Development of a CEWP prior to study activation serves to:

- Ensure that recruitment and retention plans are developed in conjunction with the site community educators (CE), outreach teams and CAB members
- Inform clinical research staff of potential social harms that may emerge prior to study activation or during implementation and ensure that these social harms are addressed as part of the sites' CEWP

The CEWP should address how the CTU/CRS will provide community education about HIV, HIV prevention research in general and the HPTN research (planned or ongoing) at the site.

The CTU/CRS CEWP should include the following:

- A community assessment that identifies community education needs, potential benefits and barriers to study participation and appropriate educational and community-entry strategies to facilitate the trials
- Measurable goals, objectives and a description of educational strategies to increase community understanding of HIV prevention research; that are responsive to community and ethical questions in the design and implementation of clinical trials; and that address issues specific to CTU/CRS studies
- Methods of monitoring and evaluating the implementation of the CEWP, including whether the objectives have been met
- Suggested budget and justification for CAB-related activities for the upcoming year

HPTN LOC Community Engagement Program staff will request CEWPs for site activation and determine on a case-by-case basis when CTU/CRS community education teams should submit an updated annual CEWP. Study phase, target population, and intervention are the criteria that will be considered. HPTN LOC Community Engagement Program staff assigned to the study will communicate the decision about developing and implementing a CEWP to the CTU/CRS community engagement teams. The CEWP should be developed by the site's community educator with input from CAB members or a similar community advisory body, a CRS leader and a site/study coordinator. The CRS leader, site/study coordinator and CAB Chair (or designee) must approve and sign off on the work plan prior to its submission to the HPTN LOC Community Engagement Program staff (community@hptn.org).

The CTU/CRS community education staff oversee the local implementation of the CEWP. The HPTN Leadership expects that each CTU/CRS budget will include financial resources and community engagement staff for the ongoing development, implementation and coordination of community engagement initiatives and the support of community members' participation in the HPTN's activities.

The CTU/CRS community education staff participate in routine conference calls with HPTN LOC Community Engagement Program staff to provide updates on community activities and progress reports on meeting the goals and objectives of the CTU/CRS CEWP. Conference calls with the CTU/CRS are a means for:

- The CEs to provide routine updates based on community-program goals and objectives for assessing community activities
- Exchanging information among CTUs/CRSs regarding the successes and challenges of the community-involvement activities

5.5.3 Study Completion, Results Dissemination and Potential Next Steps

As studies near completion, research sites should inform their study participants, CAB members, community partners, key stakeholders and agencies as to when they can expect results, how the results will be communicated and potential next steps. The HPTN LOC Communications Team works with CTUs/CRSs and protocol teams to disseminate the results of the research study. Dissemination efforts should enable any interested community members to learn about the study findings, pose questions and have the opportunity to suggest follow-up studies or additional investigations that might build on the completed work.

Communities should participate in discussions on how to disseminate research results have access to the published results of the study and. When study results are published in journals that are not accessible, sites should provide hard copies of papers upon request. The CTU/CRS community education/recruitment staff and CAB members should be supported and encouraged to develop publications (such as abstracts, manuscripts and posters) describing community efforts that contributed to the successful implementation of the research.

6 NETWORK MEETINGS AND COMMUNICATION

The Leadership and Operations Center (LOC) supports and coordinates much of the communications within the HPTN through conference calls, in-person and virtual meetings, electronic and written materials, social media and through the HPTN's website. The website includes study-specific information and postings about Network-wide activities. The Communications Team at the LOC is primarily responsible for the creation and dissemination of HPTN materials.

6.1 HPTN Annual Meeting

In collaboration with the HPTN leadership, the LOC organizes an HPTN Annual Meeting to bring together HPTN members and collaborators to discuss study designs and research goals, review data from ongoing trials, examine cross-cutting issues, and provide an overview of the HPTN scientific agenda. In addition, the meeting provides opportunities for training, identifying key issues, defining and discussing Network procedures, and clarifying roles and responsibilities of HPTN members. The Annual Meeting generally includes plenary sessions to update HPTN members on the latest scientific research concerning HIV prevention. The Executive Committee (EC), Science Committees (SCs), Working Groups (WGs), and protocol teams may schedule meetings in conjunction with this yearly event. The LOC is responsible for the overall logistics of the meeting; preparation of agendas and background materials; and subsequently, dissemination of summaries for the EC, SCs, WGs, protocol teams, and protocol-specific sessions in collaboration with the chair of the respective committee, team, or group. Additionally, the Annual Meeting may provide NIH training opportunities.

6.2 Conference Calls and Virtual Meetings

Conference calls and virtual meetings are used extensively to facilitate the Network's research activities.

The LOC provides a broad range of administrative support for conference calls and virtual meetings, such as preparation and/or distribution of call agendas and pre-meeting materials; sending email meeting reminder notices; and preparation, distribution, and archiving of pre-determined conference call summaries. LOC staff also document and distribute summaries of EC, SC, WG, protocol team and investigator conference calls.

6.3 Material Distribution

Staff of the HPTN central resources (LOC, Statistical and Data Management Center [SDMC] and Laboratory Center [LC]) disseminate HPTN information and study materials using a variety of techniques including newsletters, email, social media, website postings, and mail and shipping services.

Key HPTN information is posted on the HPTN website and/or other shared web-based portals for access by all Network members and study team members. Information from HPTN central resources and from the Division of AIDS (DAIDS) at the National Institutes of Health (NIH) is included and maintained regularly to ensure timeliness of material availability and dissemination. Other websites with information relevant to the Network include: Regulatory Support Center (RSC), Office of Human Research Protections (OHRP), US Food and Drug Administration (FDA), NIH, Office of Clinical Site Oversight (OCSO) and US Centers for Disease Control and Prevention (CDC).

6.4 HPTN Website and Social Media

The HPTN website provides a wide range of materials, as discussed below. The general philosophy governing the design, maintenance, and content of the website is to provide a site that contains useful and up-to-date information on the Network organization and studies.

6.4.1 Website Structure and Organization

The HPTN website includes information about the HPTN's structure, ongoing studies, community engagement programs, presented research, and publications. Study-specific pages are developed to suit the needs of each study. At a minimum, each study-specific page includes the Study Protocol and current study status, as well as Clarification Memos, Letters of Amendments and Full Protocol Amendments as needed. The study pages may also include key study personnel, participating sites and publications.

The HPTN website also includes Network resources such as the HPTN Manual of Operations (MOP), a searchable Network directory, regulatory information, current announcements, and the HPTN newsletter.

The design and maintenance of the HPTN website is the responsibility of the LOC. Questions and comments on the website may be sent to: communications@hptn.org.

6.4.2 HPTN Use of Social Media

The HPTN uses social media (e.g., Facebook, Twitter and YouTube) tools to increase community engagement in all aspects of HPTN's research agenda among members of communities that are disproportionately impacted by HIV/AIDS but are traditionally underrepresented in HIV prevention research. The HPTN engagement efforts on those sites primarily focus on building a dialogue with HIV and non-HIV specific health organizations, advocacy, professional, academic and civic groups in an effort to encourage community partners to build a more comprehensive understanding of the critical need for an ongoing, robust HIV prevention research agenda and, in turn, transfer that knowledge to their staff and to the community members whom they serve.

Posts made to the HPTN's social media sites include announcements and updates about HPTN studies and about activities such as webinars, conference presentations and publications. In addition, information about relevant articles, conference announcements, and links to other materials such as community partner and HPTN sites' community events are posted by HPTN staff as well as by social media followers. Other HPTN social media activities include promoting posts and hosting and participating in Twitter Chats and Facebook Events.

6.5 Study-Specific Communications

6.5.1 Study-Specific Roles and Responsibilities

The HPTN Communications Team will provide study-specific communications guidance to HPTN protocol teams. The Communications Team will be responsible for developing a comprehensive study-specific communications plan which will include study-specific roles and responsibilities, media communications, and plans for dissemination of study results. They will coordinate with the Protocol Team leadership to provide timely responses to emerging issues while reinforcing key messages about the study. This may include the need for a press release, official public statement or talking points. The HPTN Communications Team tracks all media coverage for HPTN and individual studies.

Study sites are responsible for monitoring how the study is portrayed/discussed by local media outlets in their respective regions. Any issues should be reported to the Protocol Team leadership, who will consult with the HPTN Communications Team, as necessary. This allows the team to identify any potential crisis communication issues and craft appropriate responses.

For each study, spokespersons/leaders who can speak on behalf of the study will be identified and listed in the study-specific plan. Site spokespersons and backup contacts will be identified for each site, who can respond to emergent issues. Additionally, site staff will develop a list of key local contacts for information dissemination as needed, including their respective institutions, community stakeholders, advocacy groups, health/scientific journalists, scientific leaders, websites, blogs, etc.

6.5.2 Development of Study Materials

If development of web-based, print, or other materials are required for a study (dependent on the phase of study), this will be managed by the HPTN Communications team, in collaboration with study site and/or community representatives. If materials are developed locally for site-specific use, these should be shared with and approved by the HPTN Communications Team. When discussing study-related information and results with media, community or other key stakeholders, study personnel will use communication documents generated and approved by the HPTN Communications team. The HPTN Communications team is responsible for ensuring that review of materials is obtained from the study team and HPTN leadership as appropriate. This includes, but is not limited to, fact sheets, FAQs, brochures, flyers, study websites, study advertisements (print and web), and talking points. Guidelines for the development of manuscripts, research presentations, and posters may be found in Section 21 and the study-specific publication guidance document (as applicable)*. (Note: *All press releases, statements, and public announcements must include an approved statement acknowledging NIH funding.)* Documents related to the dissemination of study results MUST be shared with the applicable NIH communications representative(s).

Materials developed for study participant use must be reviewed and/or approved by all responsible review bodies, including Institutional Review Boards/Ethics Committees (IRB/ECs), and in-country or site-specific Community Advisory Boards (CAB) or Community Advisory Groups (CAG) as applicable.

For any study that will be conducted at more than one US site, materials developed for study participant use are submitted by the LOC for single Institutional Review Board (sIRB) review on behalf of all US sites.

6.5.3 Study-Specific Media Inquiries

The HPTN Communications Team should be notified of **all** inquiries regarding the study from reporters/news organizations/bloggers and other media contacts. Media inquiries may be handled by the HPTN Communications Team, or a study or site spokesperson in coordination with the HPTN Communications Team. When discussing study-related information and results with the media, community or other key stakeholders, the spokesperson's responses should be consistent with any messaging/materials already developed by the study communications team.

6.5.4 Press Releases/Public Announcements

All press releases and public statements developed by HPTN must be approved by NIAID and, as appropriate, other sponsors. Before any materials undergo NIH review, the HPTN LOC ensures they have been reviewed and/or approved by relevant parties within the Network. Study-related press releases and materials must be approved by the Protocol Chair and the HPTN Principal Investigators (PIs). For all press releases and public statements, it is the responsibility of the NIAID Communications Office, DAIDS Program staff, and HPTN LOC to ensure that all appropriate Network, study leadership, and NIH program leadership reviews and approvals are obtained. For any locally-developed press releases or public statements (not including recruitment materials/advertisements), sites are responsible for sending a draft to the DAIDS Medical Officer and HPTN Communications Team for review and approval.

When study results are to be published or presented at a scientific meeting, the HPTN LOC and NIAID Communications Office coordinate press announcements with the authors and the publishing journal or scientific meeting organizer to comply with all required embargo guidelines. For studies conducted under a Clinical Trials Agreement (CTA), the publication guidelines and procedures described in the CTA also must be followed. In case of specific points of discordance between CTA requirements and this policy, the CTA requirements shall be followed.

The HPTN LOC ensures that NIAID, NIMH, and NIDA program leadership and their respective communications offices are notified in advance of all HPTN news releases and statements before they are publicly disseminated.

6.5.5 Study-Specific Documentation for Communications Purposes

The HPTN Communications Team will work with protocol teams to remain apprised of noteworthy study updates and story ideas for possible dissemination across communications channels of the HPTN. Whenever possible, the HPTN Communications Team will encourage sites and study staff to take photos and/or video to capture the various aspects of the study on-the-ground, as appropriate. All subjects of photos or video will be required to give written consent. The HPTN Communications Team has a template consent form for photos/videos. Photos and video should not violate IRB policies, informed consent for study participants, nor the multimedia policies of local partners/establishments where photos are taken. Any photos or video should be shared with the HPTN Communications Team for archiving and possible dissemination, which may include updates in the HPTN newsletter or on HPTN social media.

6.5.6 Study-Specific Results Dissemination

Protocol leadership will develop a timeline and plan for communications activities related to the dissemination of results for the HPTN study which will be detailed in the study-specific Communications Plan. For Phase III studies that are overseen by a Data and Safety Monitoring Board (DSMB), these plans will include scenarios related to early stopping or unblinding of the trial based on DSMB recommendations.

In preparation for results dissemination, sites will work with the HPTN Communications Team to ensure local contacts, spokespersons and community stakeholders are up to date.

The HPTN Communications Team will work in collaboration with the protocol leadership and study sponsor(s) to develop and review materials/tools for communicating results of the study. This may include the development of press releases, fact sheets and FAQs.

In general, results from HPTN studies are not released until completion of the study at all participating sites. Any exceptions to this policy require explicit approval of the HPTN Leadership in consultation with the study chair(s).

Prior to results dissemination, the HPTN Communications Team will work with protocol leadership and the study sponsor(s) to ensure that the results dissemination section of the study-specific communications plan is updated with specific information relevant to the dissemination process. Ideally, study results are revealed to the protocol team, sponsor(s), and other relevant parties at a meeting that includes a review of the key analyses and planning for public release of results and coordination of future publications (see Section 21.1.4.1).

Results will be released to host country officials, sites, study participants, community representatives, sponsoring industry collaborators, relevant non-governmental organizations and other governments in an accurate, well-controlled and timely manner. Ideally this will happen before, or at the same time, as the results are released to the general public.

6.6 Public Information Policy

Investigators and CTU staff may have access to proprietary and sensitive information as a result of their participation in HPTN protocols. The following guidelines relate to disclosure of product and study-related information to the public and are aligned with NIAID policies.

Inquiries from the press, community representatives, and public officials concerning general study status may be addressed by the study investigators to whom questions are addressed; however, more specific comments related to study outcomes or adverse events will be coordinated between the investigators and HPTN leadership as well as the protocol team and the DAIDS (and other NIH institutes as necessary).

Press inquiries more specifically or generally about HPTN activities should be referred to the Network leadership and DAIDS.

Proprietary information about study products in development or used in a trial conducted under an Investigational New Drug (IND) application may not be discussed publicly by anyone without written permission of the product's manufacturer.

6.7 HPTN Branding

6.7.1 Identity

When referencing an HPTN study in manuscripts, presentations, posters, study-specific printed materials, or other study-related documents or communications, the full study name/number must always be used (e.g., "HPTN [Insert Study Number]"). If the study has a branded name (i.e., "The LIFT Trial") it may be written as "HPTN 123, The (NAME) Trial."

When submitting abstracts, manuscripts, posters and presentations, the corresponding author should list the named authors and then recognize the study team (e.g., "Ann Smith, William Jones and the HPTN [Insert Study Number] Study Team.")

6.7.2 Acknowledgement and Logo Use

The HPTN logo or an official study logo should be used on all study-specific materials as well as general HPTN materials. The current HPTN logo is available on the HPTN website. If materials are developed for local use only AND space is limited, it is permissible for in-country sites to use their logos, with prior approval of the HPTN Communications Team.

Per NIH policy, NIH/NIAID/NIDA/NIMH logos should not be used on any study communications materials (presentations, posters, brochures, websites, etc.). As an NIH grantee, **HPTN is required to acknowledge NIH funding support through text only** (see Section 21.1.11).

6.7.3 Slides, Posters and Printed Materials

General and study-specific HPTN templates for posters and presentations will be developed by the HPTN LOC. These templates should always be used for communicating about a study. Logos and sponsor text already incorporated in these templates should not be moved, re-sized, overlapped or deleted. Templates are available on the HPTN website and in internal LOC file libraries (i.e., SharePoint and Teams).

7 HPTN FUNDING, CONFLICT OF INTEREST AND CERTIFICATE OF CONFIDENTIALITY

The organizations that comprise the HPTN adhere to relevant US federal regulations and National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID)/Division of AIDS (DAIDS) policies as a condition of receipt of NIH funding. These regulations and policies are referenced throughout this Manual of Operations (MOP), as well as within site and Network operations Standard Operating Procedures (SOPs) and Study-Specific Procedures (SSP) manuals.

7.1 HPTN Funding Procedures

The operational components (CTUs/CRSs, LOC, SDMC, and LC) of the HPTN are funded directly through cooperative agreements (UM1 awards) with the NIAID.

The LOC financial staff collaborate closely with the Prevention Sciences Program (PSP) Chief, PSP financial liaison, Office of Clinical Site Oversight (OCSO) representative, and the Grants Management Branch (GMB) Officer on all Network financial matters (multiple-funding sources, carryover, release of study-specific funds, progress reports, annual budget renewals, financial status reports), and annual funding levels as recommended by the HPTN Executive Committee (EC). LOC staff also provide guidance to CTU staff on budget questions and issues. When sites receive funding directly from the LOC, invoices are submitted to the LOC for payment based on the payment schedule presented in the sub-agreement (cost reimbursement, per participant, fee for service, etc.).

7.1.1 HPTN Funding Process and Timeline

The CTUs receive funding through UM1 awards directly from the NIH for their core (infrastructure) funding. Each year, the CTU or institutional recipient of the award must complete a non-competing grant progress report (PHS 2590 package), including a budget and budget justification for the coming year. Unless otherwise instructed, this package is due to NIAID (or the funding institution, like the LOC) 60 days prior to its annual anniversary date. The format and forms for this report are located on the NIH web site and include:

- Face Page
- Detailed Budget for Next Budget Period
- Budget Justification
- Biographical Sketch (new key personnel only)
- Active Other Support
- Progress Report Summary
- Checklist
- Personnel Report

As part of the renewal package, the CTU provides NIH (and other funding partners) with an overall budget to participate in the development and implementation of the HPTN research agenda for the upcoming funding cycle. This participation requires two types of funds: Core and Protocol Funds (PF).

- Core funds are provided to HPTN CTUs in order to maintain the scientific and administrative expertise and the infrastructure to support the CTU and each affiliated CRS. Continued support will be based on a satisfactory evaluation at the end of a time period designated as appropriate by each Network. Costs in this category include:
    - CTU Principal Investigators (PI) to maintain CTU administration and an ongoing contribution to the HPTN
    - Personnel for CTU administration, oversight and evaluation, including CTU Coordinator, financial and administrative staff
    - Regulatory, pharmacy, data management, and laboratory oversight staff
    - Community education and engagement structures and activities
    - Clinical quality management activities
    - Maintenance and replacement of equipment
    - Travel to attend HPTN meetings
    - Mentoring and training of staff
- Protocol Funds (PF) are an additional amount provided to support protocol-related expenses attributable to protocol development, protocol implementation, and protocol close-out. PF will be calculated annually and will be determined in collaboration with the networks responsible for the protocols. Costs in this category that are protocol specific include:
    - Salary for additional staff or expanded commitment of core staff to carry tasks attributable to the specified protocol
    - Participant recruitment and retention
    - Protocol required tests and evaluations
    - Participant reimbursement
    - Equipment and supplies
    - Community education and engagement structures and activities
    - Additional support for regulatory, pharmacy, data management, and laboratory activities

For direct core funding from NIAID, the OCSO representative and Grants Management Specialist send a letter to the CTU Principal Investigators (PIs) to provide guidance on budget development for their annual 2590 package representing the upcoming year.

Each year, the HPTN leadership provides an annual PF plan based on study-specific budgets. Based on PF plan, some sites receive salary directly from LOC based on being identified as a protocol-specific site. The plan takes into consideration anticipated study initiation dates, number of trials implemented by each CTU, number of participants, and other factors that have cost implications. The recommendations are submitted to appropriate NIH personnel. The LOC will work closely with all NIH partners to ensure adequate review and compliance. NIH will inform the HPTN leadership of the PF level they intend to fund and request a plan to allocate the funding across the Network sites. Given the role of the NIH in the funding of the HPTN scientific portfolio, HPTN and NIH leadership engage in an ongoing dialogue to ensure adequate funding levels to advance the science.

In addition to submitting a renewal package 60 days prior to the anniversary date of each year (i.e., October 1 for a December 1 due date), CTUs must account for expenditures by funding source(s) through their annual Federal Financial Report (FSR). The FFR includes information on unliquidated balances (funds obligated to the CTU, but not expended). The CTU is required to file the FFR within 90 days of the end of the funding cycle. This report is submitted directly to NIH's Office of Financial Management (OFM).

The OFM will review and accept the FFR. The OFM reviews electronic submissions first. If sites are submitting paper copies, they should send a copy directly to the OCSO Program Officer and the NIH GMB Officer who can expedite OFM's review and acceptance. GMB staff are notified by the OFM when the FFR has been accepted. Only then can GMB staff act on any carryover requests received. This process will continue for all core funded activities provided directly from NIAID. If funding for protocol funds is made available through the LOC, sites are required to provide monthly invoices to the LOC.

Most importantly, if a site identifies a need for additional funds, they should first review the existing budget in the current CTU award and determine if there are funds that can be re-budgeted/reallocated, which they can manage given their expanded authority.

7.2 Conflict of Interest Policy

Key members of protocol teams and HPTN committees are required to complete a Financial Disclosure Form. Annually, the Office of HIV AIDS Network Coordination (HANC) distributes the "Statement of Financial, Equity, and Intellectual Property Interests" (Appendix A of the cross-network SOP) to Network members who are required to disclose financial information. Included in this distribution is a list of Network-affiliated companies (referred to as relevant entities in the cross-network SOP) and their related products to serve as a guide to Network members completing their Statements. This list must not be regarded as an exhaustive list of relevant entities. It is the responsibility of Network members to report all significant financial interests as outlined in the cross-network SOP. A cover letter accompanying the distribution provides a deadline for submission.

7.2.1 HPTN Financial Conflict of Interest and Disclosure Policy

The HPTN seeks to maintain objectivity in all of its research by ensuring that the selection of products for testing, as well as the design, conduct and reporting of research is not biased by conflicting financial interests of HPTN leaders and/or investigators who are responsible for the research.

In accordance with the provisions of the US Code of Federal Regulations (CFR) 42 CFR 50/F and 45 CFR 94 and with 21 CFR Part 54, HPTN is required to ensure that:

- Investigators have disclosed any significant financial interests
- Records of financial disclosure are maintained according to the sponsor's requirements
- Conflicting interests of investigators are managed, reduced or eliminated

Specifically, all individuals who meet the definition of "key personnel" as defined in the NIH HIV/AIDS Clinical Trials Networks Financial Disclosure Policy and Procedure described below must provide the required financial disclosure information annually. There are two financial conflict of interest policies to be aware of: an NIH policy (Section 7.2.2 below) and an FDA policy (Section 7.2.3 below).

7.2.2 Compliance with 42 CFR 50/Subpart F and 45 CFR 94 – NIH Financial Conflict of Interest Policy

The HPTN is subject to the NIH HIV/AIDS Clinical Trials Networks Financial Disclosure Policy and Procedure which describes the requirements and procedures for financial disclosure for all named networks. These policies and procedures were developed to identify significant financial interests of researchers in the NIH HIV/AIDS Clinical Trials Networks and avoid conflicts of interest, or the appearance of such conflicts, in the networks' activities.

HPTN members (key personnel) required to disclose under this policy include:

- All members of the Scientific Leadership Group
- All members of a Study Monitoring Committee and Endpoint Review Committee.
- Protocol Chairs, Co-Chairs, Vice-Chairs, and other protocol team members who make direct and significant contributions to the study and/or the study data, as determined by network leadership (e.g., pharmacologist, LC and SDMC personnel)

Members of a protocol team who do not have key decision-making roles, including industry representatives and federal government employees (who are required to report under other federal guidelines) are not required to disclose under this policy.

Annually, the Office of HIV AIDS Network Coordination (HANC) distributes the "Statement of Financial, Equity, and Intellectual Property Interests" (Appendix of the cross-network SOP which offers guidelines for completing the statement) to Network members who are required to disclose financial information. A Review Committee including the Network Chair, Vice Chair, Operations Center Director or designee, and the DAIDS Program Officer is responsible for review and mitigation of potential conflicts. This process and the responsibilities of the Operations Center are detailed in the cross-network SOP.

7.2.3 Compliance with 21 CFR 54 – FDA Financial Disclosure by Clinical Investigators (for IND Studies ONLY)

As part of marketing applications for new human drugs and biological products, and marketing applications and reclassification petitions for medical devices, sponsors of clinical research studies are required to disclose to the US Food and Drug Administration (FDA) certain financial arrangements between sponsors and clinical investigators and certain interests of clinical investigators in the product under study or in the sponsor of the study. To fulfill this requirement, Clinical Research Sites (CRSs) involved in the conduct of HPTN studies conducted under an Investigational New Drug (IND) application with the FDA are required to maintain documentation of certain financial arrangements and interests.

HPTN has developed a Financial Disclosure Form for accessibility on the DAIDS Regulatory Support Center website which may be used to record the required financial disclosure information at each site. Alternatively, an equivalent form provided by a pharmaceutical company co-sponsoring a study may be used.

For each study being conducted under an IND, the designated form must be completed by the CRS Investigator of Record (IoR) and all other investigators and study staff listed on the Form FDA 1572, to disclose their own financial interests as well as those of their spouses and dependent children, prior to enrolling any study participants. IoRs will be required to confirm that the forms have been completed by all applicable CRS staff and placed on file as a condition for site-specific study activation. As new CRS personnel are added to the Form FDA 1572, these personnel must also complete the designated form. These disclosures may only need to be completed once by a staff person if nothing changes for that staff person throughout the course of the study (as part of your own internal QC, you may want to check these periodically throughout a study to ensure there

are no updates. Also, if a new staff person joins the study while the study is on-going, that new staff member must complete this FDF). These forms should be kept in your regulatory files, and these are the forms that we asked all sites to submit to us a couple of months ago This will be confirmed through the site activation checklist (See Section 10).

Upon completion of the study, as part of study close-out procedures, all forms will be reviewed and updated as needed to add any new financial interests that may have occurred since initial completion of the forms. All forms must be available for review by site monitors and other sponsor and HPTN representatives, as well as FDA representatives.

The deadline for submission by the solicited Network members is May 31. The final report to the Review Committee is due no later than June 30.

7.3 NIH Certificate of Confidentiality

NIH provides Certificates of Confidentiality (CoCs) automatically to any NIH-funded recipients conducting research applicable to the NIH Policy for Issuing Certificates of Confidentiality, for which all HPTN research is applicable.

Certificates will be issued to recipients for applicable research regardless of the country where the investigator or the protected information resides. However, Certificates may not be effective for data held in countries outside of the US.

The CoC does not cover voluntary disclosures (e.g., voluntary disclosure by the participant to his/her health provider or insurer) or suspected harm to a child or self. The LOC Clinical Research Manager (CRM) ensures that language describing the CoC is included in the informed consent form, as needed. Site staff will inform participants of the limitations of coverage of the CoC as part of the informed consent process.

For more information on the CoC, refer to the https://grants.nih.gov/policy/humansubjects/coc.htm.

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 Study-Specific

Procedures (SSP) manuals. 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 manuals (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.

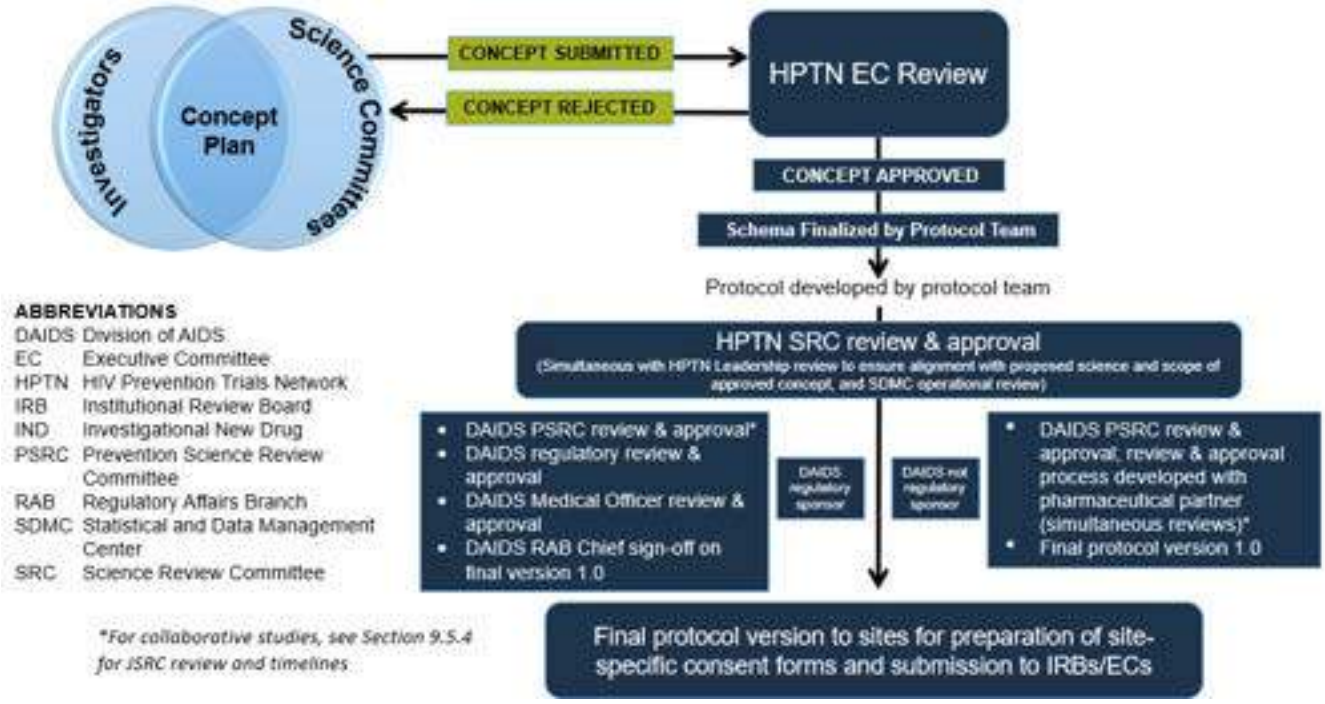
8.13 Communicable Disease Reporting Requirements

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.

9 PROTOCOL DEVELOPMENT

HPTN studies are developed through multidisciplinary collaboration among HPTN investigators, the Statistical and Data Management Center (SDMC), the Laboratory Center (LC) and the Leadership and Operations Center (LOC), together with non-HPTN investigators, pharmaceutical partners, and researchers/experts who bring complementary expertise. Key steps in the process are shown in Figure 9-1 and are further described below. For studies where DAIDS is not the regulatory sponsor, deviations from these steps will be described and documented in central study files.

Figure 9-1 Protocol Development Process



9.1 Selection/Approval of Concepts for Protocol Development

9.1.1 Concept Plan Development

Overall scientific priorities will be determined by the Executive Committee (EC) in collaboration with the Science Committees (SCs) and Working Groups (WGs), and in alignment with the scientific agenda of the network (Integrated Strategies and Pre-Exposure Prophylaxis). See Section 9.5 for considerations related to the protocol development process for collaborative studies. In cases where a specific priority study is identified, a concept team will be established to develop the concept plan. For newly identified research priorities, Network leadership will release a call for concepts to meet specified scientific needs. Investigators (both within and outside of the Network) can submit ideas for consideration. The number of concept plans developed into protocols will be based on the Network's current and future priorities and availability of resources.

A concept team will include a lead investigator(s), as well as relevant contributors to support the proposed work (e.g. statistician, behavioral scientist (Socio-Behavioral and Structural Working Group (SBSWG) will be consulted to determine need), mathematical modeler, etc.). Central Resources will be assigned only after the approval of the concept by the EC.

The team will submit the developed concept to the EC where it will be reviewed as needed (see Section 9.1.2 below).

The concept plan presents, as concisely as possible, sufficient information for reviewers to evaluate the scientific merit and feasibility of a proposed study. The concept plan should be a maximum of 10 pages (unless otherwise specified). The template concept plan is posted on the HPTN website, and includes key elements, such as background/rationale, study objectives, study design, budget, timeline, etc.

9.1.2 Concept Plan Review

All HPTN-only concept plans must be reviewed and approved by the EC. Concepts submitted as part of an HVTN/HPTN network collaboration will be reviewed by the HVTN/HPTN Joint Science Review Committee (JSRC) as described in Section 9.5.4.1.

Concept plans must be submitted to the LOC at minimum two weeks prior to the planned EC review conference call or meeting. At that time, the EC Chair assigns a primary and secondary reviewer per concept, and the following groups assign their own reviewers: NIH, LOC, LC, SDMC (statistical and operational), and the Community and Ethics Working Groups. Assigned reviewers submit written comments in advance of the review. The proposing investigator presents a brief description of the concept during an EC call or at an in-person meeting, using a provided template slide deck. Reviewers ask any clarifying questions, and then the authors are asked to leave. The concept and reviewers' comments are discussed by the reviewers. The criteria for review are described below:

- Scientific merit (50%)
  - hypothesis is scientifically sound and answerable by the proposed design
  - study design and methods will yield the proposed outcomes
  - plan for analysis of data is adequate and appropriate
  - population is appropriate for the research; relevance of research to the community is considered
- Importance/public health impact (30%)
  - relevance of the planned research to the prevention of HIV infection
  - proposed study is part of a critical path in a research continuum (including would potentially lead to an efficacy trial)
- Research advantage of the HPTN (20%)
  - study is aligned with the scientific agenda and priorities of the HPTN (refer to the HPTN concept page for HPTN priorities listing)
  - proposed research will benefit from a multi-site, multidisciplinary collaboration involving different populations either in the initial phase or in a subsequent phase

Following review discussion, all voting EC members must cast a vote. The EC votes are kept confidential and anonymous. Any identifying information is known only to the EC Administrator. Concepts will be approved for protocol development if a "Yes" vote of 80% of the eligible EC voting members is received. Eligibility is defined by the Conflict of Interest policy that is reiterated prior to each review process in addition to participation in the review/discussion. If more than one concept is being considered and prioritization is required due to budgetary constraints, concepts could be scored by the reviewers using the guidance mentioned above and a scoring system of 1 to 5 with 1 being the highest.

The EC follows a strict conflict of interest policy throughout all of its discussions and votes. Any EC member (or his or her institution) directly involved in a concept, protocol, or study recuses himself or herself from the discussion and vote.

Investigators who submit concept plans are informed directly of the outcome of the review and vote through a summary of the review discussion and all reviewers' comments.

9.2 Protocol Development, Review and Approval

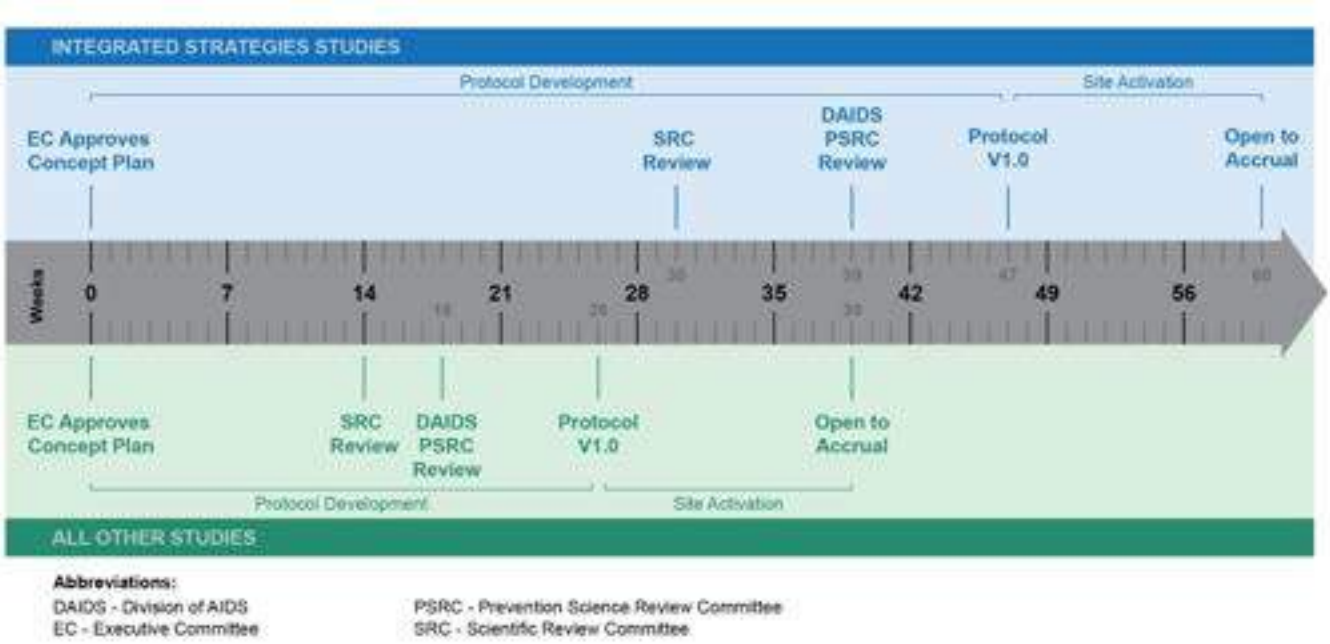
9.2.1 Protocol Development Process

Once a concept plan proceeds to the protocol development stage, the EC will approve a proposed Protocol Chair for the study, who will work with the Central Resources groups and others as necessary to assemble a protocol team. Section 4.5.2 has more information about protocol chair selection. The protocol team is typically an expansion of the concept plan team and will include investigators with expertise pertinent to the study, investigators (and other site staff as necessary) from the participating sites, as well as representatives from the Community Working Group (CWG), LOC, LC, SDMC, DAIDS Medical Officer, DAIDS PAB Pharmacist, and other members as applicable. HPTN Leadership will decide after concept approval whether the proposed study requires a socio-behavioral scientist or an ethicist. If required, the chairs of the SBSWG and the Ethics Working Group will identify an appropriate representative, in discussion with the protocol chair. If the study team has identified a socio-behavioral scientist external to the SBSWG, the rationale for doing so will need to be provided to Leadership for their approval.

HPTN protocols are developed through an iterative drafting and review process led by the Protocol Chair(s) and a primary protocol writing group (a subgroup of the protocol team), coordinated by the LOC Clinical Research Manager (CRM) assigned to the protocol. To initiate the protocol development process, the LOC CRM inserts all relevant information from the approved study concept plan into the HPTN protocol template. The LOC CRM documents all key decisions made during the process, by updating the draft protocol document.

Protocol language should give consideration to suggestions made in the NIAID HIV Language Guide and the DAIDS Cross-Network Transgender WG Guidance on the Use of Gender-Inclusive HIV Research Practices: Protocol Design, Data Collection, and Data Reporting. Inclusion of representative populations should be considered as well based on suggestions made in the HANC Representative Studies Rubric (RSR): A Tool to Enhance the Representativeness of Study Populations in Clinical Research. The LOC CRM, with input from the Community Programs Manager and Protocol Chair(s), will complete the RSR Questionnaire for HPTN Studies. The completed questionnaire will be submitted along with the protocol at the time of PSRC review (see Section 9.2.2.3),as well as posted alongside Version 1.0 of the protocol on the HPTN website (as applicable).

The timeline for protocol development may differ based on the type of study; specifically, protocols for most studies, including biomedical interventions, are expected to be developed more expeditiously (PSRC submission within 16 weeks) than integrated strategies protocols (PSRC submission within 37 weeks). The LOC CRM develops a study-specific timeline with standard timeframes for the type of study and monitors and adjusts as needed during protocol development.



The protocol writing team will convene either virtually or in person. During this meeting, the LOC CRM will review the protocol development process and expected timeline based on whether the study is an integrated strategies study. The team will develop writing assignments, roles, responsibilities, and expectations for team members. For integrated strategy protocols, a schema is expected as a meeting goal. For all other studies, the development of a schema, a schedule of evaluations (SOE), a site selection method/criteria and draft budget are expected. Integrated strategy studies will hold a second core virtual or in-person meeting to develop these items.

Once the study design, objectives, measurements, safety monitoring and the schedules for visits and procedures have been well defined, another in-person or virtual protocol development meeting with the full protocol team will take place to finalize the protocol. The LOC CRM will draft the sample informed consent form(s) that must be appended to the protocol. For some studies, only one sample informed consent form may be needed. For others, multiple forms may be needed (e.g., screening, study participation, assent). All sample forms will follow Division of AIDS (DAIDS) informed consent templates and will include all required elements of informed consent specified in 45 CFR 46 and 21 CFR 50, as delineated in Section 8. A template Informed Consent Form is located in the HPTN protocol template.

Early in the process of protocol development, the team may seek input from research sites where the study is likely to be conducted, from site CABs, the HPTN CWG and other community fora. Additionally, if deemed appropriate, stakeholder meetings may be conducted to foster engagement of a broad range of local stakeholders in the impacted communities.

The protocol writing team will determine when the draft protocol is ready to enter the protocol review process described below and shown in Figure 9-1.

9.2.2 Protocol Review Process

After initiating the protocol development process, the protocol goes through a series of protocol review steps, each of which is described below. When DAIDS is not the regulatory sponsor or for specialized protocols, the process may be modified on a case by case basis.

9.2.2.1 Protocol Review by the Science Review Committee and HPTN Leadership

The HPTN Science Review Committee (SRC) will conduct the first step in the protocol review process. Refer to Section 4 for composition of the SRC.

The primary charge of the SRC is to ensure the protocol is ready for the next review stages – not to rethink the scientific merit of the concept (the EC has already approved the concept to move forward). This review will ensure that study protocols are scientifically rigorous, accurate, consistent and complete. The SRC will also review the protocol for operational feasibility, focusing on key issues such as site participation, infrastructure and capacity, relevance to the community and any ethical concerns.

The LOC CRM is the primary organizer of the SRC call and review process. The SRC will review the draft protocol and comment within five working days of receiving the draft, with a call scheduled immediately following. Comments should be sent to the LOC CRM. Comments will be organized into overall summary and major and minor comments; typically, major comments should be reserved for fundamental study design, scientific, operational, or ethical issues, while minor comments should be used for stylistic input, correcting inconsistencies or errors, wordsmithing, or other editorial concerns.

On the day of the call, a closed SRC discussion takes place in which the primary SRC members summarize their major comments and review the comments of the contributing (non-voting) members; SRC voting members' attendance on this call is required. Following the closed discussion, the Chair(s) of the protocol being reviewed join(s) the call to answer questions, provide clarifications and discuss key review findings from SRC primary review group members. The LOC CRM will summarize the call and its outcome in writing and, following concordance by the SRC chair, distribute the summary to the SRC and protocol team. The approved summary is provided electronically to the protocol team typically within five working days of the review call. The summary documents one of three review outcomes:

- Approved without major revision — the protocol team may proceed to the next review step (DAIDS Prevention Science Review Committee [PSRC] review)
- Major revisions required — the protocol team prepares a written response to any "major" review findings which must be reviewed and approved by the SRC Chair and the voting SRC members.
- An additional review may be required as determined by the SRC Chair
- Protocol disapproved as written — the protocol team will work with HPTN leadership to determine next steps
- Not Approved

If revisions are needed, the protocol team will strive to provide a written response to the comments of the voting SRC members to the SRC and a revised draft within 15 working days of receiving the comments. However, consideration will be given to the magnitude and extent of the SRC's feedback. Formal responses are only required for major comments. If the protocol team has concerns about the SRC's decision, and these are not resolved through discussion between the SRC Chair and the Protocol Chair, the HPTN EC will assist in resolving the matter.

Simultaneous to the review of the protocol the HPTN Leadership ensures that the protocol is in alignment with the approved concept and the goals of the Network.

9.2.2.2 SDMC Operational Review

The SDMC conducts a detailed operational review of HPTN protocols simultaneous to the HPTN SRC and HPTN Leadership reviews.

During the review, SDMC staff from data management, statistical, clinical and programming groups review the protocol with an emphasis on data management and analysis (e.g., enrollment, randomization, visit schedule, adverse event (AE) reporting, study product discontinuation, endpoints and objectives) to ensure that the protocol is clear and thus can be efficiently and accurately implemented. The SDMC incorporates all comments and suggested edits into the draft protocol or review summary document and sends it to the LOC CRM.

9.2.2.3 DAIDS PSRC Review

After obtaining SRC approval, the protocol team submits the revised protocol and completed RSR Questionnaire for HPTN Studies, along with the SRC comments and team response, to the DAIDS Medical Officer for DAIDS PSRC review.

The PSRC meets twice monthly (typically on the first and third Tuesdays) to review protocols for which DAIDS provides funding. The readiness of the protocol and timing of submission for PSRC review should be determined in consultation with the DAIDS Medical Officer in advance. If the DAIDS Medical Officer agrees that the protocol is ready, the LOC CRM will then submit the full protocol and other required documents electronically to the DAIDS Medical Officer, at least 10 working days prior to the scheduled PSRC meeting. As part of the protocol development team, the DAIDS Medical Officer will then forward them to the PSRC Administrator at PSRC@tech-res.com with a copy to the Clinical Study Information Office (CSIO) at CSIO@tech-res.com.

The PSRC Administrator will confirm the PSRC review date and coordinate with the DAIDS Medical Officer to communicate this date to the Protocol Chairs and LOC CRM. An invitation for the Protocol Chair(s) and LOC CRM to join an open session prior to closed PSRC review of the protocol will be sent by the PSRC Administrator.

The PSRC provides a scientific overview and general evaluation of research plans specified in the protocol on the basis of:

- NIAID's and other cosponsoring institutes' research agenda and other NIH clinical studies
- Participant safety
- Compliance with United States (US) federal regulations
- Study oversight and monitoring
- Feasibility of timely completion
- When appropriate, plans for interim monitoring and analysis

The PSRC review comments are summarized in a consensus review memorandum that is provided to the protocol team typically within 10 working days after the review. The memorandum identifies major and minor review findings, along with one of four review outcomes:

- Protocol approved without revision (minor revisions may be suggested) — the protocol team proceeds to the next review step (DAIDS regulatory review).
- Protocol approved contingent upon revisions — the protocol team must respond in writing to the PSRC review within 15 working days, and the DAIDS Medical/Program Officer and/or PSRC Chair must approve the team's response within 3 working days.

- Revision of protocol and re-review by the PSRC required — the protocol team revises the protocol, develops a response to the review comments for re-submission and then the PSRC repeats the review process.
- Protocol disapproved — the protocol team will work with the DAIDS Medical/Program Officer, SC Chair and/or other members of the HPTN leadership to determine next steps. The protocol may be resubmitted to the PSRC after incorporation of revisions that address the PSRC's concerns.

If the protocol is disapproved, the Protocol Chair may contact the PSRC Chair to discuss possible modifications. If the Protocol Chair believes there is a reasonable basis for proceeding despite the PSRC denial, he or she should contact the EC. If the EC is in concurrence with the Protocol Chair, the EC Chair may notify DAIDS and request that an appeal process be initiated. The appeal process will involve an impartial third party. If a protocol is disapproved, DAIDS will not permit expenditure of NIH funds for the proposed investigation.

Although the time required for a protocol team to respond to the PSRC review comments will vary with the magnitude and extent of the comments (major versus minor comments), teams are encouraged to provide a written response to the PSRC, if required, and/or a revised draft of the protocol within 15 working days following the receipt of comments. This provides time for team discussion, drafting, and internal team approval of the response.

9.2.2.4 DAIDS Regulatory Review

The protocol team prepares a revised protocol version — labeled "Regulatory Review Version" — reflecting its approved response to the PSRC review. The LOC CRM submits the protocol along with the ClinicalTrials.gov Protocol Registration Checklist to the DAIDS RSC at the time of Full Regulatory Review (copying the CSIO), which is completed within 10 working days of protocol receipt. During this review, an RSC staff member reviews the protocol and sample informed consent form(s) in detail and forwards the protocol and review comments to the DAIDS Regulatory Affairs Branch (RAB). A RAB staff member reviews the protocol and the RSC review findings and may add further comments. The RSC incorporates all comments into a review summary document and transmits the document electronically to the LOC CRM.

9.2.2.5 DAIDS Medical Officer Review

The protocol team addresses the regulatory review findings in a revised protocol version within 15 working days. This revised version — labeled "Medical Officer Review Version" — is submitted to the RSC for a Medical Officer review (copying the CSIO). This review is completed within 10 working days of protocol receipt.

Along with the protocol, the team also submits any supporting documentation needed to explain its response to the regulatory review. In particular, if any regulatory review comments are not adopted, the team must provide adequate justification for this. During the 10-day review period, an RSC staff member reviews the protocol to ensure that all regulatory review findings have been satisfactorily addressed and then forwards the protocol for review by the Medical Officer.

The Medical Officer reviews the protocol to confirm an acceptable response to the regulatory review, including incorporation of all responses into the protocol document, and to complete a final quality assurance check of the protocol on behalf of DAIDS.

The RSC incorporates any review comments into a review summary document and transmits the document electronically to the LOC CRM or confirms that the Medical Officer has approved the protocol as written and that it can be submitted for final regulatory sign-off.

9.2.2.6 RAB Chief Sign-Off

The protocol team addresses any Medical Officer review findings, generally within three working days of receipt of comments, in a revised protocol version — labeled "Final Version 1.0" — and submits this version to the RSC for final review and sign-off by the RAB Chief (copying the CSIO). Along with the protocol, the team also submits any supporting documentation needed to explain its response to the Medical Officer review.

RAB Chief sign-off is expected within approximately 3 (non-IND) or 5 (IND) working days of submission. Once sign-off is obtained, the RSC informs the LOC CRM electronically and files the final protocol. When applicable, the RSC also prepares the protocol for submission to the US Food and Drug Administration (FDA).

9.2.2.7 Distribution of FINAL Version 1.0

Upon notification of RAB Chief sign-off, the LOC CRM electronically distributes the final approved protocol as a PDF file and a Word file, if needed, to the protocol team and participating study sites. Concurrent with distribution to the protocol team and participating study sites, the protocol is posted as a PDF file on the HPTN website.

Once Version 1.0 is approved, for any study that will be conducted at more than one US site, the protocol and informed consent forms are submitted by the LOC for single Institutional Review Board (sIRB) review on behalf of all US sites. After approval by the sIRB, study sites will proceed as per Section 10. For sites that are outside of the US, or for a study that is only being conducted at one US site, those study sites will seek local Institutional Review Board/Ethics Committee (IRB/EC) approval of the protocol, site-specific informed consent, and other associated documents, and complete DAIDS protocol registration procedures for the study, as part of the study activation process described in Section 10. Conduct of the study at a site may not be initiated before IRB/EC approval is obtained from all responsible IRBs/ECs, protocol registration is completed, and all other HPTN study activation requirements are met (for additional information on study activation refer to Section 10).

For DAIDS-sponsored studies, although a ClinicalTrials.gov Protocol Registration Checklist was submitted to DAIDS RSC at the time of Full Regulatory Review, the LOC CRM will also submit the checklist to the assigned DAIDS contractor after Version 1.0 is approved if the study is a DAIDS-sponsored IND study.

9.2.2.8 Expedited Development of High Priority Concepts

Emergent needs in the HIV epidemic and other health crises warrant expedited development and implementation. When these opportunities arise, the EC will discuss the potential study and will vote on whether or not to move the study directly to protocol development. In these cases, the EC or HPTN Leadership will facilitate expedited concept and protocol development, following the steps outlined in the MOP. The decision to expedite protocol development will be determined at the concept stage. The timelines outlined in the MOP may be shortened to facilitate expedited development and review.

9.3 Protocol Modifications

DAIDS-sponsored protocols may be modified by three methods:

- Clarification Memo (CM)
- Letter of Amendment (LoA)
- Full Protocol Amendment

These three methods, which are described in the following sections, are used for both Investigational New Drug (IND) and non-IND protocols. The protocol team determines the method to use in conjunction with the Medical Officer assigned to the protocol. Depending on the method used, the modification may or may not result in a change to the protocol version number, may or may not require IRB/EC review and approval, and may or may not require protocol registration through the RSC.

As with the first final version of the protocol, the LOC CRM is responsible for developing protocol modifications in conjunction with key protocol team members, and issuing final versions to the protocol team and participating study sites. Copies of all final protocol modifications are posted on the study specific page of the HPTN website and sent to the DAIDS RSC and CSIO.

During the time when protocol modification documents are in development and under review, study implementation proceeds per the specifications of the prior approved version of the protocol. Protocol modifications specified in the modification documents may only be implemented after the documents are fully approved, as described below.

9.3.1 Clarification Memos

CMs typically are short documents prepared to provide further explanation or more detailed information related to current protocol specifications. CMs also may be used to correct minor errors in a protocol. The content of a CM should have no impact on participant safety, the risk-to-benefit ratio of study participation, or the study informed consent form(s). If a proposed modification requires a change to the study informed consent form(s), a CM may not be used to incorporate the modification.

CMs must be reviewed and approved by the Medical Officer prior to finalization and distribution. Once finalized, CMs are distributed to all protocol team members and study sites by the LOC CRM. IRB/EC approval of CMs is not required by DAIDS. However, sites are encouraged to submit CMs to their IRBs/ECs for their information. Individual IRBs/ECs may require that CMs be approved by them before implementation. All IRB/EC requirements must be followed. CMs may be implemented by sites upon final issuance by the LOC unless the IRB/EC requires approval.

For any study that will be conducted at more than one US site, CMs are submitted by the LOC for sIRB review on behalf of all US sites.

9.3.2 Letters of Amendment

LoAs typically are short documents prepared to specify changes to a protocol that have minimal impact on participant safety and the risk-to-benefit ratio of study participation, and involves relatively minor modifications of study informed consent forms, if any. LoAs are developed by the protocol team according to the LoA Template. When a LoA is prepared, any prior protocol modifications specified in CMs are incorporated into the LoA. LoAs are prepared and follow the same DAIDS review steps outlined above for original protocols (PSRC review, unless this requirement is waived as determined by the Medical Officer, and the three-step regulatory review process through the RSC).

Once finalized, DAIDS submits LoAs to the US FDA if applicable, and the LOC CRM distributes LoAs to all protocol team members and participating study sites. LoAs must be reviewed and approved by the responsible IRBs/ECs prior to implementation. They typically include instructions to study sites with regard to seeking IRB/EC review and approval and recommendations on how to notify participants of the changes, if applicable. In some circumstances, re-consenting of enrolled participants may be required. In other circumstances, protocol teams may recommend providing a letter to participants informing them of the modifications or ask that the information be provided to the participant and noted in the case history record. Regardless of the protocol team's recommendations, responsible IRBs/ECs may require modification of the study informed consent

forms and/or re-consenting of enrolled participants to reflect a LoA; in such cases, IRB/EC requirements must be followed. Modified procedures specified in the LoA may not be conducted at a site until IRB/EC approval is obtained from all responsible IRBs/ECs for that site.

For any study that will be conducted at more than one US site, LoAs are submitted by the LOC for sIRB review on behalf of all US sites.

LoAs do not result in a change of the protocol version number but do require protocol registration through the RSC (refer to the DAIDS Protocol Registration Manual).

***NOTE: Amendments including any revised site-specific informed consent forms should be implemented immediately upon CRS receipt of all required IRB/EC approvals. Please refer to the latest DAIDS Protocol Registration Manual, section "Amendment Registration," for details.**

9.3.3 Full Protocol Amendments

Full protocol amendments are prepared to incorporate significant changes — involving more than minimal impact on participant safety and risk-to-benefit ratio of study participation — and result in the generation of a new protocol version with a new version number. Amendments also are typically required to incorporate a significant increase in the number of participants to be enrolled in an IND study. When amendments are prepared, any prior protocol modifications specified in a CM or LoA are incorporated into the amendment.

Examples of changes requiring a full protocol amendment may include:

- New study product added to the protocol
- Change to inclusion or exclusion criteria
- New safety information on study product in the protocol

Protocol amendments are developed by the protocol team and, as shown in the table above, must complete many of the protocol review and approval steps described in Section 9.2. Protocol amendments must be reviewed by the PSRC unless a waiver is granted. The Medical Officer for the protocol will confirm whether PSRC review is required. If so, the PSRC review steps described in Section 9.2.2.4 must be followed. In addition, the regulatory review, Medical Officer review, and RAB Chief sign-off steps specified in Sections 9.2.2.5 through 9.2.2.7 must be completed for all amendments.

Once finalized, DAIDS submits amendments to the US FDA if applicable, and the LOC CRM distributes amendments to all protocol team members and participating study sites. Sites must then seek IRB/EC approval of the protocol and other associated documents and complete DAIDS protocol registration procedures (see Section 10) for the amended version of the protocol. Revised procedures specified in the amendment may not be conducted until after IRB approval is obtained. Participants enrolled in a study after approval of a protocol amendment must be consented to the study using the revised informed consent form(s) associated with the amended version of the protocol. For participants enrolled prior to approval and registration of an amendment, guidance on whether re-consenting is required (using the revised informed consent form(s) associated with the amendment) will be provided by the protocol team, typically in the summary of changes that accompanies the amended protocol. Regardless of protocol team's recommendations, site IRBs/ECs may require re-consenting of previously enrolled participants; in such cases, IRB/EC requirements must be followed.

For any study that will be conducted at more than one US site, full protocol amendments are submitted by the LOC for sIRB review on behalf of all US sites.

HPTN Requirements and Procedures for Protocol Modifications

Modification Requirements	Clarification Memo	Letter of Amendment	Protocol Amendment
Content involves change of risk-to-benefit ratio?	No	Yes, but impact should be minimal.	Yes
Content must be reported to study participants?	No	Yes	Yes
Content requires change of informed consent form	No	Yes	Yes
Results in change of protocol version number?	No	No	Yes
Requires approval by Medical/Program Officer?	Yes	Yes	Yes
Requires approval by PSRC?	No	Yes, unless requirement waived. Medical/Program Officer determines whether PSRC review is required.	Yes, unless requirement waived. Medical/Program Officer determines whether PSRC review is required.
Requires DAIDS regulatory review?	No	Yes	Yes
Requires final Medical Officer review following regulatory review?	No	Yes	Yes
Requires RAB chief sign-off following Medical Officer review	No	Yes	Yes
Requires approval by site IRBs/ECs?	No, unless required by IRB/EC (but FYI submission is recommended).	Yes. Amended procedures may not be undertaken until after IRB/EC approval is obtained.	Yes. Amended procedures may not be undertaken until after IRB/EC approval.*
Requires protocol registration?	No	Yes. Amended procedures may not be undertaken until IRB/EC approval is obtained. *	Yes. Amended procedures may not be undertaken until after IRB/EC approval is obtained.*

9.4 Revised Informed Consent Forms

If consent forms need revision, site staff should refer to Section 10.2.1 and consult with the LOC staff to determine the process for review and translation.

9.5 Collaborative Network Studies

9.5.1 Concept Development and Review for Collaborative Studies

Proposing investigators from collaborating networks will work with their ECs (or respective relevant body) to determine responsibilities for concept development and review process.

9.5.2 Protocol Development for Collaborative Studies

The HPTN will work with collaborating network LOCs to determine an agreed-upon approach for protocol development and implementation. Network leadership negotiations and agreements will drive protocol team representation of each network. Typically, both networks will have balanced representation on the protocol team. For monoclonal antibody (mAb) studies conducted jointly by the HPTN and HVTN, a cross-network protocol template will be used to expedite development.

A "Responsible/Accountable/Consulted/Informed (RACI)" approach, which is a collaborative responsibility assignment matrix, will be used to set expectations for all joint studies. Study leadership will first itemize all anticipated activities during the lifecycle of the trial, and for each activity, assign who (e.g., HPTN and/or other networks' LOC/SDMC/LC, DAIDS or other party) is responsible, accountable, consulted and/or informed. Responsibilities and accountabilities may either be shared across networks or fall with one network.

9.5.3 Protocol Review Process for Collaborative Studies

All collaborative protocols will be reviewed by each collaborating network per their network procedures. Where possible, and per agreement by the participating networks, joint review processes may be instituted to increase efficiencies such as for the HPTN-HVTN collaborative studies (see below). It is generally expected that DAIDS review processes as described above will be applicable to collaborative studies. The collaborating LOCs will work together to develop a combined study timeline that incorporates and integrates milestones for each network, which will be coordinated to maximize efficiencies in the review process and monitored by LOC staff. HPTN LOC staff will be responsible for keeping the HPTN EC apprised of study timelines, key points of engagement with other networks and any obstacles that must be addressed.

9.5.4 Concept and Protocol Review Process for HVTN/HPTN Collaborative Studies

For protocols jointly led between the HPTN and HVTN, the HVTN/HPTN Joint Science Review Committee (JSRC) will review concepts in place of the EC and conduct the first step in the protocol review process. Refer to Section 4 for composition of the JSRC. Refer to the HVTN/HPTN Cross-Network MOP for additional details on concept and protocol development and review processes for HVTN/HPTN collaborative studies.

9.5.4.1 JSRC Concept Review

Concepts should include a target date for PSRC review. The JSRC will review concepts based on the following criteria: scientific merit, impact on the product development pipeline, and alignment with the scientific agenda and priorities of the networks. A JSRC call will be scheduled and the concept circulated for JSRC review a minimum of five business days in advance of the call.

Following review discussion, JSRC voting members will cast their vote. The JSRC votes are kept confidential and anonymous. Concepts will be approved for protocol development if a "Yes, approved for protocol development" vote of 80% of the JSRC voting members in attendance are received. Investigators who submit concept plans are informed directly of the outcome of the review and vote through a summary of the review discussion and all reviewers' comments.

9.5.4.2 JSRC Protocol Review

The protocol review will ensure that study protocols are scientifically rigorous, accurate, consistent and complete to the extent possible relative to other network protocols. Generally, the JSRC should review the protocol to assure that it is ready for submission to the Division of AIDS Prevention Sciences Review Committee (PSRC), taking into consideration the PSRC's review criteria. The PSRC considers the following: Whether there are major safety issues; whether the objectives are clearly stated; and can the design answer the question.

The JSRC will review the protocol and provide written comments within five working days of receiving a draft, with a call scheduled immediately following. The protocol operations team members (Protocol Team Lead/Clinical Research Manager/Clinical Trials Assistant) will provide a summary of consensus comments and distribute these to the JSRC prior to the call for discussion. After the call, these will be edited as needed and finalized by the JSRC chairs. The protocol operations team will distribute the final consensus comments to the JSRC as well as the protocol team.

Following the discussion, the chairs of the protocol being reviewed may answer questions and discuss key review findings from JSRC primary group members. The approved review comments and review outcome are provided electronically to the protocol team typically within two working days of the review call. The summary documents one of four review outcomes:

- Approved for DAIDS PSRC submission without revision – the protocol team may proceed to the next review step with no or only minor revisions
- Approved for PSRC submission contingent upon response and revision, full re-review by JSRC not required – the protocol team prepares a written response to major consensus review comments, submits a revised protocol for JSRC chairs to review and grant final approval
- Protocol disapproved as written – the protocol team prepares a written response to any major consensus review comments, revises the protocol, and submits both for JSRC re-review
- Not approved

JSRC approval is required prior to PSRC submission for all HVTN/HPTN collaborative studies.

10 STUDY SPECIFIC PRE-IMPLEMENTATION, SITE ACTIVATION AND STUDY INITIATION

After finalization of an HPTN protocol, a number of pre-implementation steps must be completed before a study can be initiated. These can broadly be categorized into study-specific Network requirements and study-specific site activation requirements.

Study-Specific Network Requirements: Certain steps must be taken by the HPTN central resources, protocol team members, and the Division of AIDS (DAIDS) to prepare a study for opening. Several of these steps require collaborative work; chief among these is development of the study case report forms (CRFs), any additional data capture methods or surveys, and Study-Specific Procedures (SSP) manuals, described further in Section 10.1. All such study-specific Network requirements must be met prior to the first site being activated to begin enrollment into a study.

Study-Specific Site Activation Requirements: Key pre-implementation activities involved in the study activation process are described in greater detail in Section 10.2.

Once all study-specific site activation requirements are met at a site and documented, the HPTN Leadership and Operations Center (LOC) Clinical Research Manager (CRM) will issue a study-specific Activation Notice (see Section 10.2.9) confirming that all requirements have been met and indicating that the site may initiate study implementation. No study procedures may be undertaken before the activation notice is received. After issuing the study-specific Site Activation Notice, the LOC CRM will provide site staff with a copy of the documentation upon which activation was based.

10.1 Network Requirements

10.1.1 Clinical Trials Agreement

A Clinical Trials Agreement (CTA) is the agreement negotiated between a collaborating pharmaceutical partner and the study sponsor (typically DAIDS), to document the responsibilities and rights of each party in the agreement. The agreement includes, but is not limited to, Investigational New Drug (IND) application sponsorship, safety and data monitoring, and access to data.

The DAIDS Regulatory Affairs Branch (RAB) and the Regulatory Support Center (RSC) handle the development of CTAs for HPTN studies, and the negotiation of these agreements between DAIDS and product manufacturers or other cosponsors. Development of a CTA typically begins once a protocol is approved by the DAIDS Prevention Science Review Committee (PSRC). The RSC and RAB will seek input and review of CTAs by the DAIDS Medical Officer for that study; and as necessary, HPTN LOC, SDMC, and LC, and/or the investigators, prior to finalizing. The status of a CTA may be tracked on the NIAID Clinical Research Management System.

Copies of executed CTAs are provided to the manufacturer, the HPTN SDMC and LOC. Study sites are not expected or required to maintain copies of CTAs in their onsite essential documents files; these are maintained by DAIDS and the cosponsor(s).

10.1.2 ClinicalTrials.gov Registration

For DAIDS-held IND studies, the responsibility to meet the ClinicalTrials.gov reporting requirements falls within DAIDS and is assigned to a DAIDS contractor. For non-IND studies, the Network is responsible. Additional details about the ClinicalTrials.gov registration process, including a checklist that must be completed and submitted to DAIDS RSC at the time of Full Regulatory Review and to the assigned DAIDS contractor once Version 1.0 is approved can be found at: https://rsc.niaid.nih.gov/networks-protocol-teams/clinicaltrialsgov-checklist. See Section 9.2.2.4 for instructions to submit the checklist to DAIDS RSC and Section 9.2.2.7 for instructions to submit the checklist to the assigned DAIDS contractor.

10.1.3 Protocol-Specific Monitoring Plan Confirmation

Before any enrollment may proceed for any study, DAIDS must confirm that the protocol-specific monitoring plan is in place. DAIDS will lead the contracting of this plan providing the monitors with the plan for study monitoring.

10.1.4 Safety and Other Committee Establishment

Per Section 14.2.2, the protocol team leadership will ensure that all safety oversight groups and reviewers (i.e., Clinical Management Committee, Independent Safety Reviewers) are in place prior to study initiation, as appropriate to the safety oversight needs of the study as specified in the study protocol.

10.1.5 eCRF Development

The SDMC is responsible for developing eCRFs or EDC for each protocol. eCRFs, used with electronic data capture, are designed to collect the data used to address protocol-specified study objectives. Typical HPTN eCRF development processes are as follows:

- Development of eCRF content typically begins when the protocol is deemed stable, usually version 1.0
- The internal SDMC study team puts together a data collection plan based on protocol objectives and reporting needs
- Standardized eCRF content and examples from previous studies are gathered for protocol team review by the SDMC Clinical Data Manager (CDM)
- The draft eCRF content and relevant study materials (e.g., Schedule of Forms) are reviewed by the protocol team and additional content is developed, as needed
- As needed, finalized eCRF content is translated by the study sites or contractor (ideally before any planned operational walkthrough or pre-study operations visit, as needed). The translation process is initiated and coordinated by the SDMC. Back-translations, especially for behavioral questionnaires, will be reviewed by the SDMC and the behavioral scientists if applicable

10.1.6 Additional Data Capture Methods

Some types of studies may require methods of data collection in addition to, or instead of, EDC or eCRFs such as an "[Audio]-Computer Assisted Self-Interview" ([A]CASI, electronic pill boxes and SMS), surveillance data or evaluation metrics. The protocol chair and team will assess whether additional methods of data capture are required and if so, whether the SDMC, a contractor, or some other Network resource will be responsible for designing the required system. If the SDMC develops the system, development will follow steps similar to the design of eCRFs.

10.1.7 Study-Specific Procedures (SSP) Manuals

10.1.7.1 SSP Manual Development

In addition to study protocols, SSP manuals (generally referred to as just SSP) are prepared as stand-alone instructional and reference resources to guide conduct of HPTN studies at each site. SSP manuals contain links to applicable DAIDS policies and manuals (such as the DAIDS SCORE Manual and the Manual for Expedited Reporting of Adverse Events to DAIDS) and provide detailed standardized instructions for conducting protocol-specified procedures. The manuals are available upon request to the US FDA, other government and regulatory authorities, and site IRBs/ECs.

Development of SSP manuals proceeds in parallel with eCRF development beginning when a protocol is nearly finalized. Manuals are generally finalized shortly after the first study-specific site training. All manuals should be finalized prior to activation of the first participating site.

The LOC CRM is responsible for posting the manuals in an accessible location for the study team and study leadership; however, assembling and finalizing the individual manuals is the responsibility of the responsible network partner. For example:

- The SDMC CDM is responsible for the manual related to data collection/management, randomization, any additional methods of data collection (e.g., ACASI) developed by the SDMC and the protocol reporting plan
- The LC and/or other representative are responsible for the manual related to laboratory processing, testing, etc.
- The LOC will develop and manage the Study Management Overview; Accrual, Follow-up and Retention; and Clinical, Safety and AE Management manuals
- The DAIDS PAB protocol pharmacist is responsible for the development of the Pharmacy Study-Specific Procedures (SSP) Manual related to study product management by the site pharmacist. The PAB protocol pharmacist also provides significant input on other SSP manuals related to participant study product use. See Section 23 for responsibilities of the HPTN Pharmacist.

All manuals follow a common template table of contents that is tailored to the needs of each study.

Regardless of primary authorship assignments, every SSP manual must be circulated for review by study leadership (e.g., network resources, sponsor, and protocol chair) prior to finalization to ensure clarity, consistency, and compliance across all aspects of the study.

After incorporating all team and site input as needed, the primary author of each manual will send a finalized Version 1.0 (following good documentation practices for versioning and dating) to the LOC CRM for electronic posting. The LOC CRM will also create and maintain a master version control log for all SSP manuals.

10.1.7.2 SSP Manual Amendments

If a need for modifications to an SSP manual is identified after distribution of Version 1.0, the responsible author will revise the text and circulate the draft for review and comment from protocol team members as needed/applicable prior to finalizing a new version. The LOC CRM will post the final, revised manual and update the master version control log to document the change. The LOC CRM will inform the study team and site staff that the electronic file(s) containing the revised manual (with new version number and version date) and version control log have been posted on the study's collaborative electronic space and instruct the site staff to replace the existing manual with the new manual in all electronic and printed working copies of the SSP manual. The old manual should be moved to archive files.

It is the responsibility of the IoR to ensure that all manuals are updated and that updated procedural information is communicated to all applicable study staff in a timely manner.

10.1.8 Pre-study Site Assessment Visits

Prior to site-specific study activation and/or initiation of an HPTN study, staff from the LOC, SDMC, LC, Clinical Site Monitors and/or DAIDS may conduct one or more pre-study site assessment visits to ascertain site readiness for study implementation. Not all studies or study sites will need this visit. The need for this visit will be assessed on a case-by-case basis. The focus of the visit may vary depending on the stage of the study's development, the type of study to be conducted, and

specific requirements for study conduct. The timing of these visits will be planned with the site investigator and staff to allow participation of key site study staff.

The LOC CRM, SDMC staff, and LC staff members assess site facilities, operations, procedures, and available staff. They work with site investigators and staff to identify needs for study implementation (clinic, pharmacy and laboratory facilities, staffing needs, IT and data management best practices, etc.) and develop local plans for meeting them. Staff from the LOC, SDMC, and LC may visit together or separately. Depending on the complexity of the protocol and the site development and infrastructure, the LOC, SDMC, LC and/or DAIDS may make multiple visits.

Following the visit, the LOC, SDMC, or LC staff member typically generates a visit report and distributes it to the site investigators, DAIDS, and the other Network entities. The LOC CRM, SDMC CDM, and/or LC representative work with the site staff to address any issues raised by the visit(s) and documented in the visit report(s). Action items from pre-activation visits may also be documented in the study-specific site activation checklist (see Section 10.2).

10.1.9 Study-specific Training

LOC, SDMC, LC staff members, and the DAIDS PAB Pharmacist collaborate with site staff to plan and implement study-specific training. This training is described in Section 11.4 and may be virtual or in person. Study-specific training must be completed as a requirement for study-specific site activation (see Table 10-1 below).

10.1.10 FDA Submission and Safe to Proceed Notice

- For studies under a new IND, the sponsoring agency will submit the application to the US Food and Drug Administration (FDA). For these studies, completion of a US FDA 30-day review period/safe to proceed notice is required prior to the study opening.

10.2 Study-Specific Site Activation Requirements

Table 10-1 lists the activities that must be completed by each site in order to begin implementation of a specific HPTN study. These requirements are further described in the remaining sub-sections below.

Table 10-1 HPTN Study-specific Activation Requirements

A. For protocol-specific sites, verify OCSO site approval (refer to Section 16)

B. Pharmacy approval of site readiness from the DAIDS PAB Pharmacist may include:

- Confirmation of Pharmacy Establishment Plan and appropriateness for study
- SOP for study product management and approval from the DAIDS PAB (if applicable) (For studies where product may be managed by the HPTN Pharmacist, see Section 23.)
- All applicable import approvals for study products (non-US sites only)
- All applicable export approvals for study products (non-US sites only)
- Training for site pharmacists, if required by PAB
- Specific requirements for a particular study product
- Protocol specific prescriptions templates, as applicable

- For studies involving the HPTN pharmacist, see Section 23 for activation requirements

C. Data management approval from the Statistical and Data Management Center (SDMC) of site readiness based on the following:

- SOP(s) for data management, covering computer security, access and authentication, information security, data collection and handling, and data collection training.
- SOP for data quality assurance/quality control (QA/QC) procedures
- SOP for randomization procedures, if applicable
- Availability of required SDMC-provided materials including access to web-based EDC or survey software, randomization, and associated training modules, including the Targeted Source Document Verification (TSDV) (if required per OCSO)

D. Laboratory approval from Laboratory Center (LC) of site readiness, based on the policies found on the DAIDS Clinical Research Laboratory and Specimen Management website, which may include:

- Laboratory Quality Management Plan
- SOP for study-specific specimen management plan and "chain of custody" related to clinical/safety testing and management of samples for the study endpoints
- Confirmation of current CVs (or resumes) of key laboratory personnel
- Verification of Laboratory Data Management System (LDMS) set-up and training
- Verify current International Air Transport Association (IATA) specimen shipping certification for all staff members involved in the specimen management plan
- Good Clinical Laboratory Practice (GCLP) training for the appropriate laboratory staff
- The following for non-CLIA accredited laboratories
- proficiency in performing protocol-required tests
- appropriate validation and documentation of validation for protocol analytes
- any other applicable certifications

E. Site-specific SOPs confirmed in place by LOC for:

- Study source documentation
- Obtaining informed consent from potential study participants
- Participant eligibility determination
- Participant safety monitoring and adverse event/serious adverse event (AE/SAE) reporting (if applicable) and follow-up
- Participant accrual
- Participant retention

- Communication with responsible IRB/EC
- Communication with affiliated additional locations, if applicable
- Audits and Inspections
- Emergency unblinding (if applicable)
- Study-specific SOPs (if applicable)

F. Other requirements confirmed by the LOC:

- For DAIDS-sponsored studies with more than one US site: Single Institutional Review Board (sIRB) approval of the protocol and informed consent forms (including local language versions, back-translations and local language Translation Confirmation Documents, where applicable). For studies with no more than one US site, and for all non-US sites: local IRB/ethics committee (EC) approval, and (if applicable), regulatory authority approval, (e.g., Ministry of Health, drug controller/regulatory agency)
- Protocol registration approval from the Regulatory Support Center (RSC) Protocol Registration Office (PRO), based on the following:
- Signed FDA Form 1572 or DAIDS Investigator of Record Form
- CV of the Investigator of Record (IoR)
- Confirmation received from investigator that completion of Human Subjects Protection (HSP) training for key study staff is current (see Section 11.1)
- Confirmation received from investigator that completion of GCP training for key study staff is current (see Section 11.2)
- Study staff signature sheet, roster, and delegation of duties
- Confirmation received from investigator that current CVs (per DAIDS policies) for key staff are available on site
- For IND studies, verification that Financial Disclosures are on file for all relevant staff that are on the Form FDA 1572 (see Section 7)
- Completion of study-specific training
- Resolution of any other action items identified in any other site preparation activities
- Others as needed (site- and study-specific)

10.2.1 Informed Consent Forms, IRB Approval and Protocol Registration

The DAIDS Protocol Registration Manual includes detailed instructions on obtaining site protocol registration, including the content and formatting of ICFs that must be submitted, as well as documenting and submitting IRB/EC approvals. Section 8 further describes IRB/EC and human subjects requirements for HPTN research studies.

10.2.2 Standard Operating Procedures and/or Plans

As a condition for study activation, site- and study-specific standard operating procedures (SOPs) and/or plans that describe the requirements and operations of a particular study must be in place. A set of standard SOPs are typically required for any HPTN study (see Table 10-1); additionally, study-specific SOPs may be required depending on the nature of the study, as determined by the protocol team. The Activation Checklist will specify which SOPs are required. If a site has established site SOPs that adequately cover required procedures for specific studies, these may be used to fulfill the study activation requirements. In order for these SOPs to cover any HPTN study, they should be generic and not reference the study name or number from any specific study(ies). Sites may consider developing a library of standardized SOPs that could be applicable to any HPTN studies. If a generic SOP needs modification to make it study-specific, a study-specific addendum or appendix should be added.

Details of what must be included in study-specific SOPs will be described in each study's SSP manuals.

10.2.3 Delegation of Duties Log

Sites must create and maintain a study-specific Delegation of Duties log. This log must comply with requirements as outlined in the DAIDS SCORE Manual.

10.2.4 Study Product Acquisition and Shipment to Sites

Study product for HPTN studies is typically received from the manufacturer or other source and stored and distributed to the study sites by the DAIDS Clinical Research Product Management Center (CRPMC). The DAIDS Pharmaceutical Affairs Branch (PAB) has established the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks which describes the required pharmacy and study product management standards for the conduct of DAIDS clinical trials and includes requirements for personnel, facilities, equipment, and processes. (For studies where product may be managed by the HPTN Pharmacist, see Section 23.)

Before study product is sent to a non-US study site, documentation of local drug authority approval for importation of the product for the study use must be obtained and submitted to the DAIDS PAB. It is the responsibility of the IoR and Pharmacist of Record to know the necessary local requirements and to obtain the necessary approvals including those that may provide waivers for import fees. To aid sites in obtaining local approvals, the CRPMC will provide a *pro forma* invoice upon request, detailing the quantity, lot numbers, expiration dates (when available), value, and other details of all products and related materials to be shipped to the site for use in the study. Sample product labels will also be provided by the DAIDS PAB upon request for use in obtaining local approvals, if necessary.

Non-US study sites are encouraged to provide information to the DAIDS PAB pharmacist on the protocol team that may be helpful in shipping products to the study site, including suggestions for preferred couriers and specific wording to be used on the shipping documents to avoid unnecessary customs delays or fees.

For studies involving study products that are not under an IND with the US FDA, export approval from the US FDA may also be required before study product can be shipped to certain countries.

This approval may be sought by either the manufacturer or the local drug authority and takes approximately 8-12 weeks after receipt of the request by the US FDA.

For most studies, study product should be available at the site before the site is activated and begins screening and enrollment. However, depending on the length of the screening process and other details such as shelf-life, a site may be activated prior to study product availability at the site, if approved by DAIDS. Each study team will determine at what point a site may be activated with regards to study product availability. Questions regarding shipment of study products to sites should be directed to the DAIDS PAB Pharmacist of the protocol team. (For studies where product may be managed by the HPTN Pharmacist, see Section 23.)

10.2.5 Study Product Management

General information and guidelines for study product management are included in the latest version of the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks is accessible on the DAIDS website. All sites conducting studies with study products are required to have a copy of this document on file. The Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks details the documentation requirements associated with study product receipt, control, accountability, dispensing, and final disposition. The manual also details the responsibilities of the Pharmacist of Record. The pharmacist at each site who is designated the Pharmacist of Record for a particular study will manage and control the study products used in that study. These responsibilities include, but are not limited to, developing and maintaining a study product management system.

More detailed instructions and procedures for the handling of study products for an individual study may be provided in the protocol and Pharmacy SSP Manual. Questions regarding the management of study products should be directed to the DAIDS PAB Protocol Pharmacist. (For studies where product may be managed by the HPTN Pharmacist, see Section 23.)

10.2.6 Pharmacy Establishment Plans

A Pharmacy Establishment Plan is required for each site conducting an HPTN study involving study product(s). A copy of the DAIDS Standard Pharmacy Establishment Plan form can be found in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks. An electronic copy is made available to the site via DAIDS PAB. The Pharmacy Establishment Plan (PEP) and applicable PEP Module(s) must be approved by the DAIDS PAB as a condition for shipping study product to a site and for initiation of study procedures. This plan is submitted directly by the site Pharmacist of Record to the DAIDS PAB for review and approval.

The Pharmacist of Record is encouraged to work with study investigators and other local staff members to complete the DAIDS Pharmacy Establishment Plan. Questions regarding the completion and review of Pharmacy Establishment Plans should be directed to the DAIDS PAB. (For studies where product may be managed by the HPTN Pharmacist, see Section 23.)

10.2.7 Essential Documents

HPTN study sites must maintain a number of administrative and regulatory documents pertinent to each HPTN study in which they participate. These documents commonly are referred to as essential documents. Although sites are allowed some flexibility in their filing systems, all required documents should be stored in an organized manner and must be easily retrievable for review by the Clinical Site Monitor and other authorized individuals. Study sites are encouraged to begin organizing and filing required documentation upon receipt of the final study protocol and must maintain complete and accurate files from that time forward, in accordance with the record retention requirements stated in the study protocol. DAIDS requirements and additional guidance on management of essential documents is provided in the DAIDS SCORE Manual.

10.2.8 Study Material Translation

Certain study-related materials may be translated into local languages for HPTN studies involving non-English speaking participants. As a general rule, informed consent forms, community education materials, advertisements, questionnaires, interview forms, and other materials administered or distributed directly to study participants must be translated. The IoRs are responsible for ensuring that study site staff and participants are provided with all required study-related information in a language that is understandable to them.

SSP manuals, in whole or in part, also may need to be translated for some sites in some studies. Study sites are responsible for completing all translation tasks unless otherwise arranged with the HPTN LOC, LC and/or SDMC.

Translations are completed after the English versions are finalized. Translated informed consent forms must be submitted for protocol registration as described in the DAIDS Protocol Registration Manual.

10.2.9 Study-specific Site Activation Notification

When a site has completed all study activation requirements (see Table 10-1), the LOC CRM will send an HPTN Site Activation Notice to the site. Upon receipt of this notification the site may initiate the study. Only upon receipt of this notification may a site initiate recruitment and screening of study participants. In multi-site studies, sites are individually activated as documented fulfillment of activation requirements at each site is completed (i.e., activation of a site need not await readiness of the others).

11 TRAINING

The HPTN is committed to developing qualified, trained staff to conduct HPTN studies. Training for Clinical Trials Unit (CTU) staff adheres to the standards listed below:

- All key CTU/CRS staff are stated in the Glossary of DAIDS Clinical Research Terms as "individuals who are involved in the design and conduct of NIH funded human subjects' clinical research. This includes all individuals named on the form FDA 1572 or the Division of AIDS (DAIDS) Investigator of Record (IoR) Agreement and any clinical research site personnel who have more than minimal involvement with the conduct of the research (performing study evaluations or procedures or providing intervention) or more than minimal study conduct-related contact with study participants or confidential study data record, or specimens". Key personnel must complete the Human Subjects Protection/Human Subjects Research (HSP/HSR) training as well as Good Clinical Practice (GCP) training that is required by their institution. The Principal Investigator (PI) of the CTU grant is responsible for ensuring that the IoR maintains training records onsite and makes these records available to the Clinical Site Monitor, the DAIDS Program Officer and/or other designated DAIDS staff upon request.
- All key personnel involved in clinical trials subject to United States (US) Food and Drug Administration (FDA) regulations must receive training prior to study initiation and every three years (or sooner if required by local institution) thereafter that includes relevant aspects from the following: Electronic Records and Signature (21 CFR Part 11); Investigational New Drug Application (21 CFR Part 312); Protection of Human Subjects (21 CFR Part 50); Financial Disclosure by Clinical Investigators (21 CFR Part 54); Institutional Review Boards (21 CFR Part 56). The IoR is responsible for maintaining complete training records.
- Laboratory related training is required as specified in Section 11.3 and Section 13.
- The HPTN, in accordance with the US Code of Federal Regulations (CFR), requires study-specific site training prior to study initiation (Section 11.4).
- CTUs/CRSs are expected also to provide training for new staff and ongoing training for current staff (Section 11.5).
- CTU/CRS training must be in accordance with the DAIDS policy on personnel qualifications, training, responsibilities and documentation found in the DAIDS SCORE Manual.

An overview of mandated training is found in the table below with further details in the following sections.

HPTN Training Requirements			
Training	Required Personnel	Timing/Frequency	Sources for Training
HSP/HSR	All key CTU/CRS staff (see above)	Prior to awards being made for clinical research and every three years thereafter (or sooner depending on institutional requirements)	Online training course, e.g., CITI Program or DAIDS Learning Portal) Other online training programs, e.g., online university-based training modules Commercial training programs
GCP and US Code of Federal Regulations (CFR) training requirements	All key CTU/CRS staff (refer to DAIDS SCORE Manual)	Prior to study initiation and every three years thereafter (or sooner depending on institutional requirements)	Online training course, e.g., CITI Program or DAIDS Learning Portal) Other online training programs, e.g., online university-based training modules Commercial training programs
International Air Transportation Association (IATA) training	All staff who transport, ship or receive infectious substances and diagnostic specimens	Prior to handling infectious materials and specimens as part of an HPTN study (certification of staff members required for study specific site activation at the site); regulations reviewed annually and certification every two years thereafter	Several resources listed in Section 11.3
Laboratory Data Management System (LDMS) training	Staff of CTU/CRS laboratories	At time of installation of LDMS and as needed	Frontier Science Technology and Research Foundation (FSTRF) training at Network annual meetings and regional meetings, onsite, or at FSTRF in Amherst, NY or by an officially trained Train-the-Trainer
Good Clinical Laboratory Practice (GCLP)	Laboratory Director, Laboratory Manager/Supervisor and/or quality assurance/quality control (QA/QC) technologists	Prior to involvement in an HPTN study and then as needed	GCLP courses provided by the DAIDS contractor or online Courses available from private training companies. NOTE: these may not cover the appropriate DAIDS related regulations

HPTN Training Requirements			
Training	Required Personnel	Timing/Frequency	Sources for Training
			Refresher training is available on the DAIDS learning portal
Study-specific training	Applicable CTU/CRS study staff	Prior to initiation of study and for new staff prior to conducting study-related activities	Leadership and Operations Center (LOC) Clinical Research Manager (CRM), Statistical and Data Management Center (SDMC) Clinical Data Manager (CDM), HPTN Laboratory Center (LC) representative, DAIDS PAB Pharmacist, HPTN Pharmacist (as applicable – see Section 23) Training materials are typically posted to the HPTN website specific to each study and available to site teams for ongoing training needs. This may be in person, modules, teleconference or other.

11.1 Human Subjects Protection/Human Subjects Research Training

All key personnel must have current HSP/HSR training documentation in place prior to study initiation and every three years thereafter (or sooner depending on institutional requirements), as well as prior to specific study initiation New clinical research site personnel (hired after study initiation) must have current HSP training documentation in place prior to conducting study-related procedures.

Many universities and research institutions provide training which, when documented, fulfills this requirement. The Association of Clinical Research Professionals (ACRP) also provides a course though the DLP which meets the requirement.

11.2 Good Clinical Practice Training

All key personnel must have current GCP training documentation in place that meets International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 standards prior to study initiation and every three years thereafter (or sooner more frequent depending on institutional requirements). New clinical research site personnel (hired after study initiation) must have current GCP training documentation in place prior to conducting study-related procedures. The NIAID DLP offers GCP training modules.

Training of all HPTN site study staff is encouraged and facilitated through the provision of onsite GCP training to the extent possible. To meet immediate or broader needs for GCP training for site study staff, CTUs may seek additional sources for continuing GCP training. Local universities or research centers may offer GCP training opportunities. CTU staff members are encouraged to seek courses that provide certification of participation.

11.3 Laboratory Related Training

To ensure quality research and safeguard study participants, DAIDS requires that all HPTN studies be conducted in accordance with GCLP. The LC also requires that applicable laboratory personnel receive GCLP training prior to conducting study-related procedures and every three years thereafter or as designated. Training of all HPTN key laboratory staff is facilitated through the provision of regional GCLP training as well as through an online training program.

All HPTN studies rely heavily on the capacity of CTU laboratories to handle, process, and ship participant specimens. The work of qualified and trained laboratory staff at the research sites is essential. The HPTN requires the following training for laboratory personnel:

Laboratory Data Management System

The LDMS is the laboratory software installed at each of the CTUs to assist with specimen management, storage, and shipping. LDMS training is provided at FSTRF or at each CTU research site when a system is placed at the site.

Opportunities for refresher training are provided. At the request of the LC, FSTRF may provide refresher training on the LDMS at annual meetings, regional meetings, and protocol trainings or through web-based focused trainings. The LC staff members are typically available at these training sessions to provide information related to the HPTN and also to answer questions from site representatives. FSTRF staff will follow-up with site representatives after these training sessions to ensure that they are aware of the need to share the information with other site staff. FSTRF will also hold trainings at their headquarters in Amherst, New York.

The LC staff members (who have passed the train-the-trainer sessions) will also provide study-specific LDMS training onsite during the study-specific training, if feasible, as well as during routine site visits. International QA/QC coordinators are also a resource for handling refresher training. SDMC staff monitor the specimen management and storage modules. If problems or trends are noted that indicate more training is needed at a site, *ad hoc* training will be arranged. CTUs/CRSs, at their expense, may also request additional training if needed, for example, when new laboratory personnel are hired.

International Air Transport Association

IATA regulates the safe transportation of dangerous goods by air in accordance with the legal requirements of the International Civil Aviation Organization (see Section 13.4.1 for further details). The HPTN, in accordance with IATA requirements, requires training and certification for all HPTN members involved with the handling, transporting (by air and ground), and receiving and shipping of infectious substances and diagnostic samples. Certification of all site staff members, who transport and/or ship dangerous goods, is required prior to study activation at a site.

Site personnel should review the IATA regulations annually as well as complete required training in hazardous materials (HAZMAT) regulations as they pertain to IATA shipping regulations.

Each CTU is responsible for training the pertinent staff members on IATA shipping regulations and is required to have a current IATA manual onsite. CTUs are required to provide documentation of IATA certification of personnel upon request by the LC or a DAIDS contractor. The site's Primary Network Laboratory (PNL) is responsible for assuring that the laboratory has a current IATA Dangerous Goods Manual and appropriate training materials. Refer to the links below for IATA training resources:

http://iata.org/index.htm

http://www.saftpak.com

http://fedex.com/us/services/options/express/dangerousgoods/seminars.html?link=4

http://www.dhl-usa.com/solutions/express.asp?nav=dhlExp

http://www.dot.gov/

http://www.usps.com

Biohazard and Containment Training

Clinical and laboratory personnel are expected to complete annual clinical safety training including training on blood borne pathogens and infection control. It is the responsibility of the CTU to provide the training to all clinical and laboratory staff using information and materials provided by their institutions as well as DAIDS contractors and cross-network training groups.

Other Requirements for Laboratory Personnel

Laboratory personnel are also expected to participate and complete training as specified in this section for CTU site personnel. For key laboratory personnel, this includes HSP training, GCP training, GCLP training, and study-specific training.

11.4 Study-Specific Training

The IoR is responsible for ensuring that site study staff members are adequately trained to serve their designated site and study-specific functions. The LOC, SDMC, LC and other protocol team members collaborate with the site IoR and other designated study staff to fulfill this responsibility in preparation for initiation of new HPTN studies by conducting study-specific training. The format of study-specific training depends on experience of site staff and complexity of the study. Training may be conducted onsite, via webinar or by teleconference at each participating study site. Alternatively, all or parts of study-specific training may be conducted at a central location with staff from all study sites in attendance, or regional trainings may be conducted with staff from the countries of that region in attendance.

The objectives of study-specific training are to:

- Ensure that study staff members are informed of how the study will be conducted on a daily basis, in accordance with the protocol and GCP guidelines
- Ensure standardization of study implementation across sites, so that data can be combined for analysis

During study-specific training, site staff members and the LOC/SDMC/LC training team examine and discuss in detail the study protocol, regulatory requirements, procedural requirements, and data collection specifications. Broad responsibilities for planning for and conducting study-specific training are shown in the table below. Documentation of all study staff training is the responsibility of the site IoR and must be maintained in each site's Essential Documents files.

Responsibilities for HPTN Study-Specific Training	
Task	**Lead Group/Individual**
Scheduling training/arranging training logistics	LOC CRM, LC representative(s), SDMC CDM, site investigator
Developing the agenda	LOC CRM, SDMC CDM, LC representative(s), protocol chair(s) and relevant site investigator(s) and site staff members
Compiling, producing, and providing training materials	LOC CRM, SDMC CDM, LC representative(s), site investigator and designated staff
Arranging for translation of study and training materials and activities, as needed	LOC CRM (translation services for training presentation), Site investigator and designated site staff (training materials)
Arranging for standardized clinical training (if applicable)	LOC CRM with protocol chair(s) and relevant site investigator(s)

Responsibilities for HPTN Study-Specific Training	
Task	**Lead Group/Individual**
Conducting training	LOC CRM, LOC Community, SDMC CDM, LC representative(s) or designee, protocol chair(s), and/ or relevant site investigator(s), designated site study staff members, and others as appropriate such as clinical experts
Documenting attendance and participation of site/protocol staff	Site IoR
Maintaining ongoing training documentation	Site IoR or other protocol team members as applicable

11.4.1 Scheduling Study-Specific Site Training

The responsibility for scheduling of study-specific training should be shared between LOC, SDMC, LC, Protocol Chair(s) and IoR or designee at each site. Training is conducted as closely as possible to the actual study start date at each site. Study specific site activation requirements should be close to completion prior to conducting training of a site. The LOC CRM will confirm that activation requirements are nearing completion prior to scheduling the training.

11.4.2 Site Preparation for Training

In addition to completion of requirements for scheduling study training, site study staff will carry out other activities to prepare staff for study training and, ultimately, the conduct of the study. Under the supervision of the IoR or other designated staff member(s), the site staff should:

- Hire staff (if needed)
- Designate site study staff team and assess local training needs
- Provide orientation and background training locally, as needed, including:
    - Local staffing and organizational plan (including roles and responsibilities)
    - Local site operations
    - Local role-specific training and certification
    - Other local requirements
- Complete "mock visits" using study implementation materials, ideally in clinic and laboratory facilities that will be used for the study
- Review and become thoroughly familiar with the study protocol, informed consent documents, electronic case report forms (eCRFs), training materials, other study implementation materials [i.e., Study-Specific Procedures (SSP) manuals or other manuals], and site Standard Operating Procedures (SOPs)
- Review and become familiar with the study-specific specimen management plan and the "chain of custody" for study samples
- Discuss and develop SOPs (as needed) and other local study implementation materials
- Identify questions, issues, and problems requiring training team input

Expectations of site study staff prior to study-specific training include, as applicable:

- Work with LOC CRM/SDMC CDM/LC to plan training and finalize agenda
- Work with LOC CRM to identify and meet translation and interpreter needs
- Work with SDMC CDM to identify data management systems to be used for the protocol and key staff responsible for implementation
- Arrange access to training rooms and any required equipment
- Arrange staff backup for staff who will attend training sessions

11.4.3 Implementation of Study-Specific Training

Training may be conducted using a variety of methods depending on the needs and circumstances of the study: teleconference, video conference, regional training, in conjunction with an Annual or other meeting, or on site. Regardless of the training strategies employed, the Protocol Chair(s), LOC, SDMC, and LC are responsible for providing the agenda (developed with input from study staff at the site) and supporting training materials. A sample study-specific training agenda is provided in this section.

Ideally, all site staff members who have been delegated duties or responsibilities for a study will take part in study-specific training. This includes the IoR, the study coordinator, clinical staff (physicians, clinicians, and nurses), counseling staff, pharmacy staff, laboratory staff, data management staff, participant recruitment and retention (outreach) staff, community education staff, and administrative staff who will be involved in conducting the study. The site QA/QC coordinators also should take part.

Sample Agenda for HPTN Study-Specific Training		
Session/Module Topic	**Suggested Presenter/Facilitator**	**Expected Site Staff Attendance (minimum)**
General welcome and introduction	Protocol Chair(s) and/or Site Principal Investigator (PI) or IoR or designee	All staff
Introduction of training attendees	All	All staff
Overview of training agenda and materials	Site designee, LOC	All staff
Previous research and scientific rationale for study	Site PI/IoR	All staff
Protocol overview, group question & answer, rationale for study retention targets (optional)	Protocol Chair, site PI/IoR, LOC	All staff
Data collection overview/introduction to data collection instruments and tools, IoR CRF signoff, data query management, randomization procedures, and study reports	SDMC	Relevant staff and supervisors

Sample Agenda for HPTN Study-Specific Training		
Session/Module Topic	**Suggested Presenter/Facilitator**	**Expected Site Staff Attendance (minimum)**
Study documentation requirements, study-specific GCP/quality management issues and plans	LOC, site QA/QC coordinator	All staff
Visit-specific review of study procedures and data collection	LOC, SDMC, site designee	All staff
Interviewing and behavioral data collection strategies	Behavioral scientist associated with protocol team or site	Relevant staff and supervisors
Laboratory procedure review including specimen management plan and chain of custody	LC and site laboratory designee	IoR, the study coordinator, clinical staff, laboratory staff
Clinical procedure review	Protocol chair, site PI, LOC or designee (i.e., clinical expert)	IoR, the study coordinator, clinical staff (physicians, clinicians, nurses)
Study product management and accountability	DAIDS PAB Protocol Pharmacist HPTN Pharmacist as applicable (see Section 23)	Pharmacy staff and other relevant staff and supervisors
Documenting and reporting AEs/SAEs	LOC, SDMC	All staff
Study-specific and/or local counseling procedures	LOC, protocol team or site designee	All staff
Participant accrual and retention plans	Site designee, LOC	All staff
Study visit scheduling and visit windows	SDMC	All staff
Unblinding (if applicable)	LOC, SDMC	All staff
Other relevant site plans and procedures	Site designee	TBD
Mock study visit exercise	All	All staff
Final gathering to resolve outstanding questions/issues, presentation of certificates	All	All staff
Optional Sessions		
Network overview/update	LOC	All staff
Role of Community Advisory Board (CAB)/site community involvement plan	Site community program coordinator, CAB representative	All staff

Sample Agenda for HPTN Study-Specific Training		
Session/Module Topic	**Suggested Presenter/Facilitator**	**Expected Site Staff Attendance (minimum)**
Research ethics/human subjects protection	LOC, Site PI/IoR or designee	All staff

During training, site study staff are expected to attend all required "all staff" and role-specific trainings sessions and are encouraged to attend all sessions. Failure to do so may delay site-specific study activation. Site staff are also expected to fully engage in the training, ask questions, identify issues requiring clarification, and share any site-specific implementation plans, best practices, materials or tools and may be asked to conduct a portion(s) of the training.

11.5 Continuing Study Training

LOC, SDMC, and LC staff will make all study-specific training materials available to the sites in hard copy and/or by posting them on the study-specific website and/or study collaboration portal to be used to train study staff hired after or unable to attend the initial training.

It is the responsibility of the CTU/CRS/IoR to ensure and document that new staff members are adequately trained and prepared to serve their study roles. LOC, SDMC, and LC staff members do not routinely travel to sites to train newly hired staff following the initial onsite study training. However, LOC, SDMC, and LC staff will make every effort to be available to answer questions and provide technical assistance to new study staff members. The LOC, LC, and SDMC will be available to participate in one or more training sessions via teleconference, if requested by the site. If a new study coordinator or lead study clinician joins a site after the initial study-specific training, LOC, SDMC, and LC staff may consider making a site visit to assess study implementation soon after the new staff member begins work on a study.

Once a study is underway, LOC, SDMC and LC staff issue study-related communications, answers to frequently asked questions, and other similar documents to guide study implementation at each site (see Section 12.4) including training on amendments or other updates as applicable. Study staff will file such documents with other study implementation materials (e.g., in the SSP manuals) as well as add such materials to the training packet. Study sites are responsible for establishing SOPs for alerting staff to the release of these documents, providing training on all study documents (including updates), as needed, and incorporating their content into day-to-day study operations. All issued content from the LOC, SDMC and the LC will be posted on the website (specific to that study) or study-specific web collaboration portals.

When it is necessary, LOC, SDMC, and LC staff, as applicable, will provide study-specific "refresher" training to site staff in the context of routine site visits and/or other HPTN meetings (e.g., annual meeting) or on regular team calls. Methods such as recordings of previous training sessions, or teleconference and/or web-based training may also be options for continuing training.

12 STUDY IMPLEMENTATION

Once a site has received a study activation notice from the Leadership and Operations Center (LOC), the site may initiate study procedures. Detailed study implementation guidelines are included in the Study-Specific Procedures (SSP) manuals for each study (see Section 10.1.7).

This section includes general guidelines, applicable to all HPTN studies, on participant accrual and follow-up (Section 12.1), data collection and documentation (Sections 12.2 and 12.3), and reporting (Section 12.5).

12.1 Participant Accrual and Follow-up in HPTN Studies

12.1.1 Accrual

Study-wide accrual targets will be specified in HPTN protocols, based on the scientific objectives and statistical considerations of each study. Site-specific targets may be described in the SSP manuals. Unless otherwise specified, study-wide accrual periods are considered to begin on the first day of participant enrollment at any participating study site; site-specific accrual periods are considered to begin on the first day of participant enrollment at that site. For many studies, the time from the first day of participant screening through the end of participant accrual will also be tracked and reported.

In addition to the total number of study participants, multi-site studies typically have an estimated number of participants to be enrolled at each participating study site indicated in the protocol, often with provisions to shift enrollment targets across sites in response to actual site performance in meeting accrual targets. Protocol teams should consider whether to specify a maximum number of enrolled participants for any site to ensure that one or more sites or populations of interest are not inappropriately over-represented in the study data. The protocol team leadership will take the lead in making this determination. In studies for which enrollment targets are shifted across sites, the responsible Institutional Review Boards/Ethics Committees (IRB/EC) will be informed of increases or decreases in enrollment targets in accordance with IRB/EC and/or single Institutional Review Board (sIRB) requirements. At a minimum, updates are provided to IRBs/ECs and/or sIRB at least annually in the context of obtaining continuing review of ongoing studies.

In some cases, HPTN protocols include guidelines for adding participants to achieve a certain number of fully evaluable participants. In this setting, protocol teams should consider whether to specify a maximum total number of enrollees. The protocol team leadership will take the lead in making this determination.

The LOC clinical research manager (CRM) and the Statistical and Data Management Center Clinical Data Manager (SDMC CDM) discuss accrual plans with site staff during study-specific training. They will emphasize the importance of closely monitoring the accrual process at each site and managing the last several weeks of the accrual period (when inadvertent over-enrollment is most likely to occur). For example, training materials may highlight the need to inform potential study participants screened toward the end of the accrual period that even if they meet the criteria for enrollment, there is no guarantee that they will be enrolled in the study if the study quota is reached before the participant is enrolled.

For each HPTN study, the SDMC generates routine study enrollment and retention reports from the primary study database (see also Sections 12.5.2 and 12.5.3) as specified in the study reporting plan in the Data Management SSP Manual. Protocol teams are responsible for reviewing the SDMC enrollment and retention reports on an ongoing basis during the study accrual period and taking action as necessary to ensure that accrual and retention targets are met.

12.1.2 Enrollment

For each HPTN study, screening and enrollment procedures are described in detail in study protocols and SSP manuals. Information pertinent to participant screening and enrollment is provided in the remainder of this section.

From both a statistical and operational perspective, it is important to define the effective point of enrollment in a research study in the study protocol and/or SSP manuals. A few examples of the definition of enrollment are as follows:

- The point in time when a participant provides informed consent for study participation (adequately completed with signature and date)
- The point in time when a participant is assigned to a study group

Written informed consent must be obtained from all HPTN study participants prior to the performance of any protocol-specified screening or enrollment procedures. See Section 8.5 for additional information on the informed consent process.

It is the responsibility of each Investigator of Record (IoR) and designated staff to establish study-specific participant recruitment plans or Standard Operating Procedures (SOPs) for each HPTN study and ensure that only persons who meet study eligibility criteria are enrolled in HPTN studies. See Table 10-2 for further guidance on the content of such SOPs.

The DAIDS SCORE Manual policy on Essential Documents requires study sites to document HPTN study screening and enrollment activities on screening and enrollment logs. Screening and enrollment logs may be maintained separately or combined into one log. Sample logs that may be adapted for local use at participating study sites typically are provided in SSP manuals.

For all HPTN studies, the SDMC will either provide participating study sites with a list of participant identification numbers (PTIDs) or PTIDS will be assigned by an electronic data capture system at screening or enrollment, as appropriate to the study. Detailed information on the assignment, structure, and format of the PTIDs to be used in each study, and instructions for assigning PTIDs to individual study participants, are provided in SSP manuals. The DAIDS SCORE Manual specifies requirements for maintaining screening and enrollment logs, in addition to PTIDs.

12.1.3 Over-enrollment

In addition to ensuring that accrual targets are met, protocol teams also are responsible for ensuring that accrual targets are not substantially exceeded. During the study accrual period, based on both the site-generated and SDMC-generated accrual reports, the protocol team leadership is responsible for proactively addressing potential over-enrollment and under-enrollment issues. Toward the end of the accrual period the protocol team leadership takes the lead in determining whether to allow eligible participants who initiate, but do not complete, the study screening process before the accrual target was met to complete the screening process and enroll in the study after the accrual target was met. In most cases, over-enrollment greater than 5% of the target study sample size or more than 50 participants — whichever is smaller — should not occur. Protocol teams should consult the HPTN Study Monitoring Committee (SMC) if higher rates of over-enrollment are to be considered.

Over-enrollment is not permitted to "make up for" participant loss-to-follow-up, unless specifically directed by the SMC, Executive Committee (EC) or the Data and Safety Monitoring Board (DSMB). Adjustments to the sample size initially estimated in the study protocol may be made at the recommendation of the SMC, EC and/or the study DSMB, based on actual event rates observed among enrolled participants. If the sample size required to achieve the power specified in the study protocol is adjusted per recommendation of the SMC, EC or DSMB, the over-enrollment specifications will then apply to the final adjusted sample size.

12.1.4 Investigator-initiated Termination of Participants

HPTN study participants may withdraw their consent to participate in HPTN studies at any time, for any reason. However, to avoid biasing study results, investigator-initiated termination of HPTN study participants should occur only under extraordinary circumstances. For instance, termination may be considered if there is potential for harm to study staff or severe disruption of study operations.

In studies involving study products or interventions, IoRs will not routinely terminate study participants solely because the participants, for any reason, are non-adherent to the protocol-specified regimen for use of the study product or intervention.

In all cases, prior to terminating a participant from an HPTN study, the IoR will seek approval of the protocol team leadership; at a minimum, the Protocol Chair, DAIDS Medical Officer, LOC CRM and protocol statistician should consult the protocol specific Clinical Management Committee (if applicable). Designated members of the protocol team will assess the scientific, operational, and statistical implications of the requested termination and determine whether the termination may take place.

A designated member of the protocol team will document the team's determination in writing (email or meeting minutes are acceptable) for purposes of onsite documentation, and the determination of the designated protocol team members will rule. Site staff must always record reasons for termination in participant study records.

12.1.5 Participant Unblinding

The DAIDS SCORE Manual identifies three types of unblinding: 1) Planned unblinding, both partial (partial also has "early" where this aligns with non-emergency and full (which aligns with planned unblinding at study completion); 2) Emergency unblinding; 3) Accidental.

12.1.5.1 Partial or Early Unblinding - Non-Emergency Unblinding of Individual Participants for Medical Reasons

Whether non-emergency unblinding of individual participants for medical reasons is allowed during the conduct of a clinical trial must be stated in the protocol and the procedures documented in the SSP manuals. In general, non-emergency unblinding of participants during conduct of a clinical trial is not allowed unless there are compelling medical reasons. Such scenarios will be described in the protocol and/or SSP manuals.

12.1.5.2 Emergency Unblinding of Individual Participants

Emergency unblinding at the request of the IoR for medical or safety reasons occurs when, in the judgment of the IoR, immediate information is needed to determine appropriate care for the participant after a medical event. Per the DAIDS SCORE Manual, all protocols will include information and procedures for emergency unblinding.

12.1.5.3 Full - Planned Unblinding of Participants after Study Completion

The protocol team, in conjunction with the SDMC and LC, determines the timing of participant unblinding. Except in unusual circumstances, the unblinding of participants cannot occur until all participants have completed their final data collection visit.

For Phase I/II trials participants may be unblinded prior to complete database lock, as per the protocol team and SDMC.

For Phase IIb or III trials intended to contribute to a regulatory submission, unblinding of participants cannot occur until the study database at the SDMC is formally locked for the primary analysis.

Phase IIb or III trials that are not intended to contribute to a regulatory submission may unblind participants after all participants have completed their final data collection visit and before database lock.

Blinded trials that have been terminated before completion due to sponsor decision or DSMB recommendation will unblind participants as soon as practical even though the study database will not immediately be closed and locked. This decision and the timing of unblinding are the responsibility of the protocol team, in consultation with the DSMB when applicable.

The protocol team leadership will determine the method of informing participants of their blinded random assignment. In some situations, "Dear Participant" letters will be appropriate. In settings where mailing letters is not possible or appropriate (e.g., for reasons of confidentiality) it will be necessary to plan for disclosure of randomization to participants in person. If disclosure of the random assignment requires counseling of the participant or could cause distress, it should be done in person. The study site staff may consult with their Community Advisory Board (CAB) to determine the most appropriate method of unblinding participants and in developing participant letters or counseling materials. The site IoR will make a good faith effort to inform all trial participants of their individual treatment assignment.

The protocol statisticians at the SDMC will generate unblinding lists for each site per SDMC SOPs. The lists will be provided to the study site via password protected electronic file.

12.1.5.4 Accidental Unblinding

Accidental unblinding occurs when treatment assignment information is revealed to CRS staff and/or participants prematurely, unintentionally, or otherwise outside of the standard process (e.g., verbal or written accidental disclosure of participant's treatment assignment, identification of the blinded study product based on its appearance, study product labelling error, and/or laboratory testing conducted outside of the trial procedures). The PI/IoR must report any accidental unblinding that has occurred to the Protocol Team, DAIDS, and the IRB/EC as soon as possible.

12.2 Data Collection

Study site staff are responsible for the collection, storage, timely submission, and quality assurance of study data collected at their site and documenting the plan for these tasks in a Data Management SOP. All study data should be collected in accordance with applicable specifications of the DAIDS SCORE Manual policy on Source Documentation and SSP manuals.

In addition, the site is responsible for maintaining all documentation critical to the conduct of the study, known as "essential documents", in accordance with the DAIDS SCORE Manual policy on Essential Documents.

12.2.1 Participant Research Records

The United States (US) Code of Federal Regulations (CFR) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 guidance (use the work products drop down menu in webpage) requires study site staff to maintain adequate and accurate participant "case history records" containing all information pertinent to the study for each HPTN study participant.

12.2.1.1 Participant Research Record Contents

Participant research records should contain all of the following elements:

- Basic participant identifiers such as PTID or initials
- Documentation that the participant provided written informed consent to participate in the study prior to the conduct of any study procedures

- Documentation that the participant met the study's eligibility criteria
- A record of the participant's randomization assignment (if applicable)
- A record of the participant's exposure to study products (if applicable)
- A record of all contacts, and attempted contacts, with the participant including all clinic visits, off-site visits (e.g., at home or work), and all verbal and written contacts
- A record of all procedures performed by study staff during the study
- Complete source documents
- All electronically captured case report forms (eCRFs) and other study data collected from the onset of screening through end of participation
- Study-related information on the participant's condition before, during, and at the conclusion of study participation, including:
    - subjective data obtained directly from the participant (e.g., interview responses)
    - objective data ascertained by study staff (e.g., exam and laboratory findings)
    - objective data obtained from non-study sources (e.g., medical records, including electronic medical records (EMR) or electronic health records (EHR))

In addition to the above, the DAIDS SCORE Manual policy on Source Documentation requires that all protocol deviations involving participants be documented in participants' study records, along with reasons for the deviation and attempts to prevent or correct the deviations, if applicable. See Section 12.5.11 regarding requirements for reporting protocol deviations.

12.2.1.2 Concept of Source Data and Source Documentation

The ICH/GCP guidance defines source data and source documentation as follows:

- The term "source data" refers to all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- The term "source documents" refers to original documents, data and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subjects' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies of transcriptions certified after verification as being accurate and complete; microfiche; photographic negatives; microfilm or magnetic media; x-rays; subject files; and records kept at the pharmacy, the laboratories, and medico-technical departments involved in the trial).

Source documents are commonly referred to as the documents — paper-based or electronic — upon which source data are first recorded.

HPTN study sites must adhere to the standards of source documentation specified in the DAIDS SCORE Manual policy on Source Documentation. This policy contains both requirements and recommendations. Study sites must comply with all requirements and are advised, but not required, to comply with all recommendations. Source documentation includes original documents and certified copies that include documentation pertaining to a participant while on study.

For each HPTN study, participant case history records typically will consist of some or all the following:

- Narrative chart notes
- Visit checklists or flow sheets
- Laboratory reports
- Medical records or clinic charts, including electronic medical records (EMR) and electronic health records (EHR)
- eCRFs and other study data
- Randomization log or other documentation (when applicable)
- Study product dispensing and accountability records (when applicable)
- Other source documents and data collection tools or questionnaires

As a condition for study activation, each site must establish an SOP for source documentation that specifies the use of these documents as source documents.

Supplemental information on use of chart notes, visit checklists, and eCRFs, and electronic data capture (EDC) as source documents is provided below. Also provided below is information related to study product dispensing and accountability records, document organization, and record retention requirements.

12.2.1.3 Chart Notes

Chart notes must be used to document the following:

- Procedures performed that are not recorded on other source documents
- Pertinent data about the participant that are not recorded on other source documents
- Protocol deviations that are not otherwise captured on other source documents

All chart notes or other tools created for the study used as source documentation must document the PTID of the study participant to whom it pertains, the identity of the study staff member who entered information, and the date of the entry. Study sites are strongly encouraged to adopt a common format — such as the Subjective-Objective-Assessment-Plan (SOAP) format for all chart notes, to help ensure adequacy and consistency of note content and maximize adherence to GCP standards: Example SOAP Chart Note. Alternative standardized formats are acceptable and may be adopted by study sites; however, sites are encouraged to also adhere to the DAIDS SCORE Manual policy on Source Documentation.

12.2.1.4 Visit Checklists

The SSP manuals typically include a series of visit checklists to guide the staff performing procedures at each study visit (in accordance with the protocol). In some studies, visit checklists are also a convenient tool for study staff to fulfill the requirement of documenting all procedures performed with each study participant. The LOC CRM is responsible for developing these checklists with input from the SDMC CDM, Laboratory Center (LC), and the sites. Study sites are allowed to develop site-specific versions of these checklists. Any site-specific visit checklists should be provided to the LOC CRM for review prior to use.

Note that checklists alone often are not sufficient for documenting all procedures. For example, chart notes may be required to document procedures performed at unscheduled study visits to explain why procedures, in addition to those specified on a checklist, may have been performed or

why procedures specified on a checklist were not performed. Chart notes also may be required to document the content of counseling sessions and/or other in-depth discussions with participants (e.g., related to adherence to protocol requirements).

Study procedures for which visit checklists are used as source documentation must contain the PTID, the initials or signature of the authorized study staff member completing the procedures, and the date the procedure was completed. Individual study staff members must initial only those procedures that they complete. In addition, if procedures listed on a single checklist are completed across multiple dates, the date upon which each procedure is completed must be clearly noted. Additional detailed guidance related to proper use of visit checklists is provided in each SSP manual.

12.2.1.5 eCRFs and Other Study Data

The SOP for source documentation requires that a site must document the source for every data element collected on the eCRFs. Study staff must follow the specifications of this SOP consistently for all study participants throughout the study. In the event that study staff are not able to record source data directly onto forms designated as source documents, or directly enter the data into the study database, the following procedures should be undertaken:

- Recording the data onto an alternate source document
- Entering the alternate source document into the participant's study chart
- Transcribing the data from the alternate source document onto the appropriate eCRF
- Recording a chart note stating the reason why an alternate source document was used

12.2.1.6 Electronic Records

Electronic Records are any combination of text, graphics, data, audio, pictorial, or other information in digital form that is created, modified, maintained, archived, retrieved, or distributed by a validated computer system (21 CFR 11.3). When data are entered directly into a computer, the electronic data in the computer becomes the essential document. A paper record (printout/hard copy/"print screen") of the electronic data is considered to be a copy. Requirements for documentation, record keeping, and record retention apply to electronic records the same as they do for paper systems.

Examples of electronic records include but are not limited to:

1. Participant data, reports, and/or results
2. E-mail communications pertaining to a participant or protocol management (e.g., 171 directives from protocol chairs, CRS investigators to study nurses, etc.)
3. IRB/EC and/or sIRB correspondence pertaining to a participant or the study
4. Audio Computer-Assisted Self-Interview (ACASI) questionnaires

Each electronic record needs to be associated with an originator type, otherwise known as an authorized data originator. An authorized data originator could be a person, a computer system, a device, or an instrument that is authorized to enter, change, or transmit data into the electronic record. CRS must develop and maintain a list of all authorized data originators. This list must be made available for study-related monitoring, audits, IRB/EC and/or sIRB review, and regulatory inspection by authorized individuals at each clinical research site. In the case of electronic participant-reported outcome (ePRo) measures, list the participant (e.g., unique participant identifier) as the originator.

Examples of data originators include, but are not limited to:

1. Clinical investigator(s) and delegated clinical study staff
2. Participants or their legally authorized representatives
3. Consulting services (e.g., a radiologist reporting on a computed tomography (CT) scan)
4. Medical devices (e.g., electrocardiograph (ECG) machine and other medical instruments such as a blood pressure machine)
5. Electronic health records (EHRs)
6. Automated laboratory reporting systems (e.g., from central laboratories)
7. Other technology

12.2.1.7 LDMS Specimen Tracking Sheets Provided by the LC

The LDMS Specimen Tracking Sheet is designed to accompany specimens from the clinic to the site's laboratory and facilitate entry of specimens into LDMS. A study-specific LDMS Specimen Tracking Sheet can be provided by the LC, but sites may elect to use their own laboratory requisition forms instead.

12.2.1.8 Study Product Dispensing and Accountability Records

As indicated in Section 10.2, the receipt, dispensing, and final disposition of all study product supplies used in HPTN studies must be documented by designated study site staff in accordance with the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks or study-specific HPTN Pharmacy Study Product Management Procedures Manual as applicable (see Section 23), as well as any supplemental instructions provided in the study protocol and/or Pharmacy SSP Manual.

12.2.1.9 Document Storage and Retention

All participant study records must be stored securely at the study site in accordance with the specifications of the study protocol. See Section 8.9 for additional considerations related to participant confidentiality. Information on long-term storage and retention of study documents can be found in Section 18.2.

12.2.2 Data Collection and Management

The SDMC uses Medidata Rave or other EDC systems for CRF data entry and management for HPTN studies. The SDMC may use other systems for collection of study data, such as Audio Computer Assisted Self-Interview (ACASI) or electronic Clinical Outcomes Assessment (eCOA) software. Information and procedures for the specific data collection tools used for each study are included in the SSP.

12.3 Standard eCRF Elements and Forms

All HPTN eCRFs have been designed using standards and conventions developed by the SDMC. Certain eCRFs have been standardized within the HPTN to ensure that all required data is collected to create as much consistency as possible between protocols. These elements also align to the extent possible to the Clinical Data Interchange Standards Consortium (CDISC) standards as required by the National Institute of Allergy and Infectious Disease (NIAID). Instructions for study staff on correct completion of each of these CRF elements are included in Case Report Form Completion Guidelines (CCGs) with additional information provided in SSP manuals and online in the Medidata system.

12.4 Study Team Communications

After initial release of a study protocol and SSP manuals, several types of study-related communications may be issued to report on study progress or provide further clarification of protocol-specified procedures and study documentation requirements. Such communications may include, but are not limited to, the following:

- *Conference call and meeting summaries*: Protocol teams, and in some cases, other designated study working groups, take part in routine meetings and conference calls throughout the period of study implementation. Summaries of these meetings and conference calls, which often document key protocol-related and study implementation decisions and action items, are prepared and distributed as described in Section 6.2.
- *Protocol Clarification Memoranda (Memos), Letters of Amendment, and full amendments with an attendant summary of revisions*: These documents are developed and issued as described in Section 9.3. Development of these documents is coordinated by the LOC CRM, and final versions are distributed to all protocol team members and study sites. Final versions also are posted on the HPTN website and the study share portal.
- *SSP manual updates*: These updates are developed and issued as described in Section 10.1.7. Like the initial version of an SSP manuals, development of the updates is coordinated by the LOC CRM, and final versions are posted on the study share portal.
- *Data Communiqués*: These documents are developed and issued by the SDMC CDM to clarify issues related to study data collection. Final versions are distributed to all study sites for filing in the data-related SSP manual and are posted on the study share portal. They are considered an official part of the SSP manual.
- *Laboratory Communiqués and Operational Memos*: These documents are developed and issued by the LC HPTN QA/QC representative to clarify issues related to laboratory procedure. Final versions are distributed to all study sites for filing in the Laboratory SSP Manual and are posted on the study share portal. They are considered an official part of the SSP manual.
- *Reports:* Data reports on study progress, protocol adherence, data quality, etc., are developed and issued by the SDMC in accordance with the study reporting plan (see Section 12.5). They are also posted on the SDMC web portal.
- *Study implementation questions*: Site questions about study implementation should be directed to the LC, LOC CRM and the SDMC CDM. They will determine between them who is the most appropriate person to respond. They will also forward the query to another party for a response if deemed appropriate. In cases where the LC representative, LOC CRM and SDMC CDM determine that the question and answer may be relevant or informative to staff from other study sites, they will forward the information to relevant site staff. They also may raise the issue for discussion during study-related conference calls and/or issue a more formal communication (e.g., SSP manual updates, Clarification Memo, or Data Communiqué) to properly address the issue.

All of the above-listed communications are issued with specific instructions for filing and further distribution as appropriate. Recipients are responsible for filing copies of documents as instructed and for communicating relevant information contained in the documents to all applicable study staff members, collaborators, etc.

12.5 Reporting

The HPTN has developed standardized reporting for tracking study progress and site performance.

A study reporting plan is prepared by the SDMC CDM and statisticians prior to the start of the study. The reporting plan lists the types and frequencies of reports to be produced for a given study. The approved reporting plan is included in the study data-related SSP manual. Reports that are generally included are:

- Enrollment and retention
- Data management quality
- SMC
- DSMB

12.5.1 Confidentiality of Study Data

The disclosure of study endpoints or any follow-up data that might be predictive of/correlated to study endpoints during an ongoing study should be limited to designated committees (e.g., closed SMC, DSMB) to avoid bias in study conduct and/or interpretation of data.

12.5.2 Enrollment, Visit Completion/ Retention Reports

During the protocol accrual period, the SDMC routinely generates protocol-specific enrollment reports showing expected and actual participant enrollments. The SDMC also generates protocol-specific reports on participant visit completion, as an estimate of retention, for each scheduled study visit. Details of these reports are included in the reporting plan included in the data-related SSP manual and are available on the SDMC web portal.

12.5.3 Data Quality Control

For EDC, much of the data QC is performed by real-time field-level and cross-form data checks programmed into the system by the SDMC. In addition to these real-time checks, data queries regarding missing pages or items that require more clarification by site staff will appear in a task summary or other reports. In general, site staff should respond to any data queries within 7 days, or 48 hours for queries regarding safety data and AEs.

12.5.4 Data Management Quality Reports

The SDMC routinely generates reports on site-specific and protocol-specific data management performance. These reports include:

- Number and percentage of CRF pages entered within 7 days of study visit
- Number and percentage of Adverse Event CRFs entered within 3 days of site awareness
- Total number of items queried by the SDMC and query rate (the number of queried items per 100 CRF pages)
- Number and percentage of queries responded to within 7 days

12.5.5 SMC Reports

The SMC reviews all studies approximately every six months (see Section 4.3.2 for reporting frequency). The LOC CRM is responsible for identifying the date of each SMC review and for arranging SMC conference calls and documenting the SMC review. The SDMC prepares reports for these reviews that include:

- Trial design
- Accrual
- Demographics and other baseline characteristics
- Summaries of expedited adverse event/serious adverse event/adverse event/data or social impact reporting
- Protocol and intervention adherence
- Participant study visit completion / retention
- Laboratory performance, specimen storage and quality assurance (QA) testing (with input from the LC)
- Data quality, completeness, and timeliness
- Reportable protocol deviations
- Review of aggregate safety data, for studies with a biomedical intervention without DSMB oversight. The SMC composition for these studies should include clinicians experienced in the review of safety data, who are not affiliated with the protocol team or HPTN (if there are Independent Safety Reviewers assigned to the study, they should fill this role) . The SMC will review safety data only during a closed session with no study team present
- Endpoint summary; Review of aggregate primary endpoints rates in efficacy studies. The SMC will review endpoint data only during a closed session, for the purpose of ensuring the study is projected to have adequate power. The DSMB will be informed of the HPTN SMC review, and minutes of these deliberations may be shared with the DSMB.

Additional information about study conduct, site-specific issues, and materials other than study data collected by the SDMC may be included as an addendum to the SDMC report. Such addenda are prepared only at the request of the SMC or SDMC and are typically prepared by the LOC CRM and/or other protocol team members.

After the SMC review, the LOC distributes a summary to the protocol team, and at that time the SMC report may be shared with members of the protocol team.

12.5.6 Data and Safety Monitoring Board (DSMB) Reports

A NIAID DAIDS Multinational DSMB periodically reviews data reports from all Phase IIb/III HPTN trials and other selected studies. The primary responsibilities of the DSMB are to:

- Safeguard the interests of study participants
- Preserve the integrity and credibility of the trials in order that future participants will benefit from optimal prevention therapy
- Ensure that definitive and reliable results will be available in a timely way to the medical community

To do this, the multidisciplinary panel of DSMB members conduct comprehensive reviews to evaluate the:

- Study design and statistical analysis plan
- Accumulated efficacy data, typically according to formal interim analysis plan
- Integrity of the trial with regard to accrual, eligibility, compliance, and retention

Typically, a report is prepared by the SDMC for review by the DSMB. It is composed of an open report in which data are presented aggregated across treatment arms and a closed report containing data presented by treatment arm, masked or unmasked. Topics covered in the report include:

Open report (data not reported by arm):

- Trial design and history
- Accrual
- Baseline characteristics
- Adherence
- Participant status and retention
- Serious and non-serious adverse events
- Data quality and timeliness
- Reportable protocol deviations
- SMC review summary

Closed report (data reported by arm — masked or unmasked):

- Accrual
- Baseline characteristics
- Retention
- Adherence
- Participant status and termination
- Efficacy endpoints
- Safety endpoints
- Other secondary outcomes

After the DSMB review, a summary is distributed by the LOC to investigators for submission to the site IRBs/ECs, unless otherwise directed by DAIDS. For any study that will be conducted at more than one US site, DSMB summaries are submitted by the LOC for sIRB review on behalf of all US sites.

12.5.7 Modification of Study Recommended by DSMB

In the event of a recommendation, the information from the DSMB is shared only with NIAID. NIAID communicates the recommendation to HPTN leadership. This leadership team includes:

- Network PI/Co-PI
- LC PI
- LOC Project Director
- SDMC PI
- Others as deemed necessary

Prior to NIAID's release of a press release or public statement, it is imperative that the DSMB findings remain confidential. In an effort to ensure study confidentiality, all study team members must sign a confidentiality agreement.

Recognizing that in some cases DSMB findings may require immediate action, communication of DSMB results with network constituents and study participants will be coordinated with the Protocol Chair, HPTN leadership and NIAID in a timely fashion. Advance communication planning and development of possible DSMB outcomes will expedite this process.

12.5.8 Reporting of Protocol Deviations

The Cross-Network Protocol Deviation Reporting Guide (reporting guide) establishes standard definitions and classifications for protocol deviations (PDs) and is to be utilized for HPTN studies. In addition, the reporting guide describes the process for reporting protocol deviations via the Protocol Deviation electronic Case Report Form (PD eCRF).

Reportable PDs are those that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a participant's rights, safety, or well-being and must be reported via the PD eCRF within 5-reporting days of awareness (see reporting guide). Not reportable PDs are those that do not meet the definition of a reportable PD.

All sites must complete a Corrective and Preventive Action (CAPA) Form for any reportable PD. Sites may use their own or DAIDS CAPA form. The CAPA form in addition to the corrective plan, must minimally include the protocol number, site name, site number, participant ID, and date(s), as per the PD eCRF, for the respective protocol deviation.

Note that all protocol deviations must also be recorded in the participant's research record. See the Source Documentation Requirements section of the DAIDS Site Clinical Operations and Research Essentials Manual (SCORE) for further guidance. Full documentation of all protocol deviations including reportable deviations for each study should be maintained at the site and reported as needed to the local IRB/EC. A brief description of the deviation is sent via email to the Protocol Chair, IoR, Site Study Coordinator, Site QA/QC Coordinator(s), LOC CRM, SDMC PM, LC representative, Prevention Science Program (PSP)/Office of Clinical Site Oversight (OCSO) representative for the site, the DAIDS Medical Officer for the study and, if the deviation involves a study product, the DAIDS PAB Pharmacist or HPTN pharmacist as applicable (see Section 23). Per the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108b, site investigators are responsible for promptly reporting to their IRB/EC and/or sIRB all unanticipated problems involving risks to human subjects or others and serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs and/or sIRB.

DAIDS will review all deviations periodically. Required protocol team review may be included in the protocol and other implementation materials; if not specified in the protocol or other implementation materials, deviations may also be reviewed periodically by the protocol team. Based on this review, queries may be sent to re-classify the deviation or add greater detail to

the deviation description. In addition, DAIDS, Network groups, and/or protocol teams may request sites send the full details of the corrective/preventative action plan.

The HPTN has established a process for staff at HPTN study sites, the LOC, the LC and the SDMC to document the occurrence of protocol deviations and to report them to the protocol team, particularly those that might otherwise not be evident in the study data or reported otherwise. After consultation with LOC, SDMC, and LC representatives, all deviations that meet the criteria in the reporting guide will be recorded on the Protocol Deviation electronic Case Report Form (PD eCRF).

The Clinical Site Monitor identifies protocol non-adherence events and violations in their monitoring reports, and some of these may also be reportable protocol deviations; however, there is not a one-to-one correlation between events reported by the Clinical Site Monitor and those to be reported through the HPTN protocol deviation reporting system. The Clinical Site Monitor may report protocol non-adherence events and violations that encompass every infraction of the protocol. For example, if a blood specimen is drawn for ALT, but is not processed by the laboratory, it is a non-adherence event according to the Clinical Site Monitor. This would not be a reportable protocol deviation. If, however, an ALT is to be drawn at each patient visit and is not being done at all, this would be a reportable protocol deviation

13 LABORATORY COMPONENT

The following section applies to site laboratory (e.g., in-clinic, mobile unit, reference lab, hospital lab, local laboratory, processing lab) performing a study under the guidance of the HPTN Laboratory Center (LC). These laboratories will be referred to as Clinical Research Site (CRS) laboratories in the remainder of this document.

All CTU/CRS laboratories are required to adhere to standards of the Division of AIDS (DAIDS) Clinical Research Laboratory and Specimen Management, which includes specific requirements for US Laboratories and non-US laboratories. These policies also include compliance with DAIDS Good Clinical Laboratory Practice (GCLP) standards. For additional information on laboratory related DAIDS policies and standards, refer to the DAIDS Clinical Research Laboratory and Specimens Management policies website: https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management

The DAIDS GCLP standards outline specific elements that clinical research laboratories should follow. GCLP training is accessible online through the DAIDS Learning Portal (DLP) and through periodic regional offerings: https://daidslearningportal.niaid.nih.gov/

References for applicable United States (US) federal and non-US regulations are also included. In addition, US CTU/CRS laboratories should follow the Clinical Laboratory Improvement Amendments (CLIA) Act and CLIA certification and/or waiver policies: https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/

Each laboratory should also have the following in place (in addition to the aforementioned GCLP standards): 1) a specimen management procedure that outlines the documentation of the chain of custody throughout the acquisition, receipt, processing, testing, storage and shipment of protocol samples; 2) a laboratory data management plan that documents the data integrity and reporting of results including data quality procedures; 3) a well-defined QMP that comprehensively covers contingency plans, assay validations, training and competency, corrective action/preventive action identification and management, monitoring of Key Quality Indicators (KQI), instrument and equipment maintenance and procedures for QA and QC.

In addition to these guidelines and policies, the Laboratory SSP Manual contains laboratory procedures that includes detailed instructions for the specific protocol. For HPTN protocols, the HPTN LC, in collaboration with the protocol chair(s), will instruct the sample types and number of aliquots required for storage at study visits.

13.1 CTU/CRS Laboratory-related Site-specific Protocol Activation Requirements

A specific set of protocol activation requirements will be created for each HPTN protocol. Requirements may be study- and site-dependent. Examples of these requirements are:

- Laboratory Quality Management Plan
- Standard operating procedure (SOP) for study-specific specimen management plan and "chain of custody" related to clinical/safety testing and management of samples for study endpoints. This should be in place prior to site activation
- Confirmation of current CVs of key laboratory personnel
- Protocol Analyte Lists/spreadsheets
- Verification of Laboratory Data Management System (LDMS) training and validation

- Verify current International Air Transport Association (IATA) specimen shipping certification for all staff members involved in the specimen management plan
- GCLP training for the appropriate laboratory staff per DAIDS Laboratory and Specimen Management guidelines
- The following for non-US accredited laboratories
  - Proficiency in performing protocol-required testing
  - Appropriate validation and documentation of validation for protocol analytes
  - Any other applicable certification
  - Laboratory Data Management Plan
  - QMP

The HPTN LC will work with the DAIDS program officer to determine acceptability of laboratory evidence of the aforementioned items. After acceptance by the DAIDS Program Officer, the HPTN LC will notify the site, laboratory, Office of Clinical Site Oversight (OCSO) representative, DAIDS Program Officer, and appropriate protocol team members, that the laboratory has completed all requirements/items for protocol-specified laboratory activation. If there is a failure in maintaining key systems or requirements, such as failure to appropriately use the LDMS, follow GCLP standards or other items of concern, the HPTN LC will discuss the issues with the protocol team leadership and HPTN LC Quality Management Team (QMT) and follow the HPTN LC QM process for escalation. If the laboratory is a multi-network participating laboratory, other network laboratory centers will be informed.

13.2 CTU/CRS Laboratory Performance Assessment

CTU/CRS laboratories may be evaluated by DAIDS contracted monitoring groups to ensure that they meet an established standard for data quality and laboratory GCLP compliance. Key performance areas are monitored through collection, recording, and investigation of data pertaining to the laboratory area; findings are evaluated to identify trends and ensure overall compliance with the laboratory QMP. A DAIDS auditing contractor performs the laboratory review and generates a report while a second DAIDS contractor summarizes and lists items of non-compliance. When indicated, corrective actions will be implemented and documented. Monitoring is on-going to ensure appropriate action is taken and that those actions result in successful remediation.

13.2.1 Non-US CRS Laboratories

For each HPTN protocol the HPTN LC will send the non-US CRS laboratory a study specific Protocol Analyte List (PAL), which must be completed by the laboratory. This document is reviewed by DAIDS Clinical Laboratory Oversite Team (DCLOT) and may be forwarded to a DAIDS contractor. DAIDS has arranged for many of the existing laboratories outside of the US that participate in DAIDS-funded research to receive proficiency panels from vendors through DAIDS for protocol-related analytes as deemed appropriate. When a new CTU/CRS laboratory is included in a new or existing HPTN protocol, the HPTN LC will work with the site to produce a study-specific PAL to inform DAIDS of protocol analyte coverage. Costs related to participation in Proficiency Testing (PT) programs may be supported by DAIDS or a DAIDS-supported contractor, the site, or through the protocol. Each year, the appropriate DAIDS contractor will re-enroll sites based on the assays that are anticipated to be performed at the specific CTU/CRS laboratory in support of a DAIDS-sponsored protocol.

To facilitate communication between the LCs of different networks and CRSs outside of the US, the leadership of the various DAIDS clinical trials networks has assigned a Primary

Network Laboratory (PNL) to each non-US site. A list of PNL assignments is maintained on the HIV/AIDS Network Coordination HANC website (see Section 13.13 for URL).

DAIDS staff and/or DAIDS contractors may conduct laboratory-specific audit visits. These audits are conducted periodically, at sites outside of the US, unless the laboratory has been certified by College of American Pathologists (CAP) and/or has been deemed to be in good standing by the DCLOT. CTU/CRS laboratories will be audited for GCLP compliance. DAIDS reserves the rights to conduct for cause or ad-hoc audits at any laboratory that is participating in DAIDS-sponsored clinical trials. Audits may be performed in person or remotely. After an audit, an audit report will be distributed to the laboratory following DAIDS policy. The CTU/CRS laboratory is responsible for working with DAIDS, their DAIDS-assigned contractors, the HPTN LC, and any other affiliated network LC to resolve the audit report findings. Action items are closed by DAIDS contractor. Audit report findings must be adequately addressed by the CTU/CRS laboratory to maintain a satisfactory performance standard.

13.2.2 Non-affiliated External Laboratories Outside the US.

In certain circumstances (e.g., analyzer repair or breakdown, lack of available consumables, lack of required reagents or control material, continued failure in an External Quality Assurance (EQA) program), a laboratory may need to use back-up equipment or a back-up laboratory for testing and reporting study specimen results.

The guidelines for the use of back-up equipment and/or laboratories for DAIDS-sponsored clinical trials is available on the HANC website.

13.2.3 Proficiency Testing

Prior to protocol activation, the CTU/CRS laboratory must be in good standing for protocol-relevant EQA, as determined by the HPTN LC staff. After a protocol is activated at the site, the recommendations for PT are as follows:

- Any proficiency deficiency (<100%), regardless of the scoring, will require an investigational response by the CTU/CRS laboratory. The HPTN LC considers scores between 80% and 100% to be acceptable, which is consistent with the standards of US commercial proficiency providers. Any non-protocol analyte that has been evaluated and scores <100% requires an internal investigation.
- If a CTU/CRS laboratory fails to report to the appropriate DAIDS contractor and appropriate proficiency provider that a panel has not been received or cannot be tested for any reason this will be considered unsatisfactory.
- If the results are not graded by the proficiency provider because the results were submitted late, the appropriate DAIDS contractor, may make an effort to grade the results and will document that the panel is considered late.
- If the results of an analyte are not graded by the proficiency provider for any reason, the DAIDS contractor or designated group may decide that they will determine if grading is applicable.
- For CTU/CRS laboratories that receive unsatisfactory results (failures), the HPTN LC will provide instructions to the laboratory on what additional measures, if needed for the HPTN LC, must be taken in addition to the corrective action reporting.
- For CTU/CRS laboratories that receive unsatisfactory results on three consecutive panels, the HPTN LC may stop all testing for that analyte and implement a back-up plan at the CTU/CRS. Other LCs may communicate their decisions about

testing (e.g., stop/continue) directly with the site staff or through the PNL. Determinations will be on a case-by-case basis, depending on the reason for the PT failure and the standing of the back-up option at that time.

- DAIDS contractors may periodically provide reports regarding EQA to the network laboratories, sponsors, other DAIDS contractors.

13.2.4 US CRS Laboratory Certification

CTU/CRS laboratories within the US that participate in HPTN protocols are required to have CLIA certification and/or waiver; documentation of this certification must be provided to the HPTN LC. For US labs, due to different local and State requirements, attainment of appropriate certification and following the necessary regulatory requirements is the responsibility of the site leadership, not the HPTN LC.

13.3 HPTN LC Oversight of CTU/CRS Laboratories

In addition to the annual assessments described above, the CTU/CRS may undergo a periodic in person or remote visit (protocol training or protocol-related assessment visit) by HPTN LC QA/QC Coordinator and or Deputy Director to assess the implementation of laboratory QA procedures. The purpose and scope of the visit are discussed with site personnel prior to the visit. At these visits, the HPTN LC will provide the CTU/CRS with any recommendations or corrective actions deemed necessary and will send this information to the appropriate site representatives, LOC, other LCs if appropriate, and the DAIDS HPTN LC program officer. In some circumstances, additional visits by the HPTN LC may be warranted. HPTN LC will work directly with the site to address and resolve any QC or quality assessment problems identified either through PT or site visits, or by the site during study preparation or implementation. In addition, the HPTN LC may place an HPTN LC staff member on-site or regionally.

13.4 Laboratory Data Management

Each CTU/CRS laboratory should have documented procedures for handling and processing of specimens to be used in DAIDS-sponsored clinical trials. Such information will often be detailed in the Laboratory SSP Manual. In addition, each CTU/CRS laboratory is required to utilize the LDMS for collection, testing (specific to HIV RNA if protocol required), storage, and labeling of certain biological samples identified by the HPTN LC for each HPTN protocol, as described below. Each CTU/CRS should ensure that the laboratory has enough freezer space for storage of protocol related aliquots as per protocol requirements. Samples will be stored locally unless requested for shipment or destruction.

LDMS training may be provided at annual meetings, regional meetings, at the Frontier Science and Technology Research Foundation (FSTRF), onsite or remotely e.g., webinar. Each CTU/CRS is required to maintain the training records of their staff members and is fiscally responsible for the training. The CTU/CRS is responsible for maintaining and performing end user validations of their LDMS system, including hardware and software upgrades. HPTN LC staff will provide protocol related data entry information for the LDMS in the Laboratory SSP Manual (Laboratory Considerations). This ensures that specimens are entered correctly into the system.

All CTU/CRS laboratories must establish SOPs for weekly reconciliation and verification of all archived specimens including (but not limited to): plasma, serum, whole blood, PBMCs, dried blood spots (DBS), tissue, breast milk, amniotic fluid, and genital secretions. These SOPs must be followed throughout the study, including SOPs for the use of the SDMC Sample Data Quality Control (SDQC) Tool for specimen reconciliation.

13.4.1 Specimen Shipping

HPTN specimens must be transported in accordance with International Air Transport Association (IATA) regulations and with US federal, international, and local laws and regulations. This applies to transportation of specimens onsite, to and from clinics and laboratories, from CTU/CRS to the HPTN LC, or from sites or external laboratories to other laboratories or sites, including the HPTN LC.

IATA shipping certification renewal is required every two years with a review of the IATA Dangerous Guidelines annually to check for any new or changed requirements. Each staff member who handles shipments must be trained and certified. Each CTU/CRS is responsible for obtaining the appropriate training and annual IATA dangerous goods guidelines.

Each site should follow local regulations regarding transportation of samples by dedicated couriers. The US Department of Transportation (DOT) regulates the transportation of infectious substances within the US. Sites within the US must follow the DOT requirements (see 49 CFR Part 171). Sites outside the US are subject to their own country's government regulations for transportation of infectious substances.

Importation of human pathogens to the US from abroad requires an importation permit from the US Centers for Disease Control and Prevention (CDC). The HPTN LC maintains a worldwide importation license that covers all materials sent from CTU/CRS sites to the HPTN LC at Johns Hopkins University and its affiliated laboratories. Specimens sent from the sites to other locations within the US not part of the HPTN LC are not covered under this importation permit.

Sites may also require a separate Material or Specimen Transfer Agreement (MTA) between the site and the HPTN LC. This is determined by the site and the site is responsible for communicating with the HPTN LC about the specific details they require. The HPTN LC will liaise with the JHU Office of Research Administration (ORA) to ensure that legal concerns are addressed. The ORA official will sign on behalf of the HPTN LC.

Useful websites with information concerning specimen handling and shipment are provided in Section 13.13.

13.5 Validation of HIV Antibody Testing Algorithms

The HPTN LC may require validation of HIV testing algorithms at a CTU/CRS site. For a given protocol, the HPTN LC will determine if a validation study is needed, and if so, what type of validation study is needed for each site/algorithm. The Cross-Network Guidelines for Diagnosing HIV-1 Infection in DAIDS-sponsored Clinical Trials Protocols is available on the HANC website; however, sites should follow instructions provided in the Laboratory SSP Manual regarding determination of infection status.

13.6 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all study personnel in the drawing of blood and shipping and handling of all specimens for HPTN studies.

13.7 HPTN Laboratory Center

HPTN LC laboratories performing diagnostic assays for the HPTN protocols that will be reported back to participants are required to be CLIA- certified. Quality assurance testing performed at the HPTN LC may fall under GCLP guidelines. HPTN LC laboratories will receive guidance from the HPTN LC QMT and will adhere to the HPTN LC Cross Laboratory SOPs.

Some HPTN LC laboratories may not fall under CLIA or GCLP guidelines because they perform only research testing. Each of these labs will have their own QMP as deemed appropriate for the type of testing performed.

The HPTN LC will oversee any non-standardized or specialized testing (e.g., testing that must be standardized across the sites or across HPTN protocols) and any QA/endpoint confirmation testing, unless prior approval has been granted by the HPTN LC for another arrangement. Endpoint QA testing and specialized assays will be performed at the HPTN LC, or at a laboratory designated by the HPTN LC. Each of the HPTN LC cores will oversee their own specific testing and associated compliance with GCLP and Quality Management Plan.

13.8 QA Testing

The HPTN LC will develop a plan for each protocol to verify the HIV infection status of clinical trial participants. This may include QA testing at the HPTN LC and may include specialized testing. The plan may change during the conduct of a protocol and may vary among study sites (e.g., if testing problems at one or more sites are identified, if sites are using different testing algorithms). These assessments are typically performed at the end of enrollment (e.g., for each study site), but may occur earlier or be ongoing in larger studies or studies in which problems in site testing or sample/data management are suspected or identified. QA testing continues during the course of the study, in batched assessments and/or evaluation of specific participants, sites, or sample subsets. In certain trials, primary endpoint QA testing will occur at the end of the trial.

In most HPTN protocols, baseline plasma/serum samples from 50 participants, or ten percent (whichever is greater) of randomly-selected enrolled adult subjects at each site are evaluated at the HPTN LC to determine/confirm HIV status. Samples from all subjects enrolled at a site will be evaluated if there are fewer than 50 trial subjects at that site. If testing problems are identified (e.g., in the event of a false positive or false negative result that changes the infection status of the subject), samples from additional participants will be evaluated at the HPTN LC. In some HPTN studies, 100% of study samples will be retested at the LC (e.g., if significant testing problems are suspected or identified, if different testing assays or algorithms are used at different sites that may differ in sensitivity or specificity). Additional QA testing will be performed to confirm HIV reactive events. This may include testing samples prior to seroconversion for evidence of acute HIV infection. In some cases, QA testing may include assays such as ABO blood group back- typing (to detect sample mix-ups) or antiretroviral drug testing (to explain viral loads that are low or undetectable). Results of testing performed for QA purposes will not be returned to the sites but will be submitted to the SDMC in an agreed upon format utilizing a Data Transfer Plan (DTP). The LC will determine which QA data will be transferred to the SDMC; this will be determined for each study protocol.

The HPTN LC QA Core is responsible for:

- Preparing Specimen Data requests that are submitted to the SDMC in regards to the QA testing plan for the particular protocol
- Working with sites to ship samples to LC for testing
- Conducting the QA testing and testing for primary/secondary endpoints
- Preparing DTP with the SDMC
- Notifying the SDMC that laboratory generated data will be submitted for a protocol
- Providing the SDMC with QA test results via the Lab Upload tool

- Working with CTU/CRS laboratories to determine causes of any discrepancies
- Working with the SDMC to collate necessary material for an EAC, if necessary

The SDMC is responsible for:

- Reviewing the Specimen Data Request form submitted by the HPTN LC
- Providing specimen testing/data/shipping lists for QA analysis by the LC, which will include PTIDs, specimen IDs, global specimen IDs, specimen collection dates, visit types, and visit numbers
- Receiving the QA test results from the HPTN LC
- Comparing the retest results with the results collected on CRFs
- Notifying the HPTN LC of any discrepancies, omissions or other issues in timely manner
- Creating and distributing a report of discrepancies for an Endpoint Adjudication Committee (EAC) review, if necessary
- Generating a draft DTP and work with the LC for completion and sign off.

13.9 HIV Endpoint Determination

The HPTN LC is responsible for specifying HIV testing algorithms in HPTN protocols that are scientifically appropriate for the study population and study objectives. The site HIV testing algorithm will be described in the protocol; additional information may be found in the Laboratory SSP Manual. HPTN Investigators of Record (IoRs) will make every effort to ensure that protocol-specified HIV testing algorithms are followed throughout the period of study implementation.

Supplemental protocol-specific testing algorithms may be required for certain studies; additional details may be found in the Laboratory SSP Manual. Sites will be informed by protocol leadership whenever the use of such algorithms is required.

The HPTN LC performs QA and confirmatory HIV testing for HPTN studies as specified in HPTN protocol documents and/or the Laboratory SSP Manual. In some cases, some of this testing may be performed at a regional laboratory designated by the HPTN LC. The QA testing plan and the extent of QA testing (e.g., the proportion of study samples evaluated at the HPTN LC) are determined by the HPTN LC leadership. QA test results are reviewed by the HPTN LC QA/QC Core Director and the HPTN LC QA/QC Coordinator for the protocol.

Complex cases or cases where there are incomplete and/or discrepant results are also reviewed by the HPTN LC PI.

Protocol teams will refer all issues and questions related to HIV endpoint determination to the HPTN LC. The SDMC statistician for each study (or designee) will provide data reports to the HPTN LC as needed to support review and decision-making by the HPTN LC. For blinded studies, data provided to the HPTN LC will not include participants' treatment assignments or information regarding treatment failures, with limited exceptions (e.g., to identify samples for pharmacology testing). In some cases, an Endpoint Advisory Committee will be convened by the HPTN LC at the start of a protocol or during a protocol to evaluate primary endpoint events.

13.10 HIV Endpoint Adjudication

The HPTN LC may choose to convene a protocol-specific Endpoint Adjudication Committee (EAC) in cases where there are incomplete HIV test data (e.g., due to missed testing or loss-to-follow up at study sites); or in cases where results from the site and/or HPTN LC testing do not clearly define the infection status of one or more study participants. An EAC may also be convened to address issues such as:

- Failure of one or more study sites to follow a protocol-specified HIV testing algorithm
- Indeterminate test results persist at study exit
- An unusual pattern of test results is observed

Depending on the number of endpoints and the complexity of the endpoint data, one of three types of EACs will be convened: an Internal EAC (IEAC), an external Virology EAC, or a Specialty EAC. The type and membership of EAC convened for each study will be determined by the HPTN LC, in consultation with the Protocol Chair(s) and Study Statistician. DAIDS Prevention Sciences Program (PSP) representatives may take part in EAC meetings as non-voting discussants or observers.

13.11 HPTN LC Assessments for Primary/Secondary/Exploratory Objectives

This section describes procedures for the design and conduct of specialized testing that contributes to the HPTN collaborative science and is performed at the HPTN LC or at laboratories designated by the HPTN LC. This is distinct from QA testing which is described in Section 13.8.

The HPTN LC will collaborate with the protocol chairs, statisticians, and others as appropriate to design the laboratory assessments that are needed to address the assay-based objectives and endpoints for each protocol. Data from these assessments will not be returned to study sites or participants unless this is indicated in the protocol document or Laboratory SSP Manual. The LC will maintain a living document that describes on-going and planned laboratory assessments (LC Testing Plan). The LC Testing Plan will be drafted by the LC and will be reviewed periodically in collaboration with relevant members of the protocol team. The LC Testing Plan will be reviewed periodically with the SDMC to coordinate LC and SDMC activities needed for these assessments. Data from these assessments will be submitted to the SDMC in an agreed upon format utilizing a Data Transfer Plan (DTP). The LC Testing Plan will be updated periodically to indicate which data will be transferred to the SDMC for each protocol.

The HPTN LC is responsible for:

- Preparing and updating the LC Testing Plan, in consultation with the SDMC and key study team members.
- Obtaining approval from relevant members of the protocol team and HPTN Leadership for addition of assessments that extend beyond those needed to address study objectives and endpoints.
- Initiating Specimen Data requests. These requests will be developed with the SDMC for each protocol as assessments proceed. These requests may be submitted using individual Specimen Data request forms or a single, protocol-specific excel file with a sheet for each specimen or data request.
- Working with the sites to ship samples to LC for testing.

- Oversight of testing conducted by the HPTN LC laboratories or laboratories designated by the HPTN LC
- Preparing DTPs with the SDMC
- Notifying the SDMC that data from the LC will be submitted to the SDMC.
- Submitting LC data to the SDMC using secure electronic data transmission.
- Arranging for electronic data transmission to the SDMC from subcontract laboratories, if needed.

The SDMC is responsible for:

- Working with the LC and the protocol chair(s) to design and/or review the planned lab studies, assess study power, and propose statistical analyses.
- Reviewing the Specimen Data Request form submitted by the HPTN LC
- Providing specimen testing/data/shipping lists, which will include PTIDs, specimen IDs, global specimen IDs, specimen collection dates, visit types, and visit numbers; other study data may be included
- Initiating DTPs for each request and working with the LC for completion and sign-off of DTP documents
- Receiving data from the HPTN LC and subcontract laboratories and working with the LC to resolve any data issues
- Notifying the HPTN LC of any data omissions or other issues in timely manner

13.12 HPTN Sample Destruction

CTU/CRS laboratories are required to store samples for HPTN studies. Some of these samples may be sent to other laboratories for other testing as mandated by the respective protocols. Each protocol should address short- and long-term storage of specimens before study initiation, including the accompanying sample informed consent form.

It is the responsibility of the CRS to estimate the total number of samples for storage, the storage requirements and to provide appropriate facilities and equipment for storage that will meet GCLP guidelines. The HPTN LC does not have a repository.

During the course of a study, a participant who consented to long-term storage may change their mind and withdraw that specific consent. If this happens, sites are responsible for updating the appropriate e-CRF accordingly.

In general, at the completion of a primary manuscript for a study, when there are specimens still being stored on site, a determination will be made by the sponsor(s) of the study or the Protocol Chair(s), in consultation with the HPTN LC, when to destroy specimens from participants who did not consent to long term storage and/or to continue to store the specimens deemed for long-term storage. The laboratory will be notified by the study team(s) via the HPTN LC if specimens must be destroyed. This process will also specify exactly which samples are to be destroyed.

Each site will draft a Sample Destruction SOP that will be reviewed by the HPTN LC. This SOP should include a form that will be used to maintain the chain of custody of the samples throughout the destruction process. All hospital and/or university policies, as well as local regulations, must be followed when handling or discarding specimens. For older studies, the Leadership Group of the Network may make a determination to destroy or continue to store the specimens in question.

Copies of the storage reports will be kept along with the Destruction of Samples documentation logs. Storage will be as per DAIDS policies.

13.13 Referenced or Useful Web Links

Websites for general information related to topics covered in this section, as well as those specifically cited, are listed below:

Resources:

HIV/AIDS Network Coordination	https://www.hanc.info/resources/sops-guidelines-resources/laboratory.html
DAIDS	https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures
CLIA	https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/

Specimen Shipping, Shipping Materials and Information:

CDC Shipping Regulations	https://www.cdc.gov/cpr/ipp/shipping/index.htm https://www.cdc.gov/labtraining/training-courses/packing-shipping-division-6.2-materials.html
Code of Federal Regulations	https://www.ecfr.gov/cgi-bin/ECFR?page=browse
US Postal Service	http://www.usps.com
CDC Office of Health and Safety - Biosafety	https://www.cdc.gov/niosh/topics/healthcare/default.html and https://www.cdc.gov/niosh/topics/bbp/
International Air Transport Association	http://iata.org/index.htm
FedEx Dangerous Goods Shipping Seminars	http://fedex.com/us/services/options/express/dangerousgoods/seminars.html?link=4
Dangerous Goods	http://www.danrgerousgoods.com
DHL	http://www.dhl-usa.com/solutions/express.asp?nav=dhlExp
US Department of Transportation	http://www.dot.gov/
US DOT/Transporting Infectious Substances Safely	https://www.phmsa.dot.gov/transporting-infectious-substances/transporting-infectious-substances-overview

Risk Group Assessments:

Risk Group Classification for Infectious Agents	https://my.absa.org/Riskgroups
American Biological Safety Association	http://www.absa.org/
CDC Regulation	http://www.cdc.gov/biosafety/
CDC Select Agent Listings and Regulations	http://www.selectagents.gov/
USDA Plant and Animal Pathogen Select Agents	https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-and-animal-product-import-information/organisms-vectors/ct_organisms_and_vectors

14 SAFETY CONSIDERATIONS

Ensuring participant safety is critical to all HPTN trials. Close cooperation between the protocol chair(s), sites investigators, site staff, Division of AIDS (DAIDS) Medical Officers, Leadership and Operations Center (LOC) Clinical Research Manager (CRM), Statistical and Data Management Center (SDMC) Clinical Data Manager (CDM), Laboratory Center representative (LC), the protocol-specific Clinical Management Committee (CMC) (if applicable), and other members of the study team is necessary to closely monitor participant safety and to respond to occurrences of toxicity or social harms in a timely manner.

The requirements and procedures for identifying and reporting adverse events (AEs) and/or social impacts for each study will be specified in the protocol and Study-Specific Procedures (SSP) manuals. The study site investigators serve an important first line role in monitoring participant safety and are responsible for reporting AEs and/or social impacts according to the specified procedures. Instructions for site access to and use of the DAIDS Adverse Event Reporting System (DAERS) are found on the DAIDS Regulatory Support Center (DAIDS RSC) website.

The study protocol for clinical trials will describe the AE reporting requirements and procedures to be followed. Requirements for expedited reporting of adverse events are described in the Manual for Expedited Reporting of Adverse Events (EAE) to DAIDS, and the version to be used will be specified in the protocol. The protocol will also specify:

- The product or products considered to be under study
- The start and duration of AE reporting
- AE grading criteria (DAIDS Table for Grading of AEs version, any special grading scales)
- Any additional protocol-specific AE or EAE reporting requirements

Any exceptions to the procedures or requirements specified in the EAE Manual must be specified in the protocol. Alternative procedures for studies that do not involve investigational agents and for which there is no AE reporting (e.g., behavioral intervention trials), will be specified in the study protocol.

DAIDS has an internal process for review of AE reports submitted in an expedited manner to the DAIDS RSC by study sites. This process includes careful review by the responsible Medical Officer and a Regulatory Affairs Branch (RAB) Safety Specialist. Investigators are responsible for submitting additional information regarding AEs upon request by the RSC and as specified in the EAE Manual. When indicated, Investigational New Drug (IND) safety reports or other safety communications are prepared by the RSC and submitted to the appropriate regulatory bodies (e.g., United States (US) Food and Drug Administration [FDA]). Copies are provided to the investigators and are to be submitted to the responsible Institutional Review Boards/Ethics Committees (IRBs/ECs) as described below.

14.1 Safety Distributions to HPTN Investigators

Product safety information is provided to HPTN investigators and protocol teams of clinical trials involving study products by DAIDS prior to study initiation and during the course of a clinical trial, as needed. Product safety information is distributed in several forms including:

- Investigator's brochures (IB) for investigational products
- Package inserts for licensed products
- IND safety reports
- Safety memoranda/updates

In addition to the documents listed above, Data and Safety Monitoring Board (DSMB) review summaries are also distributed to investigators and study teams by DAIDS for all studies monitored by the National Institute of Allergy and Infectious Disease (NIAID) DAIDS Data and Safety Monitoring Board (see Section 15.8). Investigator's Brochures (IBs) are electronically distributed to Site Leaders, Principal Investigators, Investigators of Record, CTU Coordinators and CRS Coordinators through the NIAID Clinical Research Management System (NIAID CRMS) EAE Reporting Module (DAERS). A guide for CRS leaders and coordinators for access to IBs is located here or on the RSC site: Safety Information Distribution | DAIDS Regulatory Support Center (RSC) (nih.gov).

Distributions of these documents to investigators and study teams include explicit instructions regarding the requirements for handling of the information. IBs, package inserts, IND safety reports, safety memos, other product information, and DSMB summaries must be submitted by the investigators to the relevant IRBs/ECs for informational purposes (not approval) as instructed by DAIDS.

For any study that will be conducted at more than one US site, all safety information listed above are submitted by the LOC for single Institutional Review Board review on behalf of all US sites.

To ensure that all intended recipients have received relevant safety distributions issued by DAIDS, monthly reports and periodic summaries of the distributions (such as Investigator's Brochure updates and IND safety reports) are also distributed by DAIDS through the RSC. Investigators and study coordinators are responsible for reviewing this information to verify that they have received all relevant correspondence and for ensuring that this information is submitted to the IRBs/ECs overseeing the study, as instructed by DAIDS.

The SSP manuals for each study will describe the types of safety information that investigators should expect to receive from DAIDS before and during study conduct and the requirements for IRB/EC submission of these. The types of safety information to be issued for each study will vary based on whether the study is solely behavioral or observational, whether a study product is being used, and whether it is being conducted under an IND with the US FDA.

A site's obligation for receipt and processing (e.g., submission to the IRB/EC) of safety distributions begins when the site is registered to the protocol through the RSC and ends once a site is de-registered from the protocol.

14.2 Review of Safety Data for Clinical Trials

In addition to the internal DAIDS review process for AEs reported in an expedited fashion, the HPTN uses a three-tiered approach to safety data review designed to identify potential safety concerns in a timely manner and to ensure the quality and accuracy of clinical and laboratory data reported and analyzed in HPTN clinical trials. Through this system, once enrollment has begun, individual and aggregate safety data are reviewed and evaluated by qualified personnel through a consistent, methodical process.

14.2.1 Tier One

The first tier of clinical and laboratory data safety review involves study site clinicians, RSC, DAIDS, and SDMC personnel. Site clinicians are responsible for carefully assessing participant safety and reporting relevant clinical and laboratory data via case report forms (CRFs) submitted to the SDMC as well as the reporting of AEs that meet the criteria for expedited reporting to the RSC.

The SDMC staff generates and reviews protocol-specific standard reports on a routine basis to ensure that safety data is complete, accurate and timely. The SDMC clinical coding and safety and data management staff applies AE coding and clinical queries to data requiring confirmation, clarification, or follow-up.

For studies with pause criteria or rules, SDMC programmers create computer programs that alert SDMC staff when criteria for pausing the study may have been met and the protocol team may need to be notified. Pause criteria must be specified in the study protocol.

14.2.2Tier Two

Tier two of safety oversight of HPTN studies of a biomedical intervention includes a Clinical Management Committee and may also include regular review of safety data by independent safety reviewers. For some studies, especially those without DSMB oversight, the HPTN Study Monitoring Committee may also review reports of safety data.

Clinical Management Committee

For each study with a clinical component, a Clinical Management Committee (CMC) will be established, composed of appropriate protocol team clinicians (including an HPTN Safety Physician, as necessary), who will provide support to site clinicians regarding individual participant clinical management (toxicity management, clinical holds of study drug, study drug re-challenge, permanent discontinuations). Blinding will be maintained with regards to the individual participant discussion(s).

Independent Safety Reviewers

The SDMC may contract with clinicians to serve as independent safety reviewers (ISR) for studies of products that are not approved for any indication or for studies of products that need further safety evaluation. The ISR is responsible for reviewing regular reports of safety data along with the Medical Officer (MO). If there are any trends in the safety data noted the ISR or MO will notify the protocol statistician who will in turn notify the Study Monitoring Committee (SMC) or DSMB, as appropriate. The ISRs may also serve as members of the SMC, particularly for studies with no DSMB oversight.

For trials with no DSMB oversight, the HPTN SMC will also review safety data, either in aggregate or by arm. The SDMC will prepare routine study conduct and safety reports for the SMC, which will meet by conference call approximately every 6 months and will review safety data during a closed meeting. More frequent or *ad hoc* reviews of safety reports may be conducted by the SMC as needed.

A recommendation to stop the trial may be made by the SMC at any such time that the team agrees an unacceptable type and/or frequency of AEs has been observed. If at any time a decision is made to discontinue the study product in all participants, DAIDS will notify the site IoRs, who will notify the responsible IRBs expeditiously.

14.2.3Tier Three

Phase IIb and III HPTN trials are typically reviewed by a DAIDS Data and Safety Monitoring Board (DSMB) as described in Section 15.8. The DSMB examines the accumulated endpoint and safety data to make recommendations to DAIDS concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse effects of the interventions under study. This includes a closed-session review of study data by arm, often triggered by an event specified in the protocol (e.g., number of participants enrolled, or number of endpoints attained). Reviews of Phase IIb and III trials are conducted at least annually for safety and accrual, even if events that might prompt a review of efficacy have not yet occurred. Protocol Chairs (or designee) are expected to participate in the open session of these reviews.

14.3 Social Impacts

In addition to medical safety concerns, participants in HPTN studies may also experience social impacts such as discrimination, stigma or legal problems as a result of their participation in the study. Only events that participants perceive to have negatively affected them due to study participation are considered reportable. The staff's interpretation of an event is not considered in determining whether an event is a social impact. Each HPTN protocol will indicate how social impacts will be reported and assessed. Sites are also responsible for reporting social impacts to the responsible IRBs/ECs as applicable locally.

15 STUDY OVERSIGHT

Study oversight within the HPTN takes place at a number of levels. The Division of AIDS (DAIDS), as the Network sponsor, has ultimate responsibility for overseeing the HPTN research. In addition to contracting with a Clinical Site Monitor (see Section 15.3.1) and organizing and convening the NIAID DAIDS Multinational Data and Safety Monitoring Board (DSMB) where applicable, DAIDS staff provide guidance and oversight to HPTN studies. For each study, the Protocol Chair is responsible for oversight of overall study performance. The HPTN also has established oversight procedures by the Executive Committee (EC) as well as the operational components of the Network including the Leadership and Operations Center (LOC), Statistical and Data Management Center (SDMC), Laboratory Center (LC) and Study Monitoring Committee (SMC). At the Clinical Research Site (CRS), study staff and site personnel engage in continuous internal monitoring of study conduct through quality management, as outlined in the site Clinical Quality Management Plan.

15.1 Clinical Quality Management Plan

DAIDS requires that each site develop and implement a Clinical Quality Management Plan (CQMP) that addresses key aspects of a clinical research project to ensure that the rights and safety of participants are protected, and that the data collected are accurate, complete and verifiable.

Quality Management is an overall process that encompasses both quality assurance (QA) and quality control (QC). A CQMP must describe the QA and QC activities that will be performed on study records and also describe the types of "tools" and checklists that will be used in the QA and QC processes. The CQMP must also state the frequency with which QA and QC activities will be performed. A report detailing the findings of the QA/QC activities including identification of problems, identification of possible causes, and any corrective action plan must be communicated to appropriate study staff.

At DAIDS' discretion, a site CQMP may be reviewed prior to its implementation. The CRS may be required to submit revisions of the CQMP to DAIDS. On an annual basis each CRS must prepare an evaluation report of the CQMP and submit the report to DAIDS utilizing the DAIDS specified format, e.g., PHS 2590, Non-Competing Continuation (Type 5) grant progress report. The Office of Clinical Site Oversight (OCSO) Program Officer (PO) will review the CQMP annual evaluation report for trends or areas where the CQMP or related activities need revision. If significant issues are noted, the OCSO PO will provide feedback to the CRS and request modification of the CQMP.

Implementation of the CQMP may be assessed periodically by the Clinical Site Monitoring group and noted in a site monitoring report.

The requirements for CQMPs are detailed in the section on Quality Management within the DAIDS SCORE Manual.

15.2 Operations, Laboratory, Data Management and DAIDS Site Visits

Staff members from the HPTN LOC, SDMC, and LC may visit sites to:

- Assess the quality of HPTN study implementation, including data management practices
- Identify implementation strengths and weaknesses
- Troubleshoot and provide technical assistance and/or retraining related to implementation issues and problems
- Share information on successful implementation strategies identified at other sites
- Identify action items as needed to address study implementation issues and problems

While onsite, LOC, SDMC, and LC staff perform assessments and provide technical assistance, training, etc., in their respective areas of responsibility and expertise.

These visits do not replace the monitoring visits conducted by the DAIDS contracted monitors. The following types of visits may be made by the LOC, SDMC and/or LC throughout the course of the study:

- Assessment Visits: Conducted throughout course of the protocol to assess protocol implementation
- "For Cause" Visits: Conducted if needed due to problems at site such as too low or too fast enrollment, many protocol deviations, poor compliance with protocol and other procedures, unusual severe adverse events (SAE) reports, poor data management quality metrics, and/or support with close-out procedures

Site staff are required to allow LOC, SDMC, and LC staff access to inspect study facilities, specimen storage, and documentation (e.g., informed consent forms, clinic and laboratory records, regulatory documents, source documents, case report forms), and to observe the performance of study procedures. Site staff are encouraged to share with the LOC, SDMC, and LC information on study implementation successes, issues, and problems to help ensure the highest possible quality of HPTN study conduct. LOC, SDMC and LC visitors will make all possible efforts to minimize the impact that the visits have on daily study operations.

Each organization (LOC, SDMC, and LC) conducts and documents its visits according to its own organizational Standard Operating Procedures (SOPs) and/or additional directives from DAIDS. Visit reports are provided to site staff and distributed to DAIDS and key study implementation partners as appropriate. Issues and problems may be brought to the protocol team, SMC or HPTN leadership for discussion and action (see Sections 15.4, 15.5, 15.6).

The DAIDS Clinical Site Monitor also conducts periodic visits to HPTN study sites, as described in Section 15.3. DAIDS staff may visit, or accompany LOC, SDMC or LC staff on visits, on an *ad hoc* basis.

15.3 Monitoring

DAIDS has regulatory responsibility for oversight of all HPTN trials under the US Code of Federal Regulations (CFR) Title 45, Parts 46, 160, and 164; Title 21, Parts 11, 50, 54, 56, and 312; and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines E6(R2). DAIDS uses a risk-based approach to monitoring. Monitoring plans are protocol specific and developed based on the design, size and complexity of the clinical trial.

The purposes of monitoring a research study are to verify that:

- The rights and well-being of human subjects are protected
- Data integrity; the reported trial data are attributable, legible, contemporaneous, original, accurate, and verifiable from source documents
- Quality systems compliance; the data are complete, consistent, enduring and available (CCEA)
- The conduct of the trial is in compliance with the currently approved protocol/amendment, ICH Good Clinical Practice (GCP) guidelines, and the applicable regulatory requirements

15.3.1 Clinical Site Monitor

In keeping with this regulatory oversight obligation, DAIDS has delegated the responsibility for onsite or remote monitoring to a contractor, the clinical site monitor.

Under some circumstances, DAIDS may elect to delegate a specific monitoring assignment and/or auditing duties to an alternative contractor instead of the primary contractor. In such situations, DAIDS will advise the Clinical Trials Unit (CTU) Principal Investigator (PI) and/or in-country investigator, also known as the CRS Site Leader, in advance of the specific assignment so that required arrangements can be made.

The primary goals and objectives of clinical site monitoring are:

- Performing source document verification and lab specimen verification to ensure the accuracy and completeness of trial data
- Reviewing informed consent forms, procedures, and documentation
- Identifying problems with protocol compliance relative to protocol procedures, ICH GCP guidelines, and all applicable regulatory requirements (US and in-country)
- Verifying the proper storage, dispensing, and accountability of study products under investigation, when applicable
- Documenting the implementation of appropriate internal site quality control and quality assurance procedures
- Assessing the need for additional site personnel training

All sites are expected to use the Clinical Site Monitoring (CSM) module of the NIAID Clinical Research Management System (NCRMS) to view the status of the Clinical Site Monitor's report.

15.3.2 Clinical Monitoring Visits

Clinical monitoring visits may be conducted onsite or remotely. DAIDS will determine the frequency of clinical monitoring visits based on the risk, size, and complexity of the trial. The clinical site monitor will contact site staff in advance to schedule the monitoring visits confirming the dates of the visit and listing the items to be monitored during the visit.

Site monitoring visits may be protocol-specific, site-specific (i.e., examining all studies and procedures at the site), or targeted (e.g., laboratory monitoring). The purpose of the visit will depend on the assignment, but may include:

- CTU/CRS site initiation
- Review of participant records and source document verification of trial data
- Review of informed consent forms
- Regulatory file review
- Study close-out review

In addition, the monitor may assess the adequacy of the pharmacy, clinic, laboratory, and other facilities; medical records; case report forms; and any aspect of the clinical research that may affect participant safety. Special monitoring assignment visits may be requested of the clinical site monitor at the discretion of the DAIDS, when necessary, to verify any particular aspect of trial conduct.

The site will arrange for the monitor to meet with the appropriate study staff during the visit and will ensure that all documentation to be monitored is readily accessible. The site must identify an appropriate place for the monitor to work during the visit.

The monitor holds a debriefing toward the end of the visit, typically on the last day, to review the findings of the visit. The monitor meets with the Investigator of Record (IoR) and any study staff that he or she would like to include. If available, DAIDS also strongly recommends that the CTU and/or in-country PI, if different from the IoR, the DAIDS Medical Officer, as well as the OCSO representative be present (in person or remotely) at the debriefing. The monitor will leave a list of the pertinent findings with the PI or IoR at the end of the visit so that, if necessary, corrective actions can begin at once.

15.3.3 Monitoring Reports

A detailed written report based on the monitor's observations during the site monitoring visit is completed by the monitor and entered into the NCRMS CSM module within 20 working days of the visit. The system will notify all appropriate persons that the report is available. The OCSO Program Officer (PO) and/or Pharmaceutical Affairs Branch (PAB) representative review the report and enter select monitoring findings, such as observational trends, into the CSM module within 15 days.

The system will automatically notify the site that there are issues that require their action.

15.3.4 Procedures for Site Response to Monitoring Reports

Upon receipt of the electronic notification, the site will respond through the CSM module to the Program Officer's requirements. The system will then automatically notify the Program Officer that a response has been sent.

The Program Officer will review the response from the site.

- If the issues were satisfactorily resolved, the Program Officer will mark them resolved in the NCRMS and the NCRMS will automatically notify the site that the issues are resolved.
- If any issues remain unresolved, the Program Officer will return them to the site via the NCRMS with appropriate comments.
- If a major issue or multiple issues were noted, the Program Officer may recommend to:
  - Pause the study
  - Pause all National Institutes of Health (NIH)-funded studies at the site
  - Close the site

A final decision on recommended actions in the case of major or multiple issues is made by the sponsor in consultation with the Network and a letter will be sent to inform the CTU PI.

Site staff will retain copies of the correspondence between the Program Officer and the site for their regulatory files.

15.4 Protocol Team Oversight

The Protocol Chair is responsible for overall oversight of the study. Under the lead of the Protocol Chair, HPTN protocol teams are responsible for actively monitoring study conduct and progress largely through required review of study-specific reports as defined in the study reporting plan (see Section 12.5). The Protocol Chair may also visit study sites. If and when these visits occur, the Protocol Chair should notify LOC, SDMC and LC staff in advance of the visit and provide them with any relevant findings from the visit. Protocol Chair(s) are responsible for ensuring that the team discusses issues and problems in a timely manner and that a corrective action plan is implemented.

If issues cannot be resolved within the protocol team, the Protocol Chair or other protocol team members may refer issues to the EC or SMC for further deliberation and guidance.

15.5 Study Monitoring Committee (SMC) Oversight

The SMC functions to provide HPTN leadership and the Protocol Team an internal review of study data, with an emphasis on participant accrual, participant retention, protocol and intervention adherence, and other key performance indicators. In addition, for trials with no Data and Safety Monitoring Board (DSMB) oversight, the SMC will review safety data, either aggregate or by arm. For Phase IIb and III trials, the SMC, when there is no DSMB oversight, will also monitor the rate of required endpoints (in a blinded fashion) for continued feasibility of the trial.

The SMC is composed of representatives of the LOC, SDMC, DAIDS, and LC, all of whom are not associated with the protocol, and one or more *ad hoc* members with relevant technical expertise (see Section 4.3.2). Whenever possible, the composition of the SMC for each study is maintained throughout study duration.

The SDMC prepares reports based on study data received from the sites (see Section 12.5.7), provides the LOC with preferred review periods, and works with protocol teams and site staff to provide any necessary additional data from sites. The LOC queries the SMC members, Protocol Chair, and protocol statistician in order to determine the appropriate date and time and sets up the review calls. The Protocol Chair will consult with the SDMC to determine if any additional information directly relevant to study implementation status should be provided or if SMC guidance on a specific issue should be sought. If so, the Protocol Chair drafts a memorandum to the SMC for review and input by the study team or prepares other materials as needed.

The Protocol Chair (and Co-Chair if applicable) is invited to join the SMC review call during the open session of the review to respond to questions or issues raised by the SMC. Observers from the protocol team, LOC, LC, and SDMC, and NIH, as well as the HPTN PIs, are invited to join the call during the open session.

Summaries of actions and findings of the SMC are communicated to the protocol team through the review summary prepared and distributed by the LOC in conjunction with the SMC Chair. The LOC sends a summary from SMC review calls to all sites and team members for distribution to Institutional Review Boards (IRBs)/Ethics Committees (ECs) as necessary. Additionally, the HPTN PIs receive the SMC open reports and summaries.

For any study that will be conducted at more than one US site, SMC summaries are submitted by the LOC for single Institutional Review Board review on behalf of all US sites.

The HPTN PIs/leadership is informed of any significant recommendations or outcomes. Recommendations involving substantive changes to the protocol (conduct or cost) are subject to sponsor and EC approval. If the protocol team does not agree with the actions recommended by the SMC, the EC will mediate.

HPTN studies are reviewed approximately four to six months after initiation, depending on the rate of enrollment and the needs of the study. Thereafter, all studies are reviewed approximately every six months and more frequently if deemed necessary, unless review is waived by the SMC. For studies subject to DSMB monitoring, the SMC reviews the open portion of the DSMB report, and in some cases, the number of endpoints (in closed session) in preparation for the DSMB reviews (see also Section 15.8). Summaries of SMC reviews and recommendations are shared with the protocol team and the EC, and with the DSMB as appropriate.

15.6 HPTN Leadership

The EC monitors HPTN studies with regard to protocol development, implementation, analysis, and reporting.

Routine EC oversight includes evaluation of study progress with respect to key implementation milestones. It is aided in this endeavor by information provided by the Performance Evaluation Committee (PEC), protocol teams, LOC and SDMC (e.g., timeliness of enrollment and follow-up targets, routine reports to the DSMB, or progress in data analysis and reporting). All monitoring and evaluation findings are reported to the EC. If significant laboratory-related issues or problems arise, the LC brings these to the attention of the EC for discussion.

The EC also monitors resource allocation and use by protocols. Based on this, the EC assists the NIH in determining the need for additional resources, for example, because of unexpected costs associated with planned study procedures or in order to support additional sites requested or ancillary studies endorsed by the protocol teams.

In addition, all protocols are routinely reviewed at least annually by the EC during an in-person meeting.

15.7 Study Oversight by the Sponsor

NIH staff members are active in overseeing and supporting study implementation in the HPTN. NIH staff members are part of the HPTN leadership through membership in the EC and also participate in all HPTN working groups and committees.

DAIDS assigns a Medical Officer to each protocol. This staff member is assigned to monitor the safety and efficacy of the intervention(s) for both in-development and ongoing studies and is provided with interim and final reports produced by the HPTN SDMC. Protocols sponsored by a collaborating institution or research group (i.e., National Institute on Drug Abuse (NIDA) or National Institute of Mental Health (NIMH)) may be monitored by that Institute's research groups medical representative(s).

Designated sponsor staff communicates with HPTN site staff as needed. They interact directly with the CRS regarding follow-up to monitoring reports and also work with the clinical site monitor to develop monitoring assignments and provide feedback for site development and evaluation.

DAIDS also monitors the progress of studies through review of DSMB reports.

The OCSO Program Officer will take corrective action when serious and/or persistent non-compliance with protocol, regulatory, or grant requirements is identified at a CRS. If necessary, a site may be temporarily suspended from enrolling new participants until problems are resolved.

15.8 Data and Safety Monitoring Board Oversight

The National Institute of Allergy and Infectious Diseases (NIAID) Prevention Data Safety and Monitoring Boards (DSMBs) are responsible for reviewing study conduct and safety and efficacy data for all Phase IIb/III trials, as well as select other trials. The members of the DSMB are independent investigators with no financial interest in the outcomes of the studies reviewed. Members include experts in the fields of biostatistics and medical ethics, clinicians, and other scientists who are experts in HIV transmission, plus *ad hoc* members. Appointments to the DSMB are made by NIAID.

The SDMC prepares reports for DSMB review (see Section 12.5.6). The DSMB meets at least annually or according to the monitoring plan put in place prior to initiation of the study. All Phase IIb/III trials are reviewed at least annually. Representatives of the protocol team (e.g., Protocol Chair/Co-Chair and protocol statistician) attend the open session of the DSMB review in person or remotely to discuss study progress, respond to questions, and receive the DSMB recommendations.

15.8.1 Data and Safety Monitoring Board Summary

The DSMB provides a written summary of all reviews to DAIDS and NIAID, which is also distributed to the protocol team and the HPTN Principal Investigators. Recommendations involving substantive changes to the protocol (conduct or cost) are subject to sponsor and EC approval. If the protocol team does not agree with the actions recommended by the DSMB, the protocol team may refer the issue to the EC.

15.8.2 DSMB Recommendations for Study Modification

Based on DSMB recommendations, NIAID may find it necessary to close or modify an ongoing study for one of the following reasons:

- Risk to subject safety
- The scientific question is no longer relevant
- The objectives will not be answered
- Slow accrual
- The objectives of the study have been met
- New information from other research is now available
- Ethical concerns

In the case of DSMB recommendations that require public dissemination, a press release or public statement will be developed following Network procedures (Section 6). It is imperative that the DSMB findings remain confidential until public release. In an effort to ensure study confidentiality, all study team members must sign a confidentiality agreement.

Recognizing that in some cases DSMB findings may require immediate action, communication of DSMB results with network constituents and study participants will be coordinated with the Protocol Chair, HPTN leadership and NIAID in a timely fashion. Advance communication planning and development of possible DSMB outcomes will expedite this process.

15.8.3 Non-DAIDS Sponsored Studies

For all non-DAIDS sponsored studies, study oversight responsibilities will be determined by the relevant protocol team and regulatory sponsor.

16 NEW SITE REQUIREMENTS

16.1 Site-specific Requirements

All new HPTN Clinical Research Sites (CRSs) or other established site at the discretion of the Division of AIDS (DAIDS) must meet certain requirements prior to receiving DAIDS Site Activation. This approval is different from study-specific site activation. Office of Clinical Site Oversight (OCSO) site approval does not indicate that a CRS may begin conducting a study. CRS staff must work with the Leadership and Operations Center (LOC), Laboratory Center (LC), Statistical and Data Management Center (SDMC) and DAIDS staff to ensure Network and protocol-specific requirements are met. The OCSO Program Officer (PO) will: (1) communicate site activation requirements to the site; (2) identify issues; (3) facilitate issue resolution to efficiently complete the site activation process.

Requirements and SOPs are reviewed and verified by OCSO.

Before site activation by OCSO, a CRS must have a PAB-approved pharmacy. The Pharmacist of Record (PoR) must complete a PAB Pharmacy Establishment Plan (PEP) and any applicable associated PEP Modules for each pharmacy associated with a CRS and submit these documents to PAB for review and approval

16.2 Site SOPs

HPTN CRSs are expected to have written SOPs for site operations and study operations to ensure compliance with HPTN and DAIDS procedures, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guidelines (use drop down menu in the webpage) and United States Food and Drug Administration (US FDA) regulations and any other regulations, where applicable. CRSs will develop certain site-specific SOPs that describe the procedures for general site operations – i.e., those that are applicable across all studies performed at that site. Existing site SOPs may be used to satisfy these requirements.

Sites must follow the policies and template outlined in the DAIDS SCORE Manual for development of SOPs: https://www.niaid.nih.gov/sites/default/files/score-quality-management.pdf

16.3 Clinical Site Monitor Special Assignment Initiation Visit

The OCSO PO may choose to have the Laboratory or Clinical Site Monitor conduct an initiation visit before the initiation of a new HPTN site. The purpose of this visit is to ensure that both the facility and staff can carry out the DAIDS research.

16.4 CRS Relocation to a New Site

Although not technically a new site, an established CRS may transfer mid-study to a new clinical research location. This is expected to be rare, but the steps needed for a successful transfer are outlined below. The lists may not be exhaustive. The initial declaration of intent to move should be made simultaneously to the CRS's OCSO Program Officer and to the HPTN Central Resources (LOC, LC, and SDMC).

16.4.1 DAIDS OCSO Responsibilities

DAIDS OCSO, including PAB (if applicable), will ensure the CRS completes the following after giving approval to complete the transfer (discussion of any HPTN Pharmacist responsibilities are considered in Section 23):

- The new CRS needs to be registered and updated in the NIAID CRMS
- After new registration is confirmed, the old CRS needs to be de-registered

- If there is a change in pharmacy location associated with the new clinical research location, the PoR must complete a new PAB Pharmacy Establishment Plan (PEP) and applicable PEP Modules and submit these documents to PAB for review and approval
- Notification must be made to the RSC safety teams so important information goes to the new site location
- OCSO decides if the participant charts can simply be transferred from the old site to the new or if certified copies need to be made and transferred

16.4.2 LOC, LC and SDMC Responsibilities

The LOC, LC and SDMC will ensure that the CRS completes the following for the new site transfer:

- Registration will signal the participants' data transfer, which will be managed by the SDMC
- The LOC will confirm if the CRS is still enrolling or not
- The LOC will ensure the creation of alias lists for the new site location
- The LC will provide their approval after laboratory requirements for the new CRS are met (e.g., new protocol analyte list (PAL), chain of custody, etc.)
- The LOC will discuss with OCSO the need for study-specific re-activation and the need for participant re-consent. Re-consenting decisions may be left to the discretion of the responsible IRB/EC

17 ANCILLARY STUDIES/INVESTIGATIONS

Ancillary studies may involve collection of additional data and/or samples from study participants or use of existing data and/or samples for analyses or laboratory assessments that are not directly related to the specific objectives of the relevant HPTN study as defined in the protocol document.

Ancillary studies may involve HPTN investigators and/or non-HPTN investigators and may be initiated by the primary study team or by investigators inside or outside of the study team and the Central Resources staff of the HPTN. They may involve all sites participating in a primary HPTN study or a subset of sites. Ancillary studies may involve the use of data, biological specimens, or other information obtained through an HPTN study and/or additional procedures related to study participation and may be either prospective or retrospective in nature. Ancillary studies may include surveys or focus groups among primary study participants and laboratory-based investigations using specimens obtained from participants in a primary HPTN study or some combination of the above.

Investigators who are interested in performing an ancillary study must submit an Ancillary Study Application. The process for proposal, review, and approval of ancillary studies is described below.

Note that laboratory assessments performed at the HPTN Laboratory Center (LC) that are related to the specific study objectives defined in the protocol are not considered ancillary studies; this includes quality assurance/quality control (QA/QC) assessments. Use of HPTN specimens for other purposes beyond the protocol objectives requires submission and approval of an Ancillary Study Application.

Additional considerations for ancillary studies involving use of stored specimens are described in Section 17.1.2.

17.1 Ancillary Study Application

All investigators proposing an ancillary study, whether internal or external to the HPTN, must complete the HPTN Ancillary Study Application. The Leadership and Operations Center (LOC), LC and Statistical Data Management Center (SDMC) should be contacted for input prior to the application being submitted. The completed Ancillary Study Application may or may not be assigned a number by the HPTN Executive Committee (e.g., HPTN 074-01, HPTN 074-02, etc.) that relates the application to a primary HPTN study.

The application should provide the information needed for the protocol team and Network Leadership to assess the merit of pursuing the proposed ancillary study, taking into account its scientific value, accord with the aims of the primary study team and network, consistency with the study consent documents, resource requirements and feasibility.

17.1.1 Management and Analysis of Ancillary Study Data

Plans for handling data generated through an ancillary study must be specified in the Ancillary Study Application. Prior to submitting the application to the HPTN, the investigator is required to discuss with the SDMC plans for data management and analysis and clarify if any input by the SDMC and/or access to primary study data will be necessary. The SDMC may or may not assume responsibility for handling ancillary data.

17.1.2 Additional Considerations for Ancillary Studies Using Stored Biological Specimens

There are additional considerations and requirements for ancillary studies/investigations involving the use of stored biological specimens. These requirements apply to all HPTN organizations, investigators, and other staff members, as well as non-HPTN investigators. The priority commitment of study specimens is the completion of work needed to address the specific study objectives defined in the protocol document.

- Stored specimens may not be used for ancillary studies until the study team leadership has confirmed that all laboratory assessments related to the specific study objectives as well as quality assurance/quality control (QA/QC) assessments have been completed, and that any associated data queries have been resolved. An exception may be granted to allow for release of specimens for ancillary studies prior to completion of this work, if the study team leadership determines that the specimens requested are not needed to complete this work.
- Prior to shipping or using specimens for an ancillary study, the protocol team must confirm that consent was provided for the proposed assays or the proposed work is consistent with the purpose indicated in the consent with regards to the use of stored specimens.

Requests for obtaining stored specimens are included in the ancillary study application process.

If an ancillary study that includes use of biological specimens is approved, the HPTN LC and SDMC will work with the investigators to determine the availability and location of the requested specimens and the procedures needed to transfer the specimens to the appropriate laboratory(ies). For studies that require shipment of specimens to a laboratory other than the HPTN LC, or shipment of samples to the HPTN LC for testing not specified in an existing Material Transfer Agreement, the investigator and/or LC must arrange for the appropriate documentation to be prepared and approved. Any costs related to specimen transfer to a laboratory outside of the HPTN LC will be the responsibility of the investigator proposing the study. In some cases, the ancillary study may require additional testing at the HPTN LC. In those cases, the HPTN LC Principal Investigator (PI) will determine whether the LC is able to do the requested testing, and whether additional funds would be needed for sample shipping or testing. If LC resources are required, this must be indicated on the Ancillary Study Application. Funding issues must be resolved before the ancillary study is approved. If an ancillary study is approved that includes biological specimens, non-HPTN investigators must also complete a Material Transfer Agreement before specimens can be provided. If applicable, a copy of the signed agreement must be attached to the ancillary study application.

17.1.3 Operational Management of Ancillary Studies and Completion of the Application Form

The operational support budgeted for completion of the primary study does not apply to ancillary studies. It is expected that the investigator proposing an ancillary study will be responsible for scheduling conference calls, coordinating study design and protocol development (if necessary), writing informed consent forms (if necessary), obtaining all required approvals (local Institutional Review Board/Ethics Committee (IRB/EC), Ministry of Health (MoH), etc.), handling all budgeting procedures, coordinating implementation at involved sites, etc. If the investigator would like to request that any of these functions be performed by the HPTN LOC, this must be made clear in the ancillary study application along with appropriate budgeting.

The Ancillary Study Application must include details as to what type of Central Resources and budgets are required to complete the proposed ancillary study (if any). If resources are needed at any of these groups, the Ancillary Study Application should specify the relevant Resources needed. Examples of operational elements are processing of samples or data, scheduling conference calls, case report form (CRF) development, protocol development, etc.

These required application elements are described in the Ancillary Study Application form.

17.2 Ancillary Study Review and Approval Process

All ancillary studies are subject to HPTN Network approval and, if applicable, DAIDS approval, as described in sub-sections below. The purpose of the review and approval process is to ensure that site and Central Resources are being used appropriately and that the rights and well-being of human subjects are protected in accordance with United States (US) Code of Federal Regulations (CFR) 45 CFR 46.

17.2.1 Protocol Chair and Team Approval

Ancillary study applications must first receive review and approval from the following before submission to the HPTN EC for review:

- The main study Protocol Chair(s), on behalf of protocol team members
- Representatives of the Central Resources (SDMC protocol statistician, LC and LOC), and DAIDS Medical Officer for the primary HPTN study. (Note: if Central Resources are being requested, the relevant protocol representative should obtain approval for use of these resources from their respective leadership as part of this review step).
- The study product manufacturer (where applicable)

Note: It is the proposing Investigator's responsibility to ensure that all approvals listed above have been obtained. Typically, approvals are communicated via email. Additionally, if study sites will be involved in or affected by the ancillary study, the proposing Investigator should work with the Protocol Chair(s) and Central Resources to determine site needs and the best process for obtaining site agreement.

17.2.2 Executive Committee (EC) Approval

If the Protocol Team approves the Ancillary Study Application, it will be reviewed for approval by the HPTN EC.

17.2.3 Development of Ancillary Study Protocol

Ancillary studies may require development of a separate protocol, potentially including a separate informed consent form. Depending on the nature of the ancillary study, a protocol number may be assigned at this stage. A separate informed consent requirement is dependent on the nature and scope of the investigation and the language included in the consent forms for the primary study. For example, if the ancillary study involves additional procedures, specimens, or visits and/or involves different risks and benefits than those described in the primary study informed consent form, separate informed consent for the sub-study would be required. Investigators will work with the HPTN LOC and DAIDS to determine whether a separate protocol and written informed consent are needed. If needed, these documents must be developed and then reviewed and approved by the Protocol Team prior to undergoing the DAIDS review process. The ancillary study protocol chair will work with the LOC CRM to determine timeline and development process.

17.2.4 DAIDS Review and Approval of Ancillary Studies

After EC approval, ancillary studies may be subject to additional DAIDS review and approval. The necessary DAIDS approval steps for ancillary studies may vary depending on the scope and nature of the activity/investigation and whether it is prospective or retrospective. Investigators will work with the LOC and DAIDS to determine the necessary steps for each specific investigation. The DAIDS Medical Officer for the primary study will work with the DAIDS Prevention Science Review Committee (PSRC) Chair to determine if a proposed ancillary study requires PSRC review based on the description of the proposed activity in the ancillary study application.

17.2.5 IRB/EC Review of Ancillary Studies

It is the responsibility of each participating site investigator or record of the ancillary study to ensure all approvals or exemptions are documented. If the study will take place at multiple US sites, it may be appropriate to utilize the HPTN single IRB (sIRB), or another contracted sIRB. The LOC will work with the proposing investigator to make this determination. Resources for use of an sIRB, if required, must be included in the ancillary study budget. If the ancillary study requires separate written informed consent, the consent form must be reviewed by the DAIDS Regulatory Affairs Branch (RAB) or its Regulatory Support Center (RSC) prior to finalization and submission to the responsible Institutional Review Boards/Ethics Committees (IRBs/ECs) or written confirmation from DAIDS RAB/RSC that review is not required must be obtained. Informed consent forms for ancillary studies must adhere to United States (US) federal requirements for inclusion of the essential elements outlined in 45 CFR 46, and the informed consent template followed for HPTN studies should serve as a guide in the development of the form.

17.2.6 Site-specific Registration to Ancillary Studies

Registration of the sites to the ancillary study may be required. The procedures and requirements for registration are detailed in the DAIDS Protocol Registration Manual (also see Section 10.10).

For ancillary studies requiring protocol registration with the RSC, no study-specific activities can begin until the site has received written notification from DAIDS that all registration requirements have been completed.

17.3 Funding of Ancillary Studies

Ancillary studies may be performed with HPTN funding, with funding from other sources, or a combination. The proposed source of funding will be specified in the application. If HPTN funding is in excess of that allocated for a primary HPTN study is needed to conduct an ancillary study, the HPTN EC will determine how these funds may be made available, if warranted.

17.4 Monitoring of Ancillary Studies

If funded by the HPTN, an ancillary study may be monitored by the Clinical Site Monitor, if specifically requested by DAIDS.

17.5 Publication of Ancillary Study Results

All data analyses, presentations, and publications resulting from ancillary studies will be prepared and reviewed in accordance with relevant DAIDS and HPTN policies (see Section 21). Acknowledgement of HPTN should be done as per HPTN policies and procedures.

17.6 Documentation of Ancillary Study Approval

Copies of all HPTN, regulatory, and IRB/EC and/or sIRB approvals (if applicable) must be maintained on file by the study site, and the lead Investigator, designee, or the LOC, as applicable.

18 STUDY SPECIFIC CLOSEOUT

The term "closeout" refers to procedures undertaken to fulfill administrative, regulatory, and human participant requirements after participant follow-up in an HPTN study has been completed at the Network Central Resources [Leadership and Operations Center (LOC), Laboratory Center (LC), and Statistical and Data Management Center (SDMC)], and at Clinical Research Sites (CRS). For the purposes of a Division of AIDS (DAIDS) Network, study closeout may be defined as the period when all participant visits have been completed, database has been locked, and all lab specimens are accounted for/reconciled. This definition is independent of the CRS study closure with their Institutional Review Boards/Ethics Committees (IRBs/ECs).

18.1 Study Specific Closeout Activities

Study specific closeout at the CRS is separate from overall study closure (in the case of a multi-site study) and site closure, both of which involve Office of Clinical Site Oversight (OCSO). OCSO is not involved in CRS study specific closeout.

To facilitate planning for study specific closeout, the SDMC will provide protocol teams with information on the projected final participant follow-up visit date for each participating study site and the study overall.

Projections initially will be made upon completion of accrual into the study. Thereafter, projections will be updated as needed depending on the study design and planned duration of participant follow-up.

The HPTN Central Resources will begin planning for study specific closeout prior to completion of participant follow-up. This planning will include the following:

- Development of the study specific closeout checklist, primarily coordinated by the LOC
- If applicable, development of plans, procedures, and materials for unblinding the protocol team, study staff, and participants (see Section 12.1.7 for participant unblinding)
- Development of plans, procedures, and materials for release of study results to the protocol team, study staff, participants, and participant communities (see Section 12.6 for the release of HPTN data from the SDMC)
- Development of plans for data analysis, manuscript preparation, and publications, taking into account that the primary manuscript should be submitted within eight months of the last participant scheduled follow-up visit. For information about publications, see Section 21
- The SDMC will develop a plan for final study data submission, cleaning, database lock and analysis.
- The SDMC will provide technical assistance or reports as needed to study sites or the LOC single IRB coordinator to fulfill IRB/EC study closeout reporting requirements
- If applicable, the SDMC will provide the LC with a listing of study participants who did not provide informed consent for post-study specimen storage and possible future research testing, so that the LC may coordinate sample destruction (see Section 18.3)

- The LC will develop a plan to complete all required post-study laboratory testing, including testing performed for verification of study endpoints. The LC also will inform study sites when all protocol-specified testing has been completed
- The DAIDS Prevention Sciences Program (PSP) Medical Officer will inform all relevant parties at DAIDS of the projected end date for participant follow-up at each study site; at a minimum this will include within-DAIDS communication to begin planning for the study closing at the site
- The Pharmacist of Record must adhere to final disposition procedures for study product(s) as outlined in the protocol and the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.
- SDMC staff will determine whether the number of outstanding data queries, particularly ones essential to analysis of protocol objectives, warrant a site data quality control visit. When appropriate, the SDMC will contact the study coordinator to arrange a visit
- The SDMC, LC, and CRS will work together to reconcile the database to each specific sample (type and number of aliquots) collected during the study, available on site, and available at LC

Each participating study site will begin planning for study specific closeout prior to completion of participant follow-up at that site. As part of this planning, the site will:

- Notify the responsible IRBs/ECs of CRS study closeout according to the IRBs/ECs' procedures (to be done in consultation with the LOC single IRB coordinator, for sites overseen by the HPTN single IRB)
- If applicable, in consultation with site-specific study staff and community representatives, tailor plans, procedures, and materials for unblinding study staff and participants to suit local site needs
- In consultation with site-specific study staff and community representatives, tailor plans, procedures, and materials for release of study results to study staff, participants, and participant communities to suit local site needs
- Develop operational and staffing plans for completion of all required study closeout procedures as listed on the study specific closeout checklist

After participant follow-up has been completed, protocol teams and study sites will implement all plans listed above. Study sites will complete all required study specific closeout procedures as listed on the study specific closeout checklist. It is recognized that closeout procedures need not be completed in the order listed on the checklist, and that some procedures will require considerably more time (up to several months) than others. Study sites should complete each requirement in as timely a manner as possible and use the checklist to document progress toward meeting all requirements throughout the closeout process.

Site staff will de-register the protocol through the DAIDS Protocol Registration System (DPRS) according to instructions on the Regulatory Support Center (RSC) website and in the DAIDS Protocol Registration Manual.

- Deregistration can occur when:
  - The CRS no longer has participants on study (all follow-up has been completed) and does not plan to enroll additional subjects
  - If no participants were ever enrolled at the CRS and the study has closed to accrual
- The DAIDS deregistration process is independent of a CRS's closure/termination of a study at their IRB/EC. The IRB/EC's determination to close or terminate a study is NOT required for a CRS to deregister with DAIDS. Completion of the DAIDS deregistration process indicates that a CRS's participation in a study is complete but does not reflect the closure of a multi-center study at all CRSs participating in the study. Refer to the DAIDS Protocol Registration Manual for complete deregistration details

After all requirements have been met, the study site Investigator of Record will sign and date the checklist, file the signed original on site, and forward a copy to the LOC CRM. The LOC CRM will forward a copy to the DAIDS PSP Medical Officer.

All study records must be retained in accordance with the DAIDS Policy on Essential Documents found in the DAIDS SCORE Manual.

18.2 Long-term Storage of Study Records

Investigational New Drug Application (IND)

For studies under an IND, investigators must retain study records for a period of at least two years following the date of approval of the product or any labeling change of a licensed product and at least three years after the completion of research or as applicable. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the United States Food and Drug Administration (FDA) is notified that the IND is discontinued (21 CFR 312.62), or longer if needed to comply with local regulations.

Completion of a clinical research study occurs when the following activities have been completed:

- All research-related interventions or interactions with human subjects (e.g. when all subjects are off study)
- All protocol-required data collection of identifiable private information described in the IRB/EC-approved research plan
- All analysis of identifiable private information described in the IRB/EC-approved research plan
- Primary analysis of either identifiable private or de-identified information

Non-IND Studies

For studies not under an IND, investigators must retain study records for a minimum of three years after completion of the research, or longer if needed to comply with local regulations. Completion of a clinical research study occurs when the following activities have been completed:

- All research-related interventions or interactions with human subjects (e.g., when all subjects are off study)
- All protocol-required data collection of identifiable private information described in the IRB/EC-approved research plan
- All analysis of identifiable private information described in the IRB/EC – approved research plan
- Primary analysis of either identifiable private or de-identified information

For more information see DAIDS Policy on Essential Documents in the DAIDS SCORE Manual. For all studies, retention of study records must also be in accordance with local regulatory requirements as well as local IRB/EC policies and procedures. **No study records are permitted to be destroyed before the study to which the records relate are included on one of the lists entitled "List of Protocols having CRF/Pharmacy Records that will not be stored by DAIDS". There is one list for IND protocols and one list for non-IND protocols. These are studies for which DAIDS no longer has any regulatory obligation.** This information can be found on the DAIDS RSC website for CRF management.

18.3 Sample Destruction

Study site staff must store all specimens collected during a study. Specimens collected during the study may not be destroyed without prior permission of the LC unless specifically requested by study participant(s).

Study participants are asked to provide written informed consent for their specimens to be stored after the end of the study for possible future testing. If participants do not consent to long-term storage and additional testing of their specimens, study staff must destroy the specimens at the end of the study after all protocol-related and quality assurance testing has been performed, the data have been cleaned, and primary and secondary analyses are completed; the SDMC will provide the LC with a listing of study participants who did not provide informed consent for post-study specimen storage and possible future research testing so that the LC may coordinate sample destruction. Study staff must obtain permission from the LC before destroying specimens.

19 CLINICAL RESEARCH SITES (CRS) AND NETWORK CENTRAL RESOURCES EVALUATION

The evaluation of the HPTN is divided into two components: 1) The evaluation of Clinical Research Sites (CRSs); and 2) the evaluation of the central resources of the network (Leadership and Operations Office (LOC); Laboratory Center (LC); and the Statistical and Data Management Center (SDMC)).

19.1 CRS Evaluation

A Performance Evaluation Committee (PEC) has been established with the sole charge of directing the evaluation of CRSs currently conducting trials in the HPTN. A PEC Chair is appointed by the Executive Committee (EC). The membership of the PEC will include the PEC Chair; representatives from the LOC, SDMC, and LC; site representatives, including an investigator, a study coordinator, and a community representatives; Division of AIDS (DAIDS) staff; and others as needed.

The evaluation serves primarily to ensure that CRSs are contributing effectively to the studies that they have undertaken, both within a single site and across studies across sites. Sites will be evaluated by the PEC at least annually, with reports provided to the HPTN Leadership and DAIDS that may include funding recommendations. Examples of site performance indicators are outlined below in Table 1.

Table 1

Activity	Measure	Standard	Source
Sites			
Enrollment	The number enrolled during the evaluation period is compared to expected enrollment for the time period to calculate evaluation period enrollment percentage	Meet the protocol specified goal	SDMC reports
Study-specific enrollment demographics are being met, as applicable (for studies with specific demographic targets)	Study-specific measures for sex assigned at birth, gender identity, ethnicity, race, age	Mainly reference measurements only (e.g., for race, Black, White, Asian, Other, etc.; Ethnicity – Hispanic or non-Hispanic). Sex assigned at birth is protocol-specific	SDMC reports
Estimated Retention	Visit completion rates at each site are compared to the protocol-specified expectation	Meet the protocol specified goal	SDMC reports

Activity	Measure	Standard	Source
Sites			
Timely submission of study data	Average number of days to enter data	90% within 7 days for EDC studies	SDMC reports
Quality of data submitted (number of queries)	Measured as queries per 100 pages of data submitted	No set standard, study-specific	SDMC reports
QC Query resolution	Percentage of queries resolved within 7 days	80% resolved ≤7 days	SDMC reports
Timely submission of AEs	Percentage of adverse events submitted within 3 days of site awareness	90% of AEs submitted ≤3 days	SDMC reports
Quality of specimen handling/shipment	Number of shipments received within the specified timeframe with little to no errors	90% received within timeframe with <10% errors	LC reports
Response to Queries from Site Monitoring reports	Response to queries	Response within 21 days	NCRMS

19.2 Evaluation of the Network

As a group, the leadership members of the LOC, SDMC and LC will be responsible for directing the evaluation of the Network for protocol development and protocol implementation (including confirmation of adequate funding to implement the protocol), and publication of results. Study teams will be charged with creating an implementation timeline that includes these milestones. Examples of performance criteria are outlined in Table 2:

Table 2

Example of Performance Criteria
Adequate resources in a timely manner to implement a protocol
Meeting agreed-upon timelines for protocol and study-specific manual development; timeliness for submission of and response to Division of AIDS (DAIDS) protocol review process; timeliness for study activation
Meeting agreed upon timelines for study-specific primary and other endpoint testing and QC testing volume
Meeting agreed-upon level of support and timeliness to data management during study implementation; timeliness of provision of primary analysis data tables relative to the last participant/last visit; timeliness of data produced for manuscript development
Meeting review timelines for abstracts and manuscripts
Timeliness for publication of results

19.3 Resolution of Performance Issues

The Network leadership will ensure that the HPTN performs at the highest standard. As such, the EC will be responsible for ensuring that performance problems are identified in a timely manner and addressed and resolved.

In all such cases of site or central resource performance issues, the EC will be notified of the issue along with the corrective action plan. For cases related to sites, DAIDS will be informed and consulted in the resolution process.

20 SELECTION OF SITES

Typically, one of the following two processes are used for Site Selection: 1) Site Selection by Committee; and 2) Site Selection by HPTN Leadership. The HPTN Leadership will ultimately decide which process will be used. The processes are described below and summarized in Figure 20-1.

1) Site Selection by Committee

   Depending on the study, large studies (typically requiring four or more sites) may be subject to the site selection process through a Site Selection Committee (SSC). If this process is used, an SSC will be formed once the concept is approved for protocol development. Typically, the SSC will be composed of a representative from the following entities who will each serve as one voting member (one equal vote per entity - not individual):

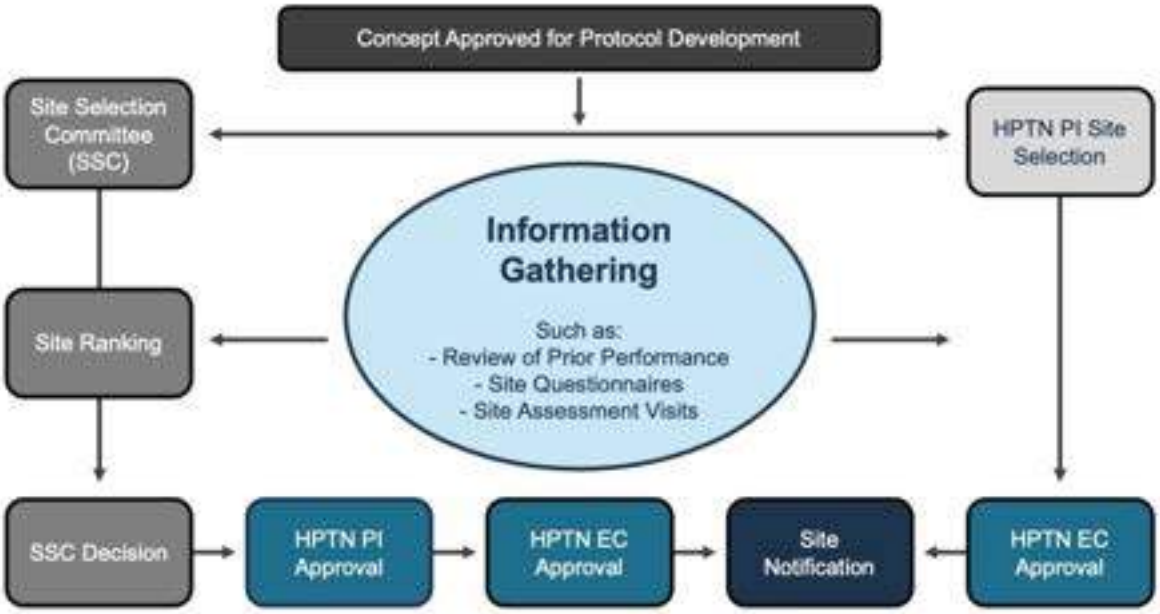
   - Protocol Leadership (Chair or if applicable, Co-Chair, if the Protocol Chair or Co-Chair have an affiliation to any proposed site they will abstain from scoring/voting on the site to which they are affiliated)
   - Laboratory Center (LC) Deputy Director or designee
   - Statistical and Data Management Center (SDMC) Associate Director or designee
   - Leadership and Operations Center (LOC) Project Director or designee
   - Division of AIDS (DAIDS) Office of Clinical Site Oversight (OCSO) representative(s)

   Additional representatives, for example, from other National Institutes of Health (NIH) institutes (if the study is also sponsored by NIDA or NIMH) should be invited to participate as non-voting discussants. It will be the responsibility of the LC, SDMC, LOC and OCSO to assign their respective representatives to the SSC.

2) Site Selection by HPTN Network Principal Investigators

   The process for studies requiring a limited number of sites, early phase studies, studies with fewer number of participants, fast track studies, ancillary studies, and collaborative studies may entail selection of sites by the HPTN Network PIs in consultation with protocol chairs as appropriate. The HPTN Network PIs will select sites for these studies based on study-related and other Network considerations to maximize efficiencies. These decisions may be guided by leadership priorities, funding source, collaboration with other networks, need for accelerated timelines, specific study population or other criteria. The Executive Committee (EC) will review and approve the sites selected by the Network PIs prior to site notification of their selection by the LOC Clinical Research Manager (CRM).

Figure 20-1. Site Selection Processes



Regardless of the process used, the LOC will track and maintain information on the research capacity of HPTN-affiliated sites. Aspects of site capacity that will be tracked include study site facilities and equipment, other on-going research, and access to and size of populations of interest.

Note: If a Protocol Chair is affiliated with a potential site (CTU/CRS), that site is not automatically selected for the study and must be considered as any other site in one of the two processes described above.

20.1 Site Selection by Committee

When site selection by committee is necessary, the SSC will review existing information maintained by the Network about each potential site to first determine a subset of appropriate sites to target for a study within the set of all HPTN-affiliated sites. The LOC CRM will develop a questionnaire with input from the SSC to solicit site interest, as well as obtain any additional information needed about specialized procedures, outreach or practices in the proposed study.

The LOC CRM will facilitate consultation with HPTN leadership regarding the SSC's plan for site selection. After consultation, the LOC CRM will distribute the questionnaire to the Principal Investigators (PIs) of the targeted sites affiliated with the HPTN Network. If additional sites are needed beyond the HPTN Network sites, preference should be given to sites in the following order:

- HPTN protocol-specific sites
- Other DAIDS Network-funded sites
- *Sites that were proposed in existing CTUs, but not funded
- *"New to DAIDS" sites (i.e., sites that have never participated in a DAIDS-funded study)

*Sites that are not fully DAIDS-funded are typically expected to complete the OCSO site activation process (further described in the DAIDS SCORE Manual).

The SSC will agree upon a set of criteria and scoring process for ranking each site. The LOC CRM will facilitate a review and scoring process per the internal LOC standard operating procedure (SOP) on site selection. At the conclusion of this process, the SSC will agree upon the set of proposed sites to bring forward to the HPTN Principal Investigators.

Once agreement has been obtained from the HPTN Principal Investigators, the LOC CRM formally submits the SSC list of proposed sites to the EC for review and approval, along with a summary of the process used to select the sites. The EC will review and vote on the recommendations. If an NIH institution providing funding for a particular study is not represented on the EC (e.g., NIDA or NIMH), a representative from that funding institution will be invited to participate in the EC call and cast a ballot during the vote. The EC will approve the recommendations of the SSC or make suggestions for changes. If the SSC does not agree with the EC's recommendations, the SSC will have the opportunity to respond to the EC and provide additional justification or documentation for the sites that are not approved by the EC.

After the final list of sites is approved by the EC, the LOC CRM will notify all potential sites by email to inform them as to whether or not they have received approval to participate in the study.

20.2 New Sites and Additional Locations to Ongoing Studies

During the conduct of a study, the protocol team may decide that the addition of a new site or Additional Location (AL) is necessary, in which case, either the HPTN Principal Investigators will choose a site or sites, or the SSC will follow the procedures described above. When adding a new site or AL, the following DAIDS principles for site expansion must be considered:

- Site expansion must be considered in the context of a specific study
- Evaluation of expansion sites to meet the needs of a specific protocol must emphasize use of existing DAIDS sites in priority order as shown below:
    1. HPTN-funded sites
    2. All other DAIDS Network funded sites
    3. Sites that were proposed in existing CTUs, but not funded
    4. "New to DAIDS" sites
- No core funding will be provided for the expansion sites
- Consider affiliating protocol specific sites with an existing Network CTU where possible and practical
- The Network is responsible for coordinating site assessment, development and training activities (see Section 10). DAIDS will partner with the Network to support site expansion and facilitate DAIDS approval requirements

If an AL needs to be added to a CTU that is participating in the study, relevant information about the AL will be obtained via a Proposed Additional Location worksheet provided by DAIDS OCSO (see DAIDS SCORE Manual for additional detail). In addition, a "new to DAIDS site" will require approval by DAIDS via the DAIDS site activation process (see the DAIDS SCORE Manual for additional details).

21 PUBLICATIONS AND DATA SHARING POLICY

Timely communication with the scientific community is an essential function of the HPTN and generally is accomplished by presentations at scientific meetings and the publication of manuscripts in peer-reviewed journals. The HPTN publication and data sharing policy is designed to facilitate rapid and accurate dissemination of HPTN study results and facilitate sharing of data within and outside of the Network.

21.1 Publications Policy

HPTN protocol team members are responsible for drafting manuscripts, abstracts, posters and presentations. Others affiliated with the HPTN, as well as individuals external to the HPTN, may also develop manuscripts, abstracts, posters and presentations that include HPTN-related data, specimens and/or are supported by HPTN resources. All documents are reviewed at several levels to ensure that they:

- Reflect accurate and consistent reporting of the design, conduct, and analyses of studies or other research sponsored by the Network
- Are developed collaboratively with the active participation of relevant investigators participating in the design and conduct of the studies
- Protect confidentiality of medical, personal, and product information in accordance with the Privacy Act, the requirements for the protection of human subjects, and any applicable Clinical Trial Agreements (CTAs)
- Meet criteria for authorship, disclosure, scientific integrity, and other requirements of peer-reviewed scientific journals
- Ensure accurate acknowledgment of HPTN resources

21.1.1 Responsibilities

Protocol Publications Committee

Each protocol has a Protocol Publications Committee (PPC), which is a subset of each protocol team and is responsible for prioritizing, reviewing and approving all submitted draft manuscripts, abstracts, posters and presentations related to that protocol. The PPC will include the Protocol Chair, Protocol Biostatistician, and a representative of each of the Central Resource groups. Others may be included as deemed necessary by the Protocol Chair. Each Central Resource member will determine if representatives from their group should be included as authors on a manuscript or abstract and will depend on authorship limitations of the journal or conference. Disagreements will be adjudicated by the protocol chair(s).

HPTN Statistical and Data Management Center (SDMC)

The central database for HPTN studies resides at the SDMC or designee. This includes electronic Case Report Form (eCRF) data, online questionnaires, results of protocol-specified laboratory analyses and ancillary study data. Section 21.2 describes the policy for site, Network investigator and non-Network investigator access to study data during conduct of a trial and after study closure and database lock. Responsibilities for qualitative data (e.g., focus group and in-depth interview transcripts and recordings) management and analysis will be specified in the study protocol.

Analysis of HPTN data to address the primary and secondary objectives of an HPTN study (i.e., Tier 1 publications; see Section 21.1.3) is the responsibility of the SDMC, led by the designated protocol biostatistician. Analysis of Tier 2 publications (Section 21.1.3) occur at the SDMC as resources permit, according to the PPC priorities. Following HPTN data sharing policies and with external funding, permission can be sought from the PPC for analysis of Tier 2 publications with non-SDMC statisticians.

Publication and presentation at conferences of HPTN trial data is generally done in collaboration with the SDMC.

Protocol Chair and Protocol Biostatistician

The Protocol Chair and Protocol Biostatistician or their designee(s) are responsible for generating the first draft of the primary manuscript within approximately 8 months of the last participant visit and distributing the draft to the co-authors (subset of the protocol team that typically includes representatives from SDMC, LOC, LC, NIH, Protocol Chairs and site representatives) for review and comment.

Lead Author

The Lead Author, approved by the PPC, is responsible for establishing a writing team consisting of protocol team members for HPTN initiated manuscripts or abstracts and, potentially, non-protocol team members for non-HPTN initiated concepts. For each manuscript, the Lead Author is responsible for manuscript development, monitoring timelines, and adhering to manuscript review procedures outlined in the Publications Guidance document. In addition, the Protocol Biostatistician is responsible for providing analyses for inclusion in manuscripts, abstracts, posters, or presentations within the specified time.

Leadership and Operations Center

For primary and other key manuscripts, the LOC is responsible for facilitating the PPC review and ensuring that authors are aware of this HPTN publication policy. The LOC, along with the Protocol Chair(s), will develop a protocol-specific Publication Guidance document to be distributed to and followed by the protocol team. Publication Guidance documents will refer to this section of the MOP and include a timeline from database lock to release of public use data set per this policy.

The PPC and the LOC are also responsible for tracking the progress of proposals through publication or presentation for each protocol. In addition, the LOC includes a current listing of published manuscripts and accepted presentations in the Monthly Study Operations Reports.

Manuscript Review Committee

The Manuscript Review Committee (MRC) is responsible for reviewing and providing recommendations to authors on manuscripts and abstracts related to the objectives of HPTN studies or the scope of HPTN work in general. The MRC will review manuscripts within **10 working days** of submission and abstract with **3 working days**. The MRC Coordinator will facilitate the review and response by the MRC members ensuring the MRC chair, Network Central Resources (Leadership and Operations Center (LOC), Statistical and Data Management Center (SDMC), Laboratory Center (LC)), and other relevant members of the committee, review the documents as appropriate. In addition to and in parallel with the MRC review, manuscripts reporting primary endpoint results, must also be reviewed by the HPTN Principal Investigators within the same timeframe as the MRC review. The composition of the MRC is described in Section 4.3.3.

Collaborating organization(s) should be given the chance to review the confidential results, abstracts for presentation and publications before submission to any conference or journal.

21.1.2 Conference Abstract Timelines

The SDMC will release specific timelines for the development and review of abstracts prior to submission to each major scientific conference (e.g., CROI, HIV R4P, etc.). The PPC should determine and incorporate timelines for reviews from all relevant partners per the agreements with NIH and/or other partners (i.e., CDC, pharmaceutical companies, etc.).

Figure 21-1 Example Timeline for Abstracts Submitted to Major Conferences

	Weeks Before Conference Deadline			
Type of SDMC Analysis	**MRC Review**	**PPC Review**	**SDMC Analysis**	**Total Lead Time**
SDMC analysis underway	2 weeks	1 week	4 weeks	7 weeks
New SDMC analysis	2 weeks	1 week	6 weeks	9 weeks
No analysis needed	2 weeks	1 week	0 weeks	3 weeks

The total lead time for abstract preparation may increase based on the total number of abstracts to be reviewed by the MRC and the total number of analyses to be performed by the SDMC.

21.1.3 Priorities

21.1.3.1 Tier 1

Tier 1 Priorities are those that report the results of primary and key secondary study objectives (as determined by the protocol team) as described in the study protocol. These are developed by HPTN Protocol Team members.

21.1.3.2 Tier 2

Tier 2 Priorities are those that report findings based on HPTN data, specimens or resources where the analysis is focused beyond the primary or key secondary study objectives; these may include findings from other secondary objectives, tertiary/exploratory objectives, baseline data, laboratory studies developed by the LC, SDMC methodology research, modelling manuscripts, ancillary studies, or results from more than one HPTN study. Any investigator irrespective of affiliation, may develop a Tier 2 Proposal. These may also include manuscripts or abstracts initiated by Clinical Research Site staff or staff at the Central Resource groups.

21.1.3.3 Tier 3

The HPTN generates manuscripts of many types that do not involve study data, such as viewpoints, ethics guidelines, community engagement, position/white papers. **All manuscripts are submitted to the MRC** to facilitate tracking of HPTN scientific output and to ensure appropriate acknowledgements however, MRC review is not required. At the request of the authors, a formal MRC review can occur. If study data are included, MRC review is required.

21.1.4 Publication Planning Process

A publication plan (contained within the Publication Guidance document) and timeline should be developed well before the last study visit, and minimally contain the following information:

- Membership in PPC
- Process for review, approval, and prioritization of manuscript or presentation concepts (refer to the guidelines in 21.1.3 and 21.1.5)
- Expected date of last participant follow-up visit, if applicable
- Estimated date of database lock
- Expected date of results meeting with protocol team (see Section 21.1.5)
- Estimated start date of manuscript preparation
- Expected date of submission of primary publications and presentations for PPC review
- Expected submission of primary publication(s) date to MRC (per SDMC timeline for major conferences where a number of abstracts would be expected to be submitted)

The Protocol Chair, Protocol Biostatistician, and LOC CRM are jointly responsible for monitoring progress and timelines set forth in the publication plan. Every effort should be made for primary manuscripts to be submitted to the MRC for review within eight months following the last scheduled participant follow-up visit.

Guidance for using study data for conferences or publication prior to study completion is outlined below; permission for exceptions from these guidelines should be sought from HPTN leadership:

- Publications/abstracts/presentations based on screening and baseline data are typically permitted prior to the completion of the study so long as information on any study objectives is not part of the findings and all sites have completed enrollment. For a randomized clinical trial, publication of any post-randomized data is not permitted until the study is complete or stopped.
- Publication of post baseline data in HPTN trials is not typically permitted until study completion (see Section 21.1.2). Publication of secondary outcomes typically follows the completion of the primary manuscript.

Using data obtained by chart review is generally not acceptable as it is not official study data - unless the concept is approved by the PPC with this information noted AND the study is complete at all sites.

21.1.4.1 Results Meetings

When a study is nearing the time of study database lock, the protocol team should plan for a Results Meeting (in-person or virtual) where the Protocol Statisticians review results of the study with members of the protocol team. The meeting may also include planning of the primary publication, abstract submissions to conferences, review of publications proposals, or a proposal or writing workshop.

21.1.4.2 Tier 1 and Tier 2 Proposals

Investigators and writing teams with a proposal for a Tier 1 or Tier 2 manuscript or presentation should complete a Publication Proposal Form (see Publication Guidance document) that outlines the planned analyses for the manuscript or presentation for PPC consideration and prioritization. However, the Protocol Chair(s) is not required to complete a Publication Proposal Form for the primary manuscript.

A proposal for review by the PPC is required for all planned manuscripts or conference presentations except for the primary publication(s). The proposal should include the rationale, hypothesis and objectives, summary of the analysis plan and recommended writing team members.

Once approved by the PPC, the proposal is prioritized by the PPC against other planned analyses and progress of the work is tracked. Tier 1 projects will be prioritized ahead of Tier 2 projects regardless of date of proposal submission.

21.1.4.3 Single Site Studies Proposals

Results of analyses using data or information from a single site may be developed into manuscripts, abstracts, posters or presentations following receipt of approval from the PPC. Single site manuscripts, abstracts, posters and presentations follow the same approval process and guidelines as described above. Sites may request a copy of the protocol Publication Guidance from the LOC CRM. With the exception of baseline publications, most reports are not published prior to the primary manuscript(s). In some cases, laboratory-focused reports may be published prior to the primary manuscript; publication of these papers should be coordinated with the protocol leadership.

21.1.4.4 Multi-Study Analyses Proposals

Results of analyses using data from more than one HPTN study must be sent for approval to each relevant PPC (at a minimum, the Protocol Chair and Statistician if the PPC is no longer active), and upon approval, then submitted to HPTN Leadership for approval. The lead author will be responsible for tracking the progress of manuscript development. Manuscripts, abstracts, posters, or presentations developed using data from more than one HPTN study follow the same approval process described above.

21.1.5 Manuscript, Abstract, Poster and Presentation Review Process

The lead author submits the manuscript, abstract, poster or presentation to the LOC CRM who coordinates the review processes through finalization.

21.1.5.1 Protocol Publication Committee Review

The LOC CRM sends the draft manuscript or abstract to the PPC, sponsor(s) and product manufacturer (if applicable) for review and comment. For manuscripts that are not study specific, the draft will be sent to the HPTN Leadership for appropriate delegation for review. Once all comments have been received and incorporated into the draft by the lead author and the PPC has approved, the LOC CRM submits the revised manuscript to the LOC MRC Coordinator review.

21.1.5.2 MRC Review of Abstracts and Manuscripts

All abstracts submitted to conferences must be reviewed by the MRC prior to submission. If accepted as a posted or oral presentation, review of the final product is the responsibility of the authors and is not reviewed by the MRC. If study data has been released by the SDMC as a Public Use data set for broad dissemination (see Section 21.1.7), presentations may be developed independent of Network oversight and do not require review of the PPC or MRC.

The primary focus of the MRC manuscript review is original research manuscripts presenting results based on data from HPTN-funded research. The MRC receives submission-ready manuscripts after PPC review. All manuscripts must be submitted with an MRC Submission Form. The MRC Coordinator will conduct an administrative check of the MRC Submission Form for completeness after which the tier of the manuscript is designated in consultation with the MRC Chair and reviewers are assigned.

Following review, the MRC will communicate back to the MRC Coordinator, who will forward to the LOC CRM for appropriate distribution. The possible MRC review outcomes are:

- Recommend for submission
- Recommend for submission with consideration of comments
- Not recommended for submission in its current form (with comments from reviewers)
- MRC review not required

Prior to conference or journal submission, a final copy of the abstract or manuscript must be provided by the lead author to the LOC CRM for tracking purposes.

The MRC will re-review a manuscript or abstract only at the request of the author(s) or if significant changes are made to the analysis or outcomes.

It is the responsibility of the writing committee to differentiate between alterations that reflect mere editorial changes and those which essentially modify the analyses and/or conclusion of the study previously endorsed by the MRC.

21.1.6 Authorship

The HPTN criteria for authorship are defined in the International Committee of Medical Journal Editors' "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" Section II.A "Authorship and Contributorship." Typically, the second author listed in primary HPTN publications is the study statistician.

When United States (US) government (e.g., National Institutes of Health (NIH); US Centers for Disease Control and Prevention (CDC) staff are co-authors, manuscripts must be approved by their institute/agency. The US government staff person is responsible for obtaining the necessary approvals. Different government agencies have different review time requirements, so authors and the LOC CRM should take those requirements into consideration during the publication review process.

21.1.7 Public Use Data Sets

If study data has been released by the SDMC and posted to a public website or data repository as a Public Use data set intended for broad dissemination (see Section 21.2), proposals and manuscripts may be developed independent of Network oversight and do not require review of the PPC, Scientific Committee (SC) or MRC but should acknowledge the HPTN.

21.1.8 Resolution of Disputes

Resolution of disputes at the PPC level (i.e. disputes over authorship or content) should be resolved by HPTN Leadership. Additionally, the HPTN Leadership will resolve disputes between MRC and authors.

21.1.9 Third Party Agreements

Third party agreements with product sponsors will include an agreement on publication policy and authorship in accordance with the guidelines set forth in the study's Clinical Trials Agreement (CTA).

21.1.10 HPTN LC and SDMC Manuscripts

In addition to assisting with Tier 1 and Tier 2 publications initiated by study teams or other investigators, the HPTN LC or SDMC also publish more technological or methods manuscripts that include work initiated within these groups. This work may or may not involve use of HPTN data and specimens. HPTN LC publications include reports of protocol-related laboratory assessments; findings from HPTN LC Quality Assurance/Quality Control assessments; work related to assay development, evaluation, and validation; and other laboratory investigations relevant to HIV prevention. SDMC publications may include reports of analytic methods, mathematical modeling, SDMC-related data analyses or statistical/analytic methods.

For work that includes use of HPTN study data and/or specimens for SDMC publications that are done to support HPTN studies, consensus will be reached with the relevant study chair(s) prior to initiation of the work by the HPTN LC or SDMC. Additionally, efforts will be made to ensure that other study team members are aware of this work and have opportunities to provide input, and that appropriate study team members are included as authors on publications that result from this work. Preparation and submission of HPTN LC and SDMC manuscripts and abstracts should be coordinated with preparation and submission of primary or secondary protocol reports. In these cases, the HPTN LC and/or SDMC will work closely with the Protocol Chair(s) to ensure that these activities are executed appropriately. For work that includes analysis of data and/or specimens from HPTN studies that extends beyond planned protocol assessments and study objectives, the HPTN LC and SDMC will obtain approval from the relevant Protocol Chair(s); in these cases, Ancillary Study approval may be required.

HPTN LC and SDMC manuscripts that use data and/or specimens from HPTN studies will be submitted to the MRC prior to journal submission. The MRC will determine what type of review is appropriate, given the content and focus of each manuscript. To ensure optimal utilization and prioritization of resources, the HPTN LC and SDMC will discuss on-going and planned work as well as publications with the HPTN LOC leadership so that this work can be considered in the context of other network activities and priorities. The HPTN LC and/or SDMC will provide updates on the status of manuscripts and abstracts to the relevant PPC(s), MRC and LOC on a regular basis.

21.1.11 Acknowledgements

All publications and presentations that result directly from HPTN studies will include a statement acknowledging the HPTN and NIH's (and others as appropriate) support for the work and listing the applicable cooperative agreement numbers unless the journal's policy precludes such an acknowledgment, or if using a public use dataset (see 21.1.7). The most current acknowledgement language is available on the HPTN website. For manuscripts related to the Network goals, but not linked to a particular study, the HPTN and NIH will be acknowledged as above if support is provided by the HPTN to the author(s) (examples: manuscripts in collaboration with other investigators, editorials, reviews etc.). Manuscripts that are authored by investigators with HPTN support, but the work described is tangential to the HPTN science agenda, it is the responsibility of the investigator to acknowledge HPTN support, where appropriate. Work that is completely unrelated should not cite HPTN support.

21.2 Data Sharing

All priority analyses agreed-upon by the PPC should be completed within 2 years of last study visit, after which de-identified data sets will be made available by the SDMC for dissemination. Once all PPC-approved analyses for a study are published, submitted for publication or are in the process of analyzing and writing for future publication, public use de-identified data sets for any remaining data will be made available by the SDMC to the public for Federal research sponsors, and increasingly scientific journals, often require that data be made available to the public in the form of "Public Use" data sets, which have been prepared by the SDMC for wide-scale dissemination. If

study data are released as a Public Use data set, i.e., formally posted on a website or data repository that allows widespread access to the data by the public, the HPTN is not responsible in any way for the content of abstracts or manuscripts developed using these data, and such manuscripts will not be reviewed by the PPC, Scientific Committee (SC) or MRC.

Although not subject to MRC review, any work that utilizes HPTN data or specimens should acknowledge the HPTN, using the sample acknowledgements statement posted with the data.

In general, all identifying information is removed from Public Use data sets per HIPAA "Safe Harbor" guidelines, so that they protect participant identifies and also may be used without consulting an Institutional Review Board/Ethics Committee (IRBs/EC). De-identified data released to HPTN investigators and posted on the SDMC web portal does not, in most cases, constitute Public Use data, and manuscripts developed with such data sets may require review by the HPTN MRC.

21.2.1 Release of HPTN Study Data from the SDMC

Analysis of data related to the protocol objectives is the responsibility of the SDMC. In order to ensure rapid, high quality analysis and dissemination of study results, the protocol statisticians at the SDMC conduct these analyses centrally. Premature distribution of the data has the potential to:

- Jeopardize the integrity of the trial
- Compromise the quality of study results that are disseminated
- Divert the resources of the SDMC from the preparation, dissemination and support of protocol analyses

This section describes how HPTN study data is released by the SDMC without compromising the interests of trial participants or the integrity and credibility of the trial.

21.2.2 Release of Data During the Conduct of a Study

No study data beyond baseline will be available to the site, protocol team or any other body, other than as reports to the DSMB and to the SMC, or to the LC as needed, to perform protocol-related activities and assessments (e.g., for QC activities, to assist with protocol testing, and for assessments related to protocol objectives). Exceptions to this rule require approval by the Leadership Group/Executive Committee (EC) and/or the DSMB, as appropriate. Baseline data may be published or presented only after all sites have completed enrollment.

Publication or presentation of site-specific follow-up data or results during the trial is not approved under the HPTN Publications Policy (Section 21.1) and should not occur unless authorized by the HPTN Leadership group and/or EC. It is the responsibility of the site Principal Investigator (PI) and the IoR to ensure that inappropriate dissemination of results or analysis of data does not occur.

After enrollment is complete, and by request, the SDMC makes participant-level baseline data available to sites as electronic files, either securely posted on the SDMC web-portal, or through the Medidata Rave system. Publication of these data are per the Publication Policy (Section 21.1).

Certain types of data are never available while the study is ongoing:

- Data that constitute primary or secondary endpoints
- Coding (e.g., by MedDRA) of AEs
- PTID identified data from Computer-Assisted Self-Interviews (ACASI or CASI)
- Laboratory data not submitted on a CRF (e.g., submitted directly to the SDMC by the LC or other central laboratory)
- For blinded trials, the participant's random assignment

21.2.3 Release of Data after Completion of a Study

21.2.3.1 Final Release of Site-specific Data to Site Investigators

Final site-specific study data sets can be requested from the SDMC by the site investigators once the database is cleaned and locked and all intended manuscripts reporting primary results of the protocol objectives have been published.

21.2.3.2 Release of Data to Protocol Team and Scholars for Analysis

In general, the HPTN SDMC conducts analysis of primary and secondary objectives data for publication. Data sets for specific analyses to be conducted by HPTN investigators and HPTN Scholars without the assistance of the HPTN SDMC may be released after completion of primary and secondary publications. Release of these data are approved by the PPC and follow the Protocol Publications Guidelines (see Section 21.1). Submission of a Proposal that documents the data requested is also reviewed by the PPC.

21.2.3.3 Final Release of Data

The timeline for the SDMC to start preparation of data sets and documentation for dissemination is approximately one year after the last study visit. In general, only primary data from the HPTN LC that has been locked is included in these datasets, along with the CRF and behavioral questionnaire data. Timing of the release of other specialized data, for example SMS data or data received from the LC after the initial release of data from SDMC, is negotiated with the SDMC PI. Any public datasets required by journals for publication will be created by the SDMC and provided to the journal or the submitting author.

Access to study data before the creation of Public Data Sets may be available to HPTN Scholars or investigators with publication proposals that have been reviewed and approved by the PPC. Access to data before the creation of public datasets should be covered by a data use agreement (DUA) or confidentiality disclosure agreement (CDA).

Two years after the final study visit, complete de-identified datasets and data dictionaries and other supporting documentation are created by the SDMC and posted to Atlas and/or other appropriate data repositories. A link to the data access page will be created on the HPTN website. Access to data will follow HPTN SDMC (or other institutional) norms and process for user authentication and authorization.

The HPTN public data access page will require completion of a brief online application form that includes the investigator's name, institution, and short description of the proposed purpose/analysis. The application will be used to capture and report information about access of the data. The SDMC will not check or validate the accuracy of data summaries and analysis computations completed outside the SDMC.

21.2.4 Limited Release of Data to Non-HPTN Investigators

Prior to final release of study data from the SDMC and or pre-specified purposes, e.g., ancillary studies external to the HPTN or grant applications, investigators may request approval for release of data to HPTN and non-HPTN entities (information on approval of ancillary studies can be found in Section 17.2). These requests require approval of the HPTN leadership group.

- Release of follow-up data prior to the final study visit and study unblinding (if applicable) requires additional approval of the Protocol Chair, the SDMC PI, the LC PI, and the EC and would typically be approved only in extraordinary circumstances.

- Release of data after the final study visit but prior to database lock and completion of publications requires additional approval of the Protocol Chair(s), LC PI, and the SDMC PI.
- Release of baseline data after completion of enrollment requires only approval of the Protocol Chair(s), LC PI, and the SDMC PI.
- The timeline for release of the data is negotiated with the SDMC and the protocol team, taking data cleaning, database lock and study analysis commitments into consideration.

21.2.5 Release of Data from a Study with a Clinical Trials Agreement

The Clinical Trials Agreement (CTA) governs the release of study data to pharmaceutical or other partners. The guidelines in this policy will hold for studies with CTAs unless otherwise specified by the CTA. Data cannot be released from the SDMC unless it is in agreement with the terms of the CTA.

21.2.6 Other Release of Data from HPTN Studies

Requests for release of data not covered in Section 21 must be negotiated with the SDMC PI and the EC. Approval from the LC PI is required for release of any data sets that include laboratory data submitted by the HPTN LC.

22 SCHOLARS PROGRAM

22.1 Program Description

In 2010, the HPTN and the NIH initiated a U.S.-based scholars program for early career investigators to nurture the professional development of underrepresented clinical and behavioral scientists from minority backgrounds and to provide opportunities for future leadership roles within the HIV prevention research field. An international component of the program was introduced in 2015. Eligibility criteria for both programs can be found on the HPTN Scholars Program webpage (https://www.hptn.org/research/scholars).

In both domestic and international programs, applicants work with a mentor scientist in the Network to complete a research project utilizing data from an existing HPTN research study. The list of studies approved for Scholar use is updated each year but is based on protocol team progress of analysis and publication the (generally after at least the primary objectives have been published), available mentors affiliated with the HPTN and/or HPTN sites, and HPTN leadership approval. Each Scholar is funded for an 18-month term and the solicitation for new Scholars is undertaken annually.

The HPTN Scholars Program is overseen by senior investigators in the HPTN as appointed by the HPTN Executive Committee and is coordinated by the HPTN Leadership and Operations Center (LOC) liaison. Detailed guidelines for scientist mentors are available in the HPTN Scholars Mentorship Manual.

22.2 Tenants of the Scholars Program:

- Scholars will develop a research project using data from a completed or ongoing HPTN HIV prevention study and complete their project within the program cycle.
- Scholars are expected to attend an orientation to the program.
- Scholars are expected to attend and present the results of their research project at an HPTN Annual Meeting during the scholarship period, and at one national or international conference, if possible.
- Scholars are expected to participate in a series of group activities designed for further career development, including monthly conference calls to discuss ongoing research projects, new funding sources for career development, and opportunities for wider collaboration as well as additional training and skills building activities.
- Scholars will submit at least one manuscript at the end of the scholarship cycle.
- Scholars will be invited to join an HPTN Science Committee or Working Group as an observer, ideally for the duration of the program tenure. This affords each Scholar an opportunity to contribute and learn from the discussions as they build their capacity as an independent investigator and become further acquainted with the processes of the Network.
- Scholars are provided funding to cover a portion of their time (typically ~ 10-30%) and expenses, including travel and research materials/supplies.
- Expectations and guidelines are further detailed in the HPTN Scholars Program Manual.

22.3 Scholar Publication Guidelines

All publications developed by the Scholar (manuscripts, conference abstracts, posters, and oral presentations) that include data from an HPTN study must reviewed and approved by the Scholars mentor, any listed co-authors, prior to submission to the HPTN LOC Scholars Program liaison to

initiate the required HPTN reviews. Once submitted, the publication will undergo review by the respective HPTN study publications team (or designated reviewers, if the study team publication team is no longer intact) in which the data is based and the Manuscript Review Committee (MRC) prior to being submitted for publication or presentation. Scholars Program Leadership will also be provided an opportunity to review the publication.

The Scholar is responsible for monitoring the timelines set forth in the HPTN Scholars Program Manual and for reporting timeline updates and/or delays in deliverables to the HPTN Scholars Program Leadership and the LOC Scholars Program liaison.

22.4 Authorship Guidelines for Scholars

The Scholar is responsible for identifying a writing team to support and contribute to development of their publication. All members of the writing team (i.e., co-authors) must review and approve a publication before it can be submitted to the HPTN LOC Scholars Program liaison for review by the respective study team, Scholars Program Leadership, and the MRC.

The following guidelines should be used if the Scholar's study's primary paper was published **less than three years** prior to the Scholar submitting his/her/their paper to the Manuscript Review Committee (MRC).

- The first author should be the person who is leading interpretation of the analysis and is writing the publication (i.e., the Scholar).
- The respective study Protocol Chair (and Protocol Co-Chair[s]) should be given the option of being included as a co-author.
- An LOC, Statistical and Data Management Center (SDMC), and/or Laboratory Center (LC) representative who contributed substantially to the writing of the publication or to the conduct of the analysis should be given consideration for inclusion as a co-author.
- A member of each site team, designated by site PIs, should be approached to determine whether they would like to be included as co-authors.

The following guidelines should be used if the Scholar's study's primary paper was published **three years or more** prior to the Scholar submitting his/her/their paper to the MRC.

- The first author should be the person who is leading interpretation of the analysis and is writing the publication (i.e., the Scholar).
- The respective study Protocol Chair (and Protocol Co-Chair[s]) should be given the option of being included as a co-author.
- A LOC, SDMC, and/or LC representative who contributed substantially to the writing of the publication or to the conduct of the analysis should be given consideration for inclusion as a co-author.

The guidelines above are to be applied to any publication (abstract, poster, or manuscript) resulting from the Scholar's use of HPTN data.

Additional details are provided in the HPTN Scholars Program and Mentorship Manuals. The HPTN Publications Policy, Section 21 of the HPTN MOP, should also be referenced.