



HIV Prevention Trials Network

Manual of Operations

July 2014

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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 in multiple geographic locations. Thirty-four million people are living with HIV infection and more than 16 million have died from AIDS. Great successes have been achieved in expansion of access to HIV care and treatment globally and a substantial decrease in HIV incidence has been noted in several countries in sub-Saharan Africa (SSA). However, new HIV infections continue to occur globally at the alarming rate of 2.5 million per year with substantial regional variability. The severity of the global HIV epidemic has led to intense efforts in HIV prevention research, with remarkable successes with antiretroviral therapy (ART) for prevention and male circumcision. Yet much remains to be done to curb the epidemic and therefore, the research evaluating interventions for prevention of HIV infection is a priority of the United States (US) [National Institute of Allergy and Infectious Diseases/National Institutes of Health](#) (NIAID/NIH), under whose auspices the HPTN was formed.

The current [HIV Prevention Trials Network](#) (HPTN) is the result of an evolution beginning in 1993, when 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. Then 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, with a research agenda focusing primarily on the evaluation of non-vaccine HIV prevention until 2006 (HPTN I), and then on non-microbicide, non-vaccine interventions (HPTN II – 2006-2013). The HPTN focuses on biomedical, structural and behavioral interventions that can be implemented in the short to medium term, recognizing that the development of an effective vaccine may take several years. At this stage of the epidemic, with no effective vaccine in sight, there is a need for integrated strategies (package of multiple interventions) that will have to be tailored for the diverse populations at risk. Even after effective microbicides or vaccines become available integrated strategies will be needed to have a major impact on the epidemic.

Going forward, the focus of the HPTN (HPTN III, 2013-2020) will be on two priority areas: Integrated Strategies and Pre-exposure Prophylaxis (PrEP). This agenda builds on the HPTN's accomplishments and ongoing work and takes advantage of recent advances in the 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. The research is conducted in diverse populations such as black men who have sex with men (MSM), African-American women and Latina in the US; injection drug users in Eastern Europe and Asia; and adolescents, heterosexual women and men, and MSM globally. Integrated Strategies catered to specific populations are needed and will be the focus of the HPTN. In order to respond to compelling research needs in HIV prevention, the HPTN has established scientific committees and working groups. The Scientific Committees (SC) have been established with a focus on populations at risk and key areas of importance for design of the HPTN

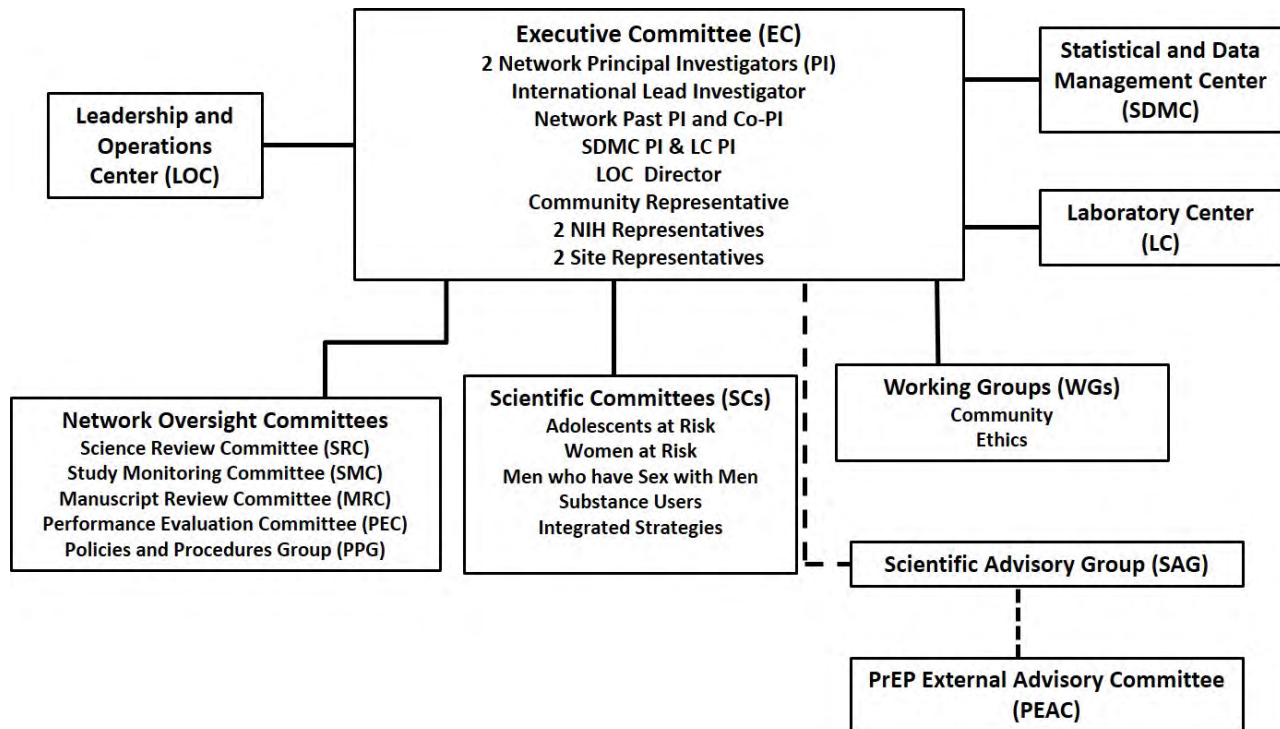
research agenda. The HPTN also has cross-cutting Working Groups (WG), providing expertise required for all HPTN research efforts. In addition, the HPTN continues to make major investments of both human and financial resources to build international research structures, enhance collaborative community 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 NIAID, the lead institute of the NIH Consortium, and with support from the Consortium institutes including [National Institute of Drug Abuse](#) (NIDA), [National Institute of Mental Health](#) (NIMH), and the [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 will be responsible for ensuring the efficient development and implementation of the HPTN research agenda as well as managing the Network and coordinating activities across the Leadership and Operations Center (LOC), Laboratory Center (LC), and Statistical and Data Management center (SDMC). Figure 1-1 outlines the organizational structure of the HPTN.

Figure 1-1 HPTN Organizational Structure



The three Central Resources of the HPTN are:

- 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

All of the HPTN Central Resources are described in Section 3.

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 Scientific Committee
- Women at Risk Scientific Committee
- Men who have sex with Men Scientific Committee
- Substance Users Scientific Committee
- Integrated Strategies Scientific Committee
- Community Working Group
- Ethics Working Group

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

In addition to the above SGs and WGs, the HPTN scientific agenda is periodically reviewed by the Scientific Advisory Group (SAG). A sub-committee of the SAG is the PrEP External Advisory Committee (PEAC) which will review the HPTN's PrEP agenda.

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

- Science Review Committee (SRC)
- Study Monitoring Committee (SMC)
- Manuscript Review Committee (MRC)
- Performance Evaluation Committee (PEC)
- Policies and Procedures Group (PPG)

These committees are described in Section 4.3.

HPTN research is conducted 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 all levels of the HPTN structure. Some studies in the HPTN will require the participation of populations and settings beyond the traditional DAIDS-funded sites. As needed, new sites will be added to meet the HPTN's research needs. Further details of the composition and functions of the operational components of the HPTN are contained 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 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) 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 NIH staff is to assist and facilitate, not to direct the research activities.

Further information concerning NIAID may be found on their [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 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 EC and conform to HPTN policies.

DAIDS has the option to file an IND on investigational agents evaluated in HPTN studies. 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 also assemble, review, and submit the required regulatory documents to the US FDA.

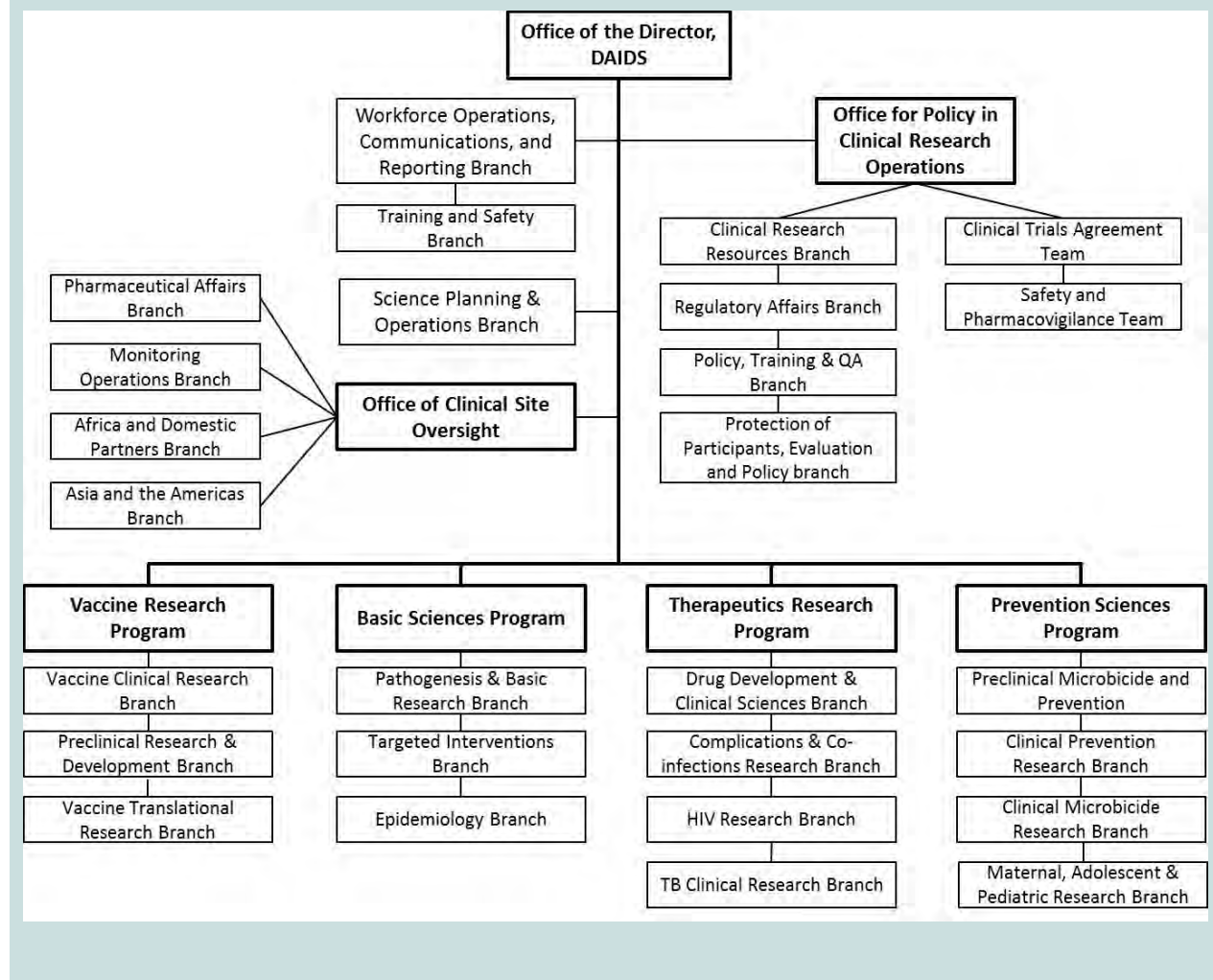
DAIDS pharmacists participate on HPTN protocol teams, consulting on available dosage forms and placebos, product packaging and supply to sites. They also interact with pharmaceutical companies to ensure adequate and timely supply of products.

To provide for consistent reporting of serious adverse events 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.

For all HPTN protocols, a DAIDS Medical Officer is assigned to monitor the safety of the intervention(s) in ongoing studies, and will be provided with the interim and final reports. When a protocol is sponsored by a collaborating institution or research group (i.e., NIDA or NIMH) monitoring activities may be conducted by their medical representative(s).

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) is the program within DAIDS which is responsible for the HPTN. A DAIDS Medical Officer and/or Program Officer participates on each protocol team. During study implementation, the DAIDS Medical Officer 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 [Office of Clinical Site Oversight](#) (OCSO) in their interactions with sites. The OCSO, of which PSP is a part, is responsible for oversight of clinical sites (see Section 1.4.1.1.3).

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 staffs are responsible for quality assurance and procedural oversight of DAIDS clinical trials.

1.4.1.1.2.1 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.

1.4.1.1.3 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 CRs 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)

1.4.1.1.3.1 Pharmaceutical Affairs Branch

The Pharmaceutical Affairs Branch (PAB) in OCSO:

- Coordinates and oversees the supply, packaging, and distribution of study products for DAIDS-supported US and non-US trials
- Advises protocol teams on all pharmaceutical aspects of protocol development
- Oversees and monitors quality assurance standards and Standard Operating Procedures (SOPs) for all pharmacy-related and product-related issues at CRs participating in HPTN trials

1.4.1.1.4 Workforce Operations, Communications, and Reporting Branch and Science Planning and Operations Branch

The DAIDS Workforce Operations, Communications, and Reporting Branch (WOCR) 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 WOCR also conducts various training activities.

1.4.2 DAIDS Contractors

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

DAIDS contracts with the Clinical Research Products Management Center (CRPMC) for centralized ordering, storage, and distribution of study products evaluated in HPTN trials. CRPMC responsibilities include:

- Receiving shipments of study products from the manufacturer
- Storing products under appropriate and secure conditions
- Distributing study products to authorized HPTN site pharmacists at US and non-US sites
- Monitoring study product inventories
- Monitoring study product expiry dates
- Recalling and processing of study product returns
- Executing final disposition of study products
- Maintaining records of study product management
- Repackaging or relabeling study products under Good Manufacturing Practices (GMP), as needed
- Preparing participant kits, if needed, for specific protocols

The CRPMC also provides the Clinical Site Monitor with reports of product shipments to the CTUs for protocol monitoring and study assessment visits.

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 test agent 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 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 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 Medical 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
- Subject 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 investigational 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 DAIDS Data and Safety Monitoring Boards (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 DAIDS 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, DAIDS 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 typically are asked to attend open portions of the DSMB meetings 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 the course of 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 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 DAIDS DSMBs can be found in the [NIAID Policy for Identifying Potential Conflict of Interest for Individuals Serving on Advisory Committees or Independent Safety Monitors Responsible for Data and Safety Monitoring of Clinical Trials, Version 1.0, dated 08/09/2012, effective 11/01/2012.](#)

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.

For the HPTN, DAIDS is responsible for protocol review, including review and approval of sample informed consent language. The approved language is subsequently distributed with

the protocol for relevant Institutional Review Board/Ethics Committee (IRB/EC) review and approval.

1.4.5.2 US Office for Civil Rights

For studies conducted in US settings in 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

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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 will be responsible for ensuring the efficient development and implementation of the HPTN research agenda as well as managing the Network and coordinating activities across the Central Resources which consist of the LOC, Laboratory Center (LC), and Statistical and Data Management Center (SDMC).

The chairmanship of the 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 facilitates EC responsibilities, including development and implementation of the HPTN research agenda
- Schedule and chair regular and special meetings and conferences calls of the EC and communicates the decisions and action items to HPTN investigators
- Ensure coordination of Network activities across Central Resources and provides 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 the Network PI 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 EC, under the direction of the HPTN PIs, with the assistance of the United States (US) National Institutes of Health ([NIH](#)) Consortium, sets the research priorities of the HPTN and directs its scientific activities. The EC:

- Sets the overall HPTN research agenda
- Reviews Scientific Committees (SCs)/Working Groups (WGs) research plans including the review and prioritization of concepts
- 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
- Establishes key standing Network committees (for example, Science Review Committee, Study Monitoring Committee, Performance Evaluation Committee, Manuscript Review Committee)
- Reviews and resolves site-related issues as needed
- Pursues new partnerships and funding opportunities

The EC, in conjunction with NIH, determines the overall capacity for the HPTN, as well as the capacity of individual CTUs and CRS or other sites. With members serving as liaisons to each SC/WG, the EC will ensure that the specific areas of prevention science addressed by SCs/WGs are effectively coordinated and are aligned with the priority areas of Integrated Strategies and Pre-exposure Prophylaxis (PrEP). The 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 EC.

The EC conducts conference calls at least monthly and holds in-person 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 EC membership includes representatives from the LOC, the SDMC, the LC, community, CRS and NIH. Representatives of the CRSs may rotate off the EC every two years.

When new members are solicited, all CRS nominees will submit a brief biosketch to the EC administrator or designee. Biosketches for nominees will be compiled, attached to the voting ballot and sent to EC members. 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	Group Director LOC
PI, Network	Finance Manager, LOC
Non-US Lead Investigator	Deputy Director, LC
Past PI, Network	Research Program Manager, SDMC
Past Co-PI, Network	
PI, LC	
PI SDMC	
Director, LOC	
Community Representative	
2 Site Representatives	
2 Representatives from NIH	

2.3 HPTN Leadership

A subset of the 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.

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3 HPTN OPERATIONAL COMPONENTS

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

- 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. The LOC staff is responsible for facilitating and managing the scientific agenda and research operations of the HPTN, from research plan development, continuing with concept and protocol review and approval, through study conduct and publication of results. The LOC staff is also responsible for logistical and administrative support of all Network activities for the HPTN Executive Committee (EC), Scientific Advisory Group (SAG), PrEP External Advisory Committee (PEAC), Scientific Committees (SC), Working Groups (WG), and selected committees.

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. [Family Health International](#) (FHI 360) located in Durham, North Carolina, functions as the LOC for the HPTN.

3.1.1 LOC Responsibilities

The LOC's specific operational responsibilities, by functional area, follow:

- Leadership and Governance Support
 - Convene and chair the EC
 - Serve on and provide logistical and administrative support for the EC, SCs, WGs, Study Monitoring Committee (SMC), Study Advisory Group (SAG), PrEP External Advisory Committee (PEAC), Science Review Committee (SRC), Policies and Procedures Group (PPG), Manuscript Review Committee (MRC), and Performance Evaluation Committee (PEC)
 - Oversee Scholars Program
 - Develop and implement with the PEC, the Network evaluation; submit regular reports on CRS and study performance to the Network leadership
 - 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)
- Research Management and Support
 - Appoint an LOC staff member to collaborate with each SC and WG Chair in the management of these committees and groups
 - Serve on the SCs and WGs
 - Appoint an LOC Clinical Research Manager (CRM) to each protocol
 - Participate in and coordinate support to the Clinical Management Committee (CMC) and other protocol-related groups
 - Provide oversight to assist CTUs/CRSs in complying with study/trial protocols and regulatory requirements and achieve protocol-specified targets for accrual and follow-up of study participants

- Protocol Development, Review, and Pre-implementation Activities
 - Collaborate with Protocol Chair and protocol team members and 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 to the HPTN and DAIDS review groups and lead in the development of response to the 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 review materials for DAIDS protocol registration and study specific site activation developed by CRSs and any other material in collaboration with the SDMC and the LC
 - Facilitate communication between study CRSs, the SDMC, the LC and DAIDS entities
- Assistance to CTUs and CRSs during Conduct of the Study
 - Respond to inquiries from CTU/CRS investigators and DAIDS staff on logistics and procedures for HPTN studies in collaboration with the SDMC and LC
 - Assess performance of CTUs/CRSs in development and implementation of study protocols and report results to the EC and DAIDS through site assessment visits and regular communication with and reporting from CRSs,
 - Collaborate with protocol teams in manuscript development and dissemination of study results
- Coordination and Facilitation of Oversight Committees
 - Coordinate of calls for SRC, Study Monitoring Committee (SMC) in association with the SDMC and other committees
 - Document committee meetings and calls and distribute as appropriate
- Community and Research Ethics Programs
 - Facilitate broad community involvement through community representation on key Network committees and by working with CTUs/CRSs to develop and enhance Community Advisory Boards (CABs)/Community Advisory Groups (CAGs)
 - Assist CTUs/CRSs to develop and implement community education efforts associated with HIV prevention trials
- Communication and Information Dissemination
 - Develop and maintain an HPTN website, 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
 - Maintain version control of key Network policies and procedures
 - Support the DAIDS Enterprise 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), 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

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 and protocol development. 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 [Statistical Center for HIV/AIDS Research and Prevention \(SCHARP\)](#) at the [Fred Hutchinson Cancer Research Center \(FHCRC\)](#) in Seattle, Washington, is the SDMC for the HPTN.

3.2.1 SDMC Responsibilities

The SDMC's specific operational responsibilities, by functional area, follow.

- Leadership and Governance
 - Serve on the EC, LG, SCs, WGs, SRC, PEC, SMC, PPG, CMC, and MRC
 - Convene and chair the SMC
 - Provide reports to the EC, SMC, PEC and DAIDS on the status of CTU/CRS performance, including participant accrual, retention 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
 - Develop statistical and data management components of HPTN concept plans and protocols
 - Provide regular reporting to the protocol team to facilitate monitoring of CRS data management, recruitment, retention, adherence, endpoint assessment, and safety
 - Contribute to assessments of CRS performance regarding data management quality, enrollment, retention, and adherence to Network leadership and to the PEC evaluations of Network performance
 - Develop and implement randomization and treatment allocation schemes for HPTN protocols
 - Conduct data analysis 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

- Data Management
 - Design and maintain the study databases
 - Provide centralized data entry and data management
 - Develop and implement data quality control (QC) systems
- Protocol Data Operations
 - Collaborate with protocol team members in developing protocols, SSP manuals and other study materials
 - Lead the development of study Case Report Forms (CRFs) or electronic means of data capture (e.g., computerized questionnaires) and procedures for collecting data from CTUs/CRSs
 - Conduct onsite operational walkthroughs of CRFs and other study materials and procedures when warranted, in collaboration with the LOC CRM
 - Conduct data management and CRF 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
 - Provide technology systems that enable CTUs/CRSs to track data transmission to SDMC
 - Provide CTUs/CRSs with access to select study data during the course of a study
 - Review CTA when study involves investigational product
- Laboratory Data Management
 - Provide operational assistance to CTUs/CRSs and the LC for specimen tracking and retrieval, including labeling and specimen tracking sheets to facilitate specimen entry into the specimen tracking system, the Laboratory Data Management System (LDMS), and reports of LDMS entry errors and discrepancies between LDMS and CRF databases
 - Provide data entry templates for laboratory results data that are not submitted on CRFs
 - Receive LC data; assure quality and matching of laboratory data to CRF data
 - Select specimens for quality assurance (QA) testing by the LC
 - Work with LC to provide data if an HPTN External Advisory Committee (EAC) is convened (section 13.14)
- 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 in set-up and maintenance of CRF relay systems
- Clinical Data Safety Monitoring
 - Provide clinical review of relevant laboratory and safety data for accuracy, consistency, and completeness
 - Provide QC and coding of adverse event (AE) data
 - Verify completeness of expedited adverse event reporting through reconciliation of AEs reported to DAIDS and those reported to the SDMC
 - Provide support to the Clinical Management Committees

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 and protocol development. The LC oversees all laboratory activities including sample collection, testing, and reporting of results from tests

performed at HPTN CRSs. The HPTN LC also performs Quality Assurance/Quality Control (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 specific study objectives. The LC assists in the development and quality assessment at CRSs, while building laboratory expertise and capacity at non-US CRSs, mostly in resource-limited settings. The LC plays a leadership role in cross-network activities, 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.

3.3.1 Laboratory Center Composition

The LC includes comprehensive QA/QC, Virology, and Pharmacology Cores, in addition to Support Laboratories in sub-specialty disciplines (Immunology, Microbiology, STDs (sexually transmitted diseases), and Toxicology); the LC also includes a Point of Care Testing (POCT) Working Group.

3.3.2 Laboratory Center Responsibilities

Responsibilities of the LC are to:

- Serve on the 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/use of laboratory data from HPTN studies, after approval by the HPTN Leadership, for presentation, publication, or ancillary studies. This includes release of data before the data set is locked at the SDMC. The LC will provide input about feasibility and regulatory issues and will inform the EC, if there are any issues relevant to its approval decision
- Release/use of specimens, after approval of the 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. The LC will provide input about feasibility and regulatory issues and will inform the EC of any issues relevant to its approval decision
- Provide each protocol with an HPTN LC QA/QC Coordinator and one or more HPTN LC representatives
- Write the laboratory sections of protocols and SSP Manuals
- Provide training for CTU and CRS laboratories, as needed, in sample collection, tracking (using the Laboratory Data Management System [LDMS]), processing, testing, storage, and shipping; provide training for specialized testing, as appropriate
- Provide support to the study team as laboratory issues arise during design and implementation of the protocol
- Design, implement, and/or monitor QA procedures for all laboratory testing (i.e., centralized, regional, or local)
- Report on local laboratory proficiency to the CTUs/CRSs, SMC and PEC
- Provide a specimen management plan (processing, storage and retrieval guidelines) for specimens at both US and non-US CRSs
- 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 a repository contractor 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 NIH-sponsored HIV clinical trial networks to harmonize laboratory methods and maximize the efficiency of protocol development, implementation, and analysis
- Provide quality assessment for specimen processing, assay performance and specimen-related data transmission for testing performed at CTU/CRS laboratories
- Provide training and infrastructure support in laboratory quality assessment, assay performance, and specimen shipping procedures at CTU/CRS laboratories
- Provide opportunities for 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 quality assessment/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
- 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 CRS, 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 for the study. The LC staff also visit CRSs, as necessary, to assess laboratory facilities and procedures.

The HPTN LC also places and oversees the work of HPTN LC International Coordinators 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 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). Additional funds will NOT be provided to the CTU or CRS for AL unless approved by DAIDS as a protocol-specific site. 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 all aspects 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 PIs are responsible for (but not limited to):

- Execution of the Network research agenda

- Coordination and collaboration with the 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 under separate cover 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 LC 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 Conference on Harmonisation Good Clinical Practice (ICH 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 not be 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 Site PI or Site Leader

The terms “Site PI”, “in-country PI” or “Site Leader” are often used — sometimes interchangeably — for investigators present at HPTN CRSs. 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 (the latter term is the official OCSO term). 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 one or more CRSs. 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, IRB/EC approvals of protocols and informed consent forms, 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
- Control distribution of the drugs, biologics, or devices under investigation (as applicable)
- Report safety information as required by the protocol, DAIDS, responsible IRBs/ECs, GCP, and all applicable local, national, and international requirements

- 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:

- PI
- In-country or Site Investigator (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

Policy: [Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials](#).

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 [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 Manual of Operations (MOP)
- Submit research protocol and protocol amendments to, and receive approval from all appropriate IRBs/ECs and relevant 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 investigational 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; timely transmit to the SDMC central database in a timely manner; respond (within two weeks of original notification) to data queries from the SDMC
- Provide periodic accrual reports to the HPTN LOC for all studies
- Store investigational 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 COMMITTEES, WORKING GROUPS AND PROTOCOL TEAMS 4-2

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4 HPTN COMMITTEES, WORKING GROUPS AND PROTOCOL TEAMS

Committees and Working Groups

The HPTN Executive Committee (EC) has provided general guidelines for the composition of HPTN 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 Scientific Committees

The Scientific Committees (SCs) develop and guide the scientific agenda of the HPTN. The SCs are:

- Adolescents at Risk
- Women at Risk
- Men who have Sex with Men
- Substance Users
- Integrated Strategies

Each SC is responsible for:

- Developing a research strategy to contribute to the overall HPTN research agenda and/or provide their expertise to other scientific committees.
- Assessing research priorities in light of new ideas and research opportunities
- Soliciting concept plans from investigators in their areas of interest
- Overseeing the formulation, review and prioritization of concept plans based on the priorities in the research plan
- Assisting in dissemination of information regarding the HPTN Scientific Research Agenda
- Representing the HPTN at relevant scientific meetings and conferences
- Monitoring the status of protocol development and implementation and reporting semi-annually to the EC (SC Chair)

The SCs integrate non-HPTN scientific expertise into the development of the research agenda established by the committees through the inclusion of leaders in their respective fields (who are not affiliated with the HPTN) as group members. The SCs also participate in interactions with industry regarding development and evaluation of new products.

The SC chair and co-chair attend EC meetings at least annually to report on activities of the committees and to discuss research priorities.

Membership

Each SC has a chair and co-chair, appointed by the EC Chair, who serves a minimum three year term (may be extended at the request of the EC Chair). The HPTN EC determines the composition of the committee within guidelines established by the EC. It is recommended to have no more than 10 voting members. Membership in the SC also includes liaisons to the Central Resources, Community Working Group (CWG) and Ethics Working Group (EWG).

4.2 Working Groups

The CWG and EWG are cross-cutting and will provide their expertise to all five SCs, the CTUs/CRSs and the Network. The goals of these cross-cutting WGs are to contribute to the design and approval of study concepts, protocols, data collection instruments and

manuscripts as needed, by having representatives participate as members of protocol teams and SCs.

4.2.3 Community Working Group

The Community Working Group (CWG) facilitates inclusion of representatives of the research community as partners in the HPTN research agenda. Community representatives and/or community staff participate in the CWG and on community educator conference calls, HPTN protocol teams, and other Network committees. In addition, once a protocol is approved for development, a protocol-specific CWG is formed.

The goals of the CWG are to:

- Assure that research conducted within the HPTN is done in partnership with the community by integrating community perspectives
- Develop community capacity at HPTN sites to participate in research collaboration
- Increase Network understanding of community collaboration in HIV prevention research
- Provide input in the science generation process

The goals of a study-specific CWG are to:

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

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

- Integrate participation of community members who represent diverse HIV 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
- Inform and advise the EC on community-related issues of concern
- Provide leadership to CTU/CRS community program 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 EC Chair and serves a minimum three year term, renewable at the discretion of the EC Chair. The CWG Chair, CWG Co-Chair and LOC community program staff determine the composition of the CWG within guidelines established by the EC. This includes members both internal and external to the HPTN.

Standing membership in the Global HPTN CWG includes:

- Voting Members
 - CWG Chair and Co-Chair (one each, US and non-US)
 - Each HPTN CRS

- 1 Community Advisory Board (CAB) Representative
- 1 Community Educator
- Non-Voting Members
 - HPTN LOC Community Program and other staff
 - HPTN Principal Investigators
 - Division of AIDS (NIAID/NIH) Representative
 - External Advocate(s)
 - *Ad-hoc* External Scientific Advisor

The Global CWG typically meets at least quarterly via conference call and at least once annually at a face-to-face meeting.

Membership in a study-specific CWG includes:

- Voting Members
 - HPTN CWG Chair and Co-Chair
 - Representative from each CRS
 - 1 Community Advisory Board (CAB) Member
 - 1 Community Educator (CE)
- Non-Voting Members
 - HPTN LOC Community Program and other staff

Study-specific CWGs typically meets at least once a quarter via conference call.

4.2.4 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 members of the Science Review Committee (SRC), protocol teams and *ad hoc* resources to SCs
- Developing guidelines and strategies to enhance ethics capacity at sites with a particular emphasis on participants' understanding of informed consent
- Developing and maintaining an ethics guidance document for the conduct of HPTN studies and for publication

The EWG developed guidelines to enhance HPTN studies, [HIV Prevention Trials Ethics Guidance for Research](#). This document has been reviewed and adopted for use in the Network by the EC. It 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.

4.3 HPTN Oversight and Operations Committees

The EC Chair recommends, and the 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 EC Chair. In addition to the EC, SCs, and WGs, five key standing Network oversight and operations committees include:

- Science Review Committee (SRC)
- Study Monitoring Committee (SMC)
- Manuscript Review Committee (MRC)
- Performance Evaluation Committee (PEC)
- Policies and Procedures Group (PPG)

4.3.1 Science Review Committee

The SRC ensures that study protocols are statistically, operationally, and ethically sound as well as accurate, consistent, complete and, to the extent possible, standardized relative to other HPTN protocols.

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 study team, is approved by the SRC Chair.

Voting Members:

- 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* members (experts knowledgeable in the research area)

Contributing Reviewers:

- SDMC Operational Representative
- CTU/CRS Investigator Representative
- LOC Operations Specialist
- LC Representative
- Site Representative
- Community Representative
- EWG Representative

Observers:

- SC Chair
- SDMC Research Program Manager (RPM)
- LOC Clinical Research Manager (CRM)
- LC QA/QC Coordinator
- [Division of AIDS](#) (DAIDS) Medical Officer or Program Officer
- Other DAIDS representative(s)

Note: The Protocol Chair participates in a debriefing session.

As a guiding principle, 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 consortium institutes
- One or two research area experts external to the HPTN

The SRC convenes as needed. The SRC reviews are conducted via conference call. Following a closed discussion among the reviewers, the Protocol Chair is invited to join the call to discuss questions and issues that have arisen during the review.

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.

4.3.2 Study Monitoring Committee

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 the SMC within the first four to six months of study implementation and thereafter, approximately every six months 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 may not be reviewed by the SMC.

The SMC also reviews aggregate or by arm safety data (adverse events, abnormal laboratory results, product holds and discontinuations) in a closed session. The review of aggregate safety data 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 concept or 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 SMC Chair, in collaboration with the protocol chair, determines the composition of the SMC for each protocol.

Voting Members:

- SDMC PI (Chair) or Senior Statistician
- LOC Representative
- LC Representative

- SDMC Statistician
- One or two *ad hoc* members (experts from within or outside of the HPTN knowledgeable in the research field) not connected to the study and with no conflict of interest

Observers:

- PSP Chief or Designee
- DAIDS Medical Officer
- LC Deputy Director or Designee
- LC QA/QC Coordinator
- SDMC Research Program Manager
- SDMC PM
- LOC Director
- LOC CRM
- Representative(s) from other collaborating NIH institutes

A schedule of routine SMC reviews (based on the phase and need of the study) is 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. An SMC quorum is defined as the SMC Chair and at least three (3) other voting members and so an 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 and also, the Chair may request that a review be carried out in his/her absence and will identify a designee to serve as Chair in his/her stead.

Once an SMC is constituted for a study, every attempt is made to maintain the same membership throughout the study.

4.3.3 Manuscript Review Committee

The primary responsibility of the MRC is to ensure that abstracts, posters, presentations, and manuscripts that contain data or statistically related content from HPTN studies are developed, reviewed and endorsed, according to the HPTN Publications Policy (see 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
- SDMC senior statistician
- LOC representative
- *Ad hoc* expert, as needed

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 the HPTN (see Section 19 for more information about the Network evaluation). The PEC designs and directs implementation and reporting of the internal evaluation of the HPTN. This includes assessing performance of the CTUs/CRSs as well as key organizations and entities that are also part of the HPTN (e.g., LOC, SDMC, LC and protocol teams).

The goal of the evaluation is to provide data to assist in leadership decisions about changes necessary to improve HPTN functioning. In regard to the CTUs/CRSs, 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 representative
- 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 on a periodic basis as determined by the HPTN EC and is submitted to the EC for review and action. In addition, a qualitative survey may be produced to facilitate improved performance of committees and groups. Results of the evaluations are also sent directly to EC, chairs of the WGs, Network committees and protocol teams, CTU/CRS PIs, and PIs of the LOC, SDMC, and LC.

4.3.5 Procedures and Policy Group

The PPG, with membership from the LOC, SDMC, LC and DAIDS, is an oversight and operations committee tasked with developing and maintaining the HPTN Manual of Operations (MOP).

4.4 Protocol Teams

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

4.4.1 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)
- LOC CRM
- SDMC lead statistician
- SDMC PM
- LC QAC

- DAIDS Medical and/or Program Officer
- NIAID collaborating institute representative (if applicable)
- DAIDS Pharmacist (if applicable)
- Pharmaceutical or industry representative (if applicable)
- EWG representative

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

4.4.2 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. Nominees will submit a paragraph indicating interest as well as describing the expertise required for the development of the specific protocol. 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.

4.4.3 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 of more than two HPTN studies.**

Protocol Chairs will need to familiarize themselves with the HPTN processes and adhere to them. An agreement outlining responsibilities will be provided to protocol chair(s), who will be required to sign it.

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; 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 study related manuscripts, abstracts and presentations.
- 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.

4.4.4 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)	<ul style="list-style-type: none"> • Provide leadership to 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)	<ul style="list-style-type: none"> • 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 SSP Manuals and data collection forms • Manage study implementation at sites • Participate in manuscript development
Community Representative(s)	<ul style="list-style-type: none"> • Provide perspective of community and potential participants; facilitate communication with site CAB: <ul style="list-style-type: none"> - 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
LOC CRM (see Section 3.1.1 for further details of LOC responsibilities)	<ul style="list-style-type: none"> • With Protocol Chair, provide scientific and operational input to the protocol, coordinate and lead development of protocol • Organize and document protocol team conference calls and meetings • 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 Manual 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-

Roles of Key Protocol Team Members	
Team Member	Primary Roles and Responsibilities
	<p>related Standard Operating Procedures (SOPs)</p> <ul style="list-style-type: none"> • Assess the performance of CTUs/CRSs and report results 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 coordinate the acquisition and distribution of study drug • 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 requirements • Coordinate and track site activation requirements
SDMC Lead Statistician (see Section 3.2.1 for further details of SDMC responsibilities)	<ul style="list-style-type: none"> • Provide design, statistical and scientific input during protocol development and throughout the conduct of the study • Develop statistical components of the protocol • 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
SDMC PM	<ul style="list-style-type: none"> • Collaborate in development of protocol • Collaborate in development and production of SSP manual, with primary responsibility for data management, reporting and randomization sections • Lead the development of data collection instruments (e.g., CRFs, computer-based questionnaires) and instructions • Collaborate with CRM to test CRFs and operations in the field before training and implementation • Collaborate with CRM on review of site SOPs related to data management prior to activation • Collaborate with CRM on study drug packaging and 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; coordinate HIV retesting and distribution of

Roles of Key Protocol Team Members	
Team Member	Primary Roles and Responsibilities
	<p>results to EAC</p> <ul style="list-style-type: none"> Facilitate closeout of data collection and cleaning Monitor publication activity and facilitate as needed
LC QA/QC Coordinator (see Section 3.3.2 for further details of LC responsibilities)	<ul style="list-style-type: none"> Define appropriate laboratory testing methods and materials Collaborate in development and production of SSP manuals, with primary responsibility for laboratory sections 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 CRF development Collaborate with CRM to enable CTUs/CRSs to meet proficiency requirements Provide support to the study team as laboratory issues arise during implementation of the protocol Participate in manuscript development
LC Representative (e.g., virologist, immunologist, pharmacologist)	<ul style="list-style-type: none"> Provide scientific input into protocol development Provide input on laboratory-related issues of the protocol and 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 Participate in manuscript development
DAIDS Medical Officer	<ul style="list-style-type: none"> 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
DAIDS Pharmacist	<ul style="list-style-type: none"> Primary responsibility for the pharmacy section of the SSP Manual Advise protocol team on all product-related issues; consult on available dosage forms and placebos Interact with pharmaceutical companies to ensure product supply Provide and monitor timely product shipment to study sites Monitor drug supply, expiration dates, and budgets for drug, where necessary

4.4.5 Relationship of Scientific Committees and Protocol Team

The appropriate SC:

- Monitors progress in protocol development, study implementation, and manuscript writing
- Adjudicates disagreements/conflicts which cannot be resolved within the protocol team

4.4.6 Relationship of HPTN Executive Committee and Protocol Team

The EC monitors each HPTN protocol team with regard 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 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 EC may direct that the protocol team membership or its leadership be modified

4.4.7 Conflict Resolution

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

4.4.7.1 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 Protocol Chair cannot resolve the issue with the protocol team, the issue is referred to the appropriate SC
- If the issue cannot be resolved through discussion with the SC Chair, it is referred to the EC

4.4.7.2 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 EC

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5 COMMUNITY PARTICIPATION 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 group from which study participants will come (e.g., a specific group of women at risk for HIV who use the services in a family planning clinic or people who inject drugs in a certain location). 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 can and should 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.

Community participation is solicited at all levels of HPTN operations, including at the Clinical Research Site (CRS), on protocol teams, Network Scientific Committees, Working Groups, cross-Network relationships and Community Partners. The HPTN supports partnerships between the community and researchers in research design, implementation, and dissemination of study information. Partnerships at sites are the foundation of the HPTN community program. 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.

The HPTN is committed to:

- Conducting ethical research of the highest scientific quality that is informed by community input
- Supporting local community education and building community partnerships at HPTN sites
- Supporting activities and infrastructure to build and sustain the community-research partnership
- Developing leadership, through the Community Working Group (CWG), to advise the Network on cross-cutting community issues
- Providing technical assistance and support to Network and CRS community activities through the Leadership and Operations Center (LOC) Community Involvement Program (CIP) staff
- Responding to concerns and misconceptions arising from study participants and communities, as needed

To support the goal of building community programs and partnerships at the HPTN sites, the HPTN encourages sites to have dedicated staff time available for coordination of the CRS community participation programs. The LOC CIP staff works closely with CRS community staff to develop local community involvement work plans that include community assessment, community education, support of CABs and other mechanisms for community input (see Section 5.1 for more details). LOC staff assists CRSs in community orientation and training, and facilitation of community input into protocol development and study implementation. Oversight, operational management, and technical assistance are also provided for CRS community program staff in the development and dissemination of

educational materials, the development of collaborative partnerships, and the ongoing education of trial participants, researchers, and affected communities. LOC CIP staff provides guidance to CRSs in the development of community program budgets and advocate for the inclusion of appropriate technology for participation by community members from the site in the Network (e.g., telephone and computer access; support for CAB member participation in local, regional, and international meetings; and training opportunities). The LOC CIP staff also support the CWG.

At the CRS level, the CRS Principal Investigator (PI) is responsible for supporting a community program that elicits involvement of community representatives in the design, development, implementation, and dissemination of results for HPTN studies. The program will include:

- Support from the CRS core budget for adequate staff and funding for a CRS community involvement program
- Development and submission of an annual CRS community involvement work plan
- Submission of routine reports on community activities per the community involvement work plan
- Adequate financial, logistical, administrative and infrastructure support for development or enhancement of CRS community advisory structures capable of working autonomously to determine their priorities, methods of organization, and activities, including the convening of routine meetings between site investigators, study staff, and the CAB for exchange of information on study progress and plans and community issues and questions.

The HPTN also ensures cross-Network community participation through its relationship with community partners. Elected site community representatives and LOC CIP staff participate on monthly conference calls to collaborate in identifying and developing programs to meet the training and support requirements of local CABs, increasing the representation and participation of community members from resource-limited settings and vulnerable populations, and identifying and addressing challenges to participation in clinical trials.

5.1 CRS Community Involvement Work Plans and Report

Developing sustained relationships and communication with community members is the responsibility of each CRS PI and assigned CRS research and community program staff. Each CRS will develop and implement a site-specific community involvement work plan to ensure broad community support for, and participation in, the HPTN. The [work plan guidance and template](#) can be found on the [HPTN website](#). The work plan will address how the CRS provides community education about HIV, HIV prevention research in general, and HPTN research, planned or ongoing, at the site.

The CRS community involvement work plan includes:

- A community assessment that identifies community education needs, potential benefits and barriers to study participation, and appropriate educational strategies
- Goals, objectives, and a description of educational strategies to increase community understanding of HIV prevention research, community and ethical questions in the design and implementation of clinical trials, and information and issues specific to studies at the CRS
- Methods of monitoring and evaluating implementation of the work plan, including whether objectives have been met

The CRS investigator, site/study coordinator, and CAB Chair (or designee) must sign off on the work plan prior to submission to LOC CIP staff as documentation that they were involved in its preparation and/or know and concur with its contents.

The CRS community education staff oversees the local implementation of the community involvement work plan. The HPTN leadership has suggested that each CRS budget includes financial and human resources for the ongoing development, implementation, and coordination of community education initiatives, and the support of community members' participation in HPTN activities.

CRS participating in HPTN research will report their community education activities during either monthly protocol team or CWG teleconferences. These calls will be used to:

- facilitate learning across sites by providing a mechanism to share experiences, best practices, and strategies;
- help to more quickly identify and address challenges (misconceptions and/or barriers to recruitment, enrollment, retention and adherence);
- provide the HPTN Community Program staff at the LOC with timely progress reports and updates that can be shared with the protocol chair/team; and
- allow the HPTN Community Program staff at the LOC to identify community-related technical assistance needs at sites.

5.2 CRS Community Advisory Boards

Typically, the CRS obtains community input into the research process through CABs, although a CRS may refer to this structure by any locally chosen name or establish an alternative structure. Community representatives provide input to protocol teams, particularly in adapting sample consent forms for local use and in developing other study materials.

The community involvement work plan should be developed with CAB (or similar community advisory) input, describing how CAB members are selected and how the CAB functions. For CRSs with an alternative mechanism for community input, the work plan should describe how the CRS obtains appropriate community input. The LOC must pre-approve any CRS community involvement work plan that does not include a CAB.

CAB and other advisory activities will be reported by the CRSs through reports on community involvement.

To ensure CAB autonomy and to reduce the potential for conflict of interest, CAB members are volunteers from the CRS community and are not paid staff members at the CRS. In order to serve on a CAB, members agree to certain terms of membership, generally having to do with roles, responsibilities, and meeting attendance. CAB members are expected to participate meaningfully so that issues requiring community dialogue can receive appropriate attention.

CAB members and community partners involved in the review of a protocol and related documents may be asked to sign a statement of confidentiality to ensure confidentiality of proprietary information and to protect CAB members and study participants from HIV-related stigma.

In-person meetings facilitated by CRS staff provide opportunities for CAB members to share their community expertise and gain new skills. Compensation for CAB members should be offered to offset legitimate costs of participation in the advisory process, such as reimbursement for transportation and meals and other reimbursements that are deemed appropriate at the local level but that do not include payment. Leadership, Central resource staff and protocol team members, can be available to participate in CAB meetings when on site. CRSs are encouraged to support representative CAB members' participation in HPTN meetings and trainings.

Local and Network-wide community education efforts include strategies to increase researchers' and staff members' knowledge of community participation and to foster strong partnerships between researchers and the community. These partnerships support research that is relevant to the community, appropriate plans for recruitment/retention, and dissemination of study findings to the community. CAB members work with site and study staff to lay the foundation for a viable research program by representing and speaking for the community. As volunteers, CAB members and other community representatives are not responsible for recruitment of study participants.

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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 meetings, electronic and written materials, social media and through the HPTN's website. The website serves as a main driver of communication, where study-specific information and postings about Network-wide activities can be found. The Senior Communications Officer at the LOC is primarily responsible for creation and dissemination of HPTN material.

6.1 Annual Network Meeting

In collaboration with the HPTN leadership, the LOC organizes an annual Network 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 meeting generally includes plenary sessions to update HPTN members on the latest scientific research concerning HIV prevention. The Executive Committee (EC), Scientific Committees (SCs), Working Groups (WGs), and protocol teams 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 Network meeting may provide NIH training opportunities.

6.2 Conference Calls

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

The LOC provides a broad range of administrative support for conference calls; preparation and/or distribution of call agendas and pre-meeting materials; sending email meeting reminder notices; and preparation, distribution, and archiving of conference call summaries. As part of their support of these groups, LOC staff document and distribute summaries of EC, SC, WG, protocol team and investigator conference calls.

In addition, webinar support is provided to allow for interactive slide presentations and other media rich methods for sharing of information and data.

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, CD-ROM, website postings, facsimile, mail, and express mail services. To ensure information transfer, each Network organization must:

- Have the capacity to send, access, and receive materials distributed using the above techniques
- Ensure that HPTN communications and materials are distributed to all appropriate staff members
- Maintain all key study and HPTN communications in a well-organized filing system

Key HPTN information is posted on the HPTN website for access by all Network members. Information from Central Resources and from [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.

The general philosophy governing the design, maintenance, and content of the website is to provide a site that (1) contains useful and up-to-date information on the Network organization and studies; and (2) accommodates various Internet connections and software and hardware limitations across this multinational Network.

6.4.1 Website Structure and Organization

Documents available on the HPTN website are in PDF unless otherwise noted. This may include posting HPTN protocols, letters of amendments, full protocol amendments. Study-specific pages are developed to suit the needs of each particular study. An updated list of site names and numbers, with contact information, and a list of protocols (numbers and titles) that includes participating sites and status of each study is also posted. The website also features a searchable HPTN publications database.

Study-specific portal pages allow each protocol team to work interactively. The portals may contain documents that are complete, such as the study-specific protocol manual or it may be used for multiple team members to create and edit documents for study use.

The design and maintenance of the HPTN website is the responsibility of the LOC. Questions and comments on the website may be sent to: hptn@fhi360.org.

6.4.2 HPTN Use of Social Media

The HPTN uses social media tools to achieve its goal of increasing 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 primary social media tools utilized by the HPTN are [Facebook](#) and [Twitter](#). The HPTN engagement efforts on those sites primarily focuses 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.

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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. Each Clinical Trials Unit (CTU)/Clinical research Site (CRS) also adheres to relevant local regulations and policies. In addition, HPTN-specific policies and procedures guide HPTN members in meeting relevant requirements and standardizing site operations for each HPTN study. These include:

- **HPTN Manual of Operations (MOP):** This manual provides general guidelines to all HPTN members and combines HPTN policies and procedures in one document.
- **Site and Study-specific Standard Operating Procedures:** Standard Operating Procedures (SOPs) for site operations and for study operations ensure standard, uniform performance of site and study-related tasks (see Table 10-1) and compliance with HPTN procedures, [International Conference on Harmonisation/Good Clinical Practices](#) (ICH/GCP) guidelines, and [US Food and Drug Administration](#) (FDA) regulations, where applicable.
- **Study-specific Procedures (SSP) Manuals:** In addition to study protocols, conduct of HPTN studies typically is guided by an SSP Manual, an instructional and reference resource developed for each study. SSP Manuals provide links to applicable DAIDS manuals (such as the [Manual for Expedited Reporting of Adverse Events to DAIDS](#)), and provide detailed standardized instructions for conducting protocol-specified procedures (see Section 10.7).

A network oversight committee, the Policy and Procedures Group (PPG), with representation from the Leadership and Operations Center (LOC), Statistical and Data Management Center (SDMC), and the Laboratory Center (LC), is responsible for reviewing the HPTN MOP and releasing revised sections as needed.

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 subagreement (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 (or the funding institution) 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.

- Core funds are provided to HPTN CTUs in order to maintain the scientific and administrative expertise as well as 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, implementation or close-out of trial. 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 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. In the future CTUs will be funded directly from FHI 360.

Each year, the HPTN leadership provides an annual PF funding plan based on study-specific budgets. 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 its anniversary date (i.e., October 1 for a December 1 date) of each year, 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 rebudgeted/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. In addition, as a study-specific requirement, all individuals listed on a [Form FDA 1572](#) for a study inducted under

an Investigational New Drug (IND) application with the US Food and Drug Administration must have on file at the site a completed financial disclosure form prior to enrollment of any participants in that study; likewise, any new personnel added to the Form FDA 1572 must complete a disclosure form within the specified timeframe.

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

The HPTN is a party to the NIH HIV/AIDS Clinical Trials Networks Financial Disclosure Policy and Procedure: https://www.hanc.info/smctl/Documents/Cross-network%20FDCOI_SOP.pdf 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 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., protocol virologist, immunologist, 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 A](#) of the cross-network SOP) 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

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.

This is not a new requirement; however, DAIDS is expected to issue a new policy related to this requirement in the near future and HPTN has established procedures to ensure compliance with the forthcoming policy network-wide. Further guidance will also be provided in an expected update of the DAIDS Protocol Registration Manual, as sites will be required to complete the required documentation prior to enrolling participants in any study for which financial disclosure is required.

HPTN has developed a [Financial Disclosure Form](#) for accessibility on the HPTN 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. 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

The HPTN has obtained a US Government Certificate of Confidentiality (CoC) that covers US-based CTUs that have been listed by protocol under the CoC. Coverage under the HPTN CoC is applied for by the LOC prior to study implementation.

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. Site staff will inform participants of the limitations of coverage of the CoC. The LOC Clinical Research Manager (CRM) works with US sites to ensure that language describing the CoC is included in the informed consent form, as needed. Once the protocol has been approved by the local Institutional Review Board (IRB), documentation of the IRB approval is submitted to the LOC clinical operations staff with accompanying application materials from the CTU PI. When CoC coverage has been obtained for the site, the LOC CRM notifies the site.

For more information on the CoC, refer to the law pertaining to the [Certificate of Confidentiality \[Public Health Service Act 301\(d\)\]](#), the [NIH Certificates of Confidentiality Kiosk](#), including information on 42 U.S.C. 241(d), as amended by Public Law No. 100-607, Section 163 (November 4, 1988)].

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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 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: [Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS funded and/or Sponsored Clinical Trials](#).

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 subjects research in general and/or the conduct of study procedures in particular

8.2 International Conference on Harmonisation Consolidated Guidance for Good Clinical Practice

DAIDS requires that all HPTN studies be conducted in accordance with the [International Conference on Harmonisation \(ICH\) Consolidated Guidance for Good Clinical Practice](#) (GCP).

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. “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.

8.4 IRB/EC Review and Approval

Consistent with the regulations and guidance referred to in Section 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 is 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, all studies must undergo continuing review and be approved at least annually.

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 (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)

Documents CRSs Must Submit to IRB/EC	Written Approval Required *
Protocol version 1.0 (or first implementation version of the protocol, if not version 1.0)	Yes
Informed consent forms: <ul style="list-style-type: none"> – Screening – Enrollment – Specimen Storage <i>Note: HPTN informed consent forms typically contain information on participant incentive amounts and schedule; however, incentives may be approved through submission of separate materials.</i>	Yes
Investigator's Brochure(s)** or Package Inserts**	No
Other safety-related information (if applicable)	No
Investigator of Record current Curriculum Vitae	No
Participant recruitment materials developed prior to study initiation	Yes
Other written information for study participants developed prior to study	Yes
Other documentation required/requested by the IRB/EC (e.g., CRFs, Standard Operating Procedures [SOPs])	If required by IRB/EC

* 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 Essential Document Files at the CRS.

8.4.1 Continuing Review

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

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

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

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

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

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

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

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

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

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

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

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

8.5 Informed Consent Process

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

Informed consent is a process by which an individual voluntarily expresses willingness to participate in research after having been informed of all aspects of the research that are relevant to his or her decision. Informed consent is rooted in the ethical principle of respect for persons and is a fundamental component of conducting ethically sound research involving human subjects. It is not merely a form or a signature, but a process that involves information exchange, assessment of comprehension, and assurance of voluntariness on the part of both the potential study participant and the study staff member who obtains informed consent from the participant. Details regarding the informed consent process to be undertaken in each HPTN study are provided in each study-specific procedures (SSP) manual. In addition, each HPTN CRS must develop a Standard Operating Procedure (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 Ethics Guidance for Research \(revised 2009\)](#), also provides points to consider in the development and implementation of the informed consent process.

CRSs 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.

DAIDS developed a policy, [Division of AIDS Review of Informed Consent Forms: Impact of the HIPAA Privacy Rule](#), which clarifies how DAIDS informed consent reviews and protocol registration will be managed in the context of HIPAA. 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. Detailed instructions for informed consent form development are provided in Section 10.2 of this manual.

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. The DAIDS Policy: [Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials](#) 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, including but not limited to those addressing mother-to-infant HIV transmission, 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.

8.7.3 Additional Considerations for Prisoners

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

8.8 Storage of Informed Consent Forms

HPTN CRSs must maintain, in a confidential and secure manner, the complete, original, signed and dated informed consent forms of all persons who screen for and/or enroll in HPTN studies, in accordance with the specifications of the study protocol (in particular the protocol

sections on Confidentiality and Investigator's Records) and the SSP manual (see also Section 8.9).

8.9 Confidentiality

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

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

- NIH
- Pharmaceutical co-sponsors
- Clinical Site Monitor
- HPTN LOC, SDMC, and Laboratory Center (LC)
- Responsible IRBs/ECs
- US FDA
- Site drug or other regulatory authorities

In addition to efforts undertaken by CRS staff to ensure confidentiality, the HPTN has obtained a Certificate of Confidentiality that protects US CRSs listed on the Certificate 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 Certificate of Confidentiality, 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).

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, child care, 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 Ethics Guidance for Research \(revised 2009\)](#) 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 Policy for HPTN

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 the course of 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 (NGO's), 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 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.

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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 and researchers/experts who bring complementary expertise. Key steps in the process are shown in Figure 9-1 and are further described below.

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 Scientific Committees (SCs) and Working Groups (WGs), and in alignment with the scientific agenda of the network (Integrated Strategies and Pre-Exposure Prophylaxis [PrEP]). Once a specific priority study is identified, then a concept team will be established to develop the concept plan. For newly identified research priorities, an SC may solicit the submission of concepts to meet predetermined scientific needs. While the generation of new science will be the primary responsibility of the SCs, investigators (both within and outside of the Network) can submit ideas for consideration by an SC as well. The number of concept plans developed into protocols will be based on the Network's current and future priorities.

A concept team should be formed, and may include a proposing investigator(s), as well as representatives from the NIH, the relevant SCs and WGs (including Ethics and Community WGs). Central Resources will be assigned only after the approval of the concept by the EC.

The team will submit the developed concept to the relevant SC, where it will be reviewed and prioritized if approved. The EC will accept concept plans for scheduled review four times a year (or more frequently to accommodate emerging science or other opportunities). Upon approval by the relevant SC, the concept team will submit the concept plan to the EC for review at one of the four scheduled timepoints (See Section 9.1.2).

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. If a concept plan is longer than 10 pages it will be considered as non-responsive (the review will not be completed). 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. All documents can be submitted electronically for review.

9.1.2 Concept Plan Review

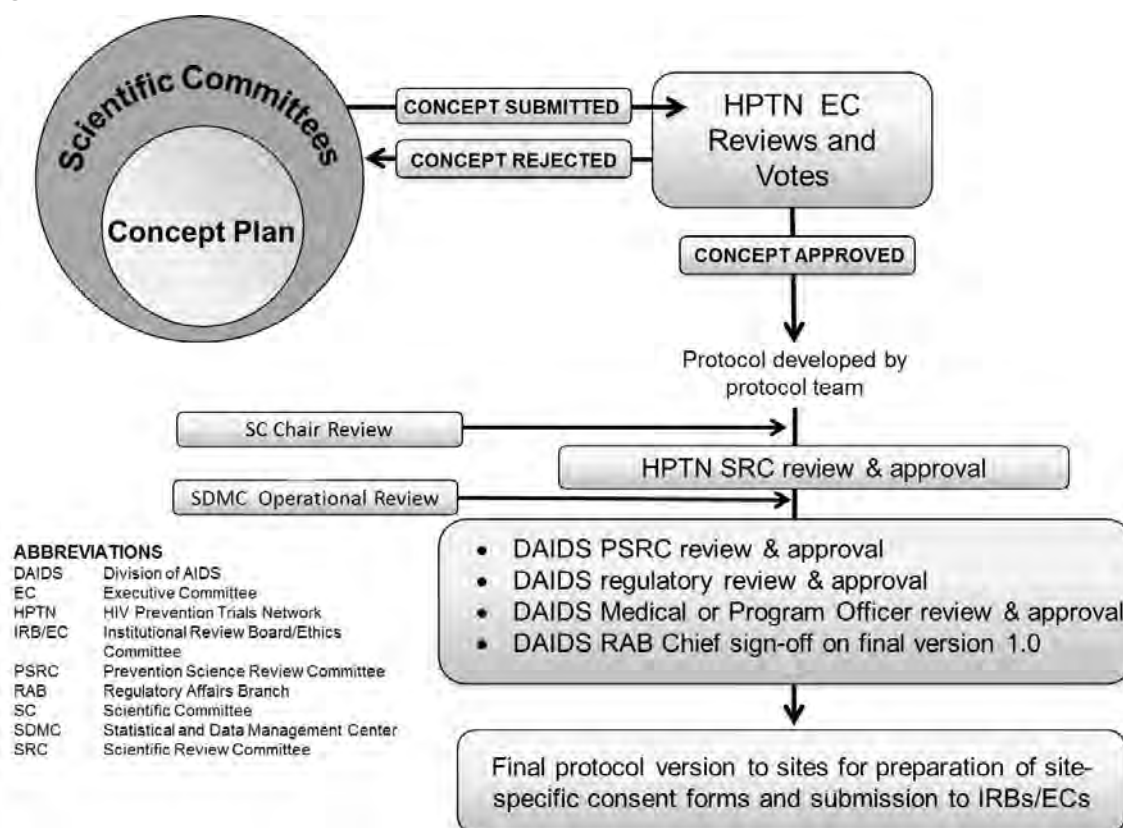
All concept plans must be reviewed and approved by the EC.

Concept plans must be submitted to the LOC 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, along with reviewers from the NIH, the LC, SDMC, and the Community and Ethics Working Groups. Assigned reviewers submit written comments in advance of the review, and the concept and reviewers' comments are discussed on an EC call or at an in-person meeting. 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 of research
 - proposed study is or would potentially lead to an efficacy trial
- Research advantage of the HPTN (20%)
 - study is aligned with the scientific agenda and priorities of the Network (i.e., integrated strategies and PrEP)
 - proposed research will benefit from a multi-site, multidisciplinary collaboration involving different populations either in the initial phase or in a subsequent phase

Figure 9-1 Protocol Development Process



Following review discussion, all voting EC members must cast a vote via email (or on paper if at an in-person meeting). 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. 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), Ethics Working Group (EWG), LOC, LC, and SDMC.

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 and the Protocol Chair will assign the various sections to different members of the protocol writing team and then will coordinate the writing of various sections of the protocol by the team to develop the first draft. The Protocol Chair and LOC CRM will also set a timeline for protocol development for the writing team. The CRM documents all key decisions made during the process, generally by maintaining and updating the draft protocol document.

Once the study design and the schedules for visits and procedures have been well defined, the 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.

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 completing the protocol development process the protocol goes through a series of protocol review steps, each of which is described below. The LOC CRM is responsible for all document submissions and for maintaining documentation of all review findings and protocol team responses to these findings.

9.2.2.1 Scientific Committee Chair Review

The protocol should be submitted to the Scientific Committee Chair; this submission can occur before or simultaneous to the submission to the Science Review Committee (SRC). Any comments received from the Scientific Committee Chair will be considered during the Scientific Review Committee's review.

9.2.2.2 Scientific Review Committee Review

The HPTN Scientific Review Committee (SRC) will conduct the first step in the protocol review process. The SRC will be comprised of the Chair, representatives from the LOC, LC, SDMC and NIH, CWG and EWG reviewers, a site investigator and coordinator, and as necessary, external reviewers who have expertise in the scientific topic of the protocol. A subset of the SRC is considered the primary review group and includes the SRC chair, SDMC statistician, *ad hoc* scientific reviewer and the NIH representative. The SRC review will ensure 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. The SRC will review the protocol via conference call within five working days of receiving a draft. The SRC members submit written comments to the Chair, either prior to or immediately following the review call. Following the closed SRC discussion, the Chair(s) of the protocol being reviewed join(s) the call to answer questions and to discuss key review findings from SRC primary review group members. The LOC CRM will summarize the call and its outcome in writing and distribute the summary to the SRC, the relevant SC chair 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 revision — the protocol team may proceed to the next review step (DAIDS Prevention Science Review Committee [PSRC] review)
- Approved contingent upon revisions — the protocol team prepares a written response to major review findings which must be reviewed and approved by the SRC Chair
- Protocol disapproved — the protocol team will work with the SC Chair and/or other members of the HPTN leadership to determine next steps

If a protocol is approved contingent upon revision, protocol teams will strive to provide a written response to the comments of the primary review group 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. 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.

9.2.2.3 SDMC Operational Review

The SDMC conducts a detailed operational review of HPTN protocols at an appropriate time as determined by the LOC CRM, and the SDMC Project Manager and Research Program Manager, but prior to or simultaneous to submission to the DAIDS Prevention Sciences Review Committee (PSRC). The review is completed within 10 working days of protocol receipt. If the protocol changes substantially due to PSRC review, the SDMC may perform an additional operational review.

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 a review summary document and sends it electronically to the LOC CRM.

9.2.2.4 DAIDS PSRC Review

After obtaining SRC approval, the protocol team submits the revised protocol (reflecting response to SRC comments) for DAIDS PSRC review. Along with the draft protocol, the protocol team may also decide to submit the SRC review comments as well as the protocol team's response to the SRC review to the PSRC.

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/Program Officer in advance. This consultation will take place at least one week before submission to the PSRC. If the DAIDS Medical/Program 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/Program Officer, at least 15 working days prior to the scheduled PSRC meeting, copying the PSRC secretary, the [Regulatory Support Center](#) (RSC) at Regulatory@tech-res.com and the [Clinical Study Information Office](#) (CSIO) at CSIO@niaid.nih.gov. The DAIDS Medical/Program Officer reviews the protocol and accompanying documents for completeness (within one week) and forwards them to the PSRC Administrator at least two weeks (10 working days) prior to a PSRC meeting.

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.

9.2.2.5 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 to the DAIDS RSC for a 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.

9.2.2.6 DAIDS Medical or Program 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/Program 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/Program Officer.

The Medical/Program 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.

9.2.2.7 RAB Chief Sign-Off

The protocol team addresses any Medical/Program 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/Program Officer review.

RAB Chief sign-off is expected within approximately 10 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).

9.2.2.8 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.

As part of the study activation process described in Section 10, study sites then seek 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 (see Section 10) for the study. 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).

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/Program 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/Program Officer prior to finalization and distribution. Once finalized, CMs are distributed to all protocol team members and study sites by the 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.

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 involve relatively minor modifications of study informed consent forms, if any. LoAs are developed by the protocol team according to a [DAIDS template](#) which is available on the [RSC website](#). 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 site 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 protocol team's recommendations, site 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 until IRB/EC approval is obtained from all responsible IRBs/ECs.

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

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	Possibly. Depends on content and requirements of site IRBs/ECs.	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.*

***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 drug added to the protocol
- Change to inclusion or exclusion criteria
- New safety information on drugs in the protocol

Protocol amendments are developed by the protocol team and, as shown in the table above, and 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/Program 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/Program 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.

9.4 Revised Informed Consent Forms

If consent forms need revision, site staff should refer to Section 10.9.1 and consult with the LOC staff to determine the process for review and translation.

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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. Several of these steps require collaborative work among the [Division of AIDS](#) (DAIDS) staff, HPTN central resources, protocol team and site study staff members; chief among these is development of the study case report forms (CRFs) and a study-specific procedures (SSP) manual, described in Sections 10.5 and 10.7, respectively.

Once all study activation requirements are met at a site and documented, the HPTN Leadership and Operations Center (LOC) Clinical Research Manager (CRM) will issue a site-specific Study Activation Notice (see Section 10.4) 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 to site staff a copy of the documentation upon which activation was based.

Study-specific Requirements: Table 10-1 lists the activities that must be completed by each site in order to begin implementation of a specific HPTN study. Key pre-implementation activities involved in the study activation process are described in greater detail throughout the remainder of Section 10.

As a condition for study activation, study-specific SOPs that describe the requirements and operations of a particular study must be in place. The Activation Checklist will specify which SOPs are required (e.g., accrual, retention). 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. (See Table 10-1.)

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

Table 10-1 HPTN Study-specific Activation Requirements

I. Required Study-specific Activities, SOPs, and Documentation

- A. Verify OCSO site approval (refer to Section 16)
- B. Pharmacy approval, if applicable, from the DAIDS Pharmaceutical Affairs Branch (PAB) of site readiness may include:
 - SOP for investigational product management and accountability review and approval from the DAIDS PAB (if applicable)
 - All applicable import approvals for study products
 - All applicable export approvals for study products
 - Training for site pharmacists, if required by PAB

- Specific requirements for a particular study agent
 - Regimens and administration
 - Protocol specific prescriptions
- C. Data management approval from the Statistical and Data Management Center (SDMC) of site readiness based on the following:
- Installation of required data transfer equipment or plan for data transfer
 - SOP for data management, including data quality assurance/quality control (QA/QC) procedures
 - SOP for randomization procedures, if applicable
 - Availability of SDMC-provided materials (e.g., DataFax forms) onsite
- D. Laboratory approval from Laboratory Center (LC) of site readiness based on the following:
- Study-specific QA/QC procedures
 - SOP for study-specific specimen management plan and “chain of custody” related to clinical/safety testing and management of samples for the study endpoints
 - Sites in the United States (US) must identify local back up laboratory arrangements. Non-US sites must identify back up for laboratory testing in their Protocol Analyte List (PAL) (see Section 13)
 - 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
 - Reference intervals Clinical Laboratory Improvement Amendments (CLIA) accreditations for US laboratories performing safety testing/CD4/Viral Load
 - The following for non-CLIA accredited laboratories
 - proficiency in performing protocol-required tests
 - appropriate validation and documentation of validation for protocol analytes
- E. Study-specific SOPs reviewed 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)
 - Participant accrual plan (may be written as SOP or plan)
 - Participant retention plan (may be written as SOP or plan)
 - Communication with responsible IRB/EC (may be site-specific SOP)
 - Communication with affiliated sub-sites, if applicable (may be site-specific SOP)
 - Others as determined by study team

II. Other Required Activities

- A. Local regulatory authority approval of the study protocol, e.g., Ministry of Health, drug controller/regulatory agency (if applicable, in addition to IRB/EC approval)
- B. Protocol registration approval from the [Regulatory Support Center](#) (RSC) [Protocol Registration Office](#) (PRO), based on the following:
- Approvals of the study protocol from all Institutional Review Boards/Ethics Committees (IRBs/ECs)

- IRB/EC-approved informed consent forms (including local language versions, back-translations and local language Translation Confirmation Documents, where applicable)
 - Signed [FDA Form 1572](#) or [DAIDS Investigator of Record Form](#)
 - CV of the Investigator of Record (IOR)
- C. Completion of US [Food and Drug Administration](#) FDA 30-day review period/safe to proceed notice (if applicable)
- D. Confirmation received from investigator that completion of Human Subjects Protection (HSP) training for key study staff is current (see Section 11.1)
- E. Confirmation received from investigator that completion of GCP training for key study staff is current (see Section 11.2)
- F. Study staff signature sheet, roster, and delegation of duties
- G. Confirmation received from investigator that current CVs for key staff available onsite
- H. Completion of study-specific training; DAIDS approval of resolution of findings/actions identified during training, if applicable
- I. Resolution of any other action items identified in any other site preparation activities
- J. Others as needed (site- and study-specific)
- K. Final DAIDS Branch Chief approval for study activation

10.1 Clinical Trials Agreement

A Clinical Trials Agreement (CTA) is the agreement negotiated between a collaborating pharmaceutical co-sponsor and DAIDS, as the study sponsor, 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. In general, terms in the CTA covering data access and sharing conform to policies developed jointly by the Executive Committee (EC) and DAIDS.

The DAIDS Regulatory Affairs Branch (RAB) and the 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 DAIDS Medical/Program 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 [DAIDS Enterprise System](#) (DAIDS-ES).

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).

10.2 Study Product Acquisition and Shipment to Sites

Study products for HPTN studies are 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). Ordering and storage instructions for US sites are found in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*. For non-US HPTN sites, instructions for obtaining study products will be provided by DAIDS PAB on a study-by-study basis.

Before study products are sent to a non-US study site, documentation of local drug authority approval for importation of the products for the study use must be obtained and

submitted to the DAIDS PAB and the HPTN LOC. 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 drugs or biologics 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 drug availability at the site, if approved by DAIDS. Each study team will determine at what point a site may be activated with regards to drug availability.

Questions regarding shipment of study products to sites should be directed to the DAIDS PAB member of the protocol team.

10.3 Study-specific Preparatory, Assessment, and Initiation Visits to Sites

Prior to initiation of an HPTN study, site readiness for study implementation must be ascertained. The LOC, SDMC, LC, Clinical Site Monitor, and DAIDS may conduct visits if needed to assist sites in preparation and to assess and confirm readiness to undertake a specific study. These visits will likely include a combination of the visits described in the following sections. The table below summarizes these visits. The timing of these visits will be planned with the site investigator and staff to allow participation of key site study staff.

Table 10-2 HPTN Pre-study Site Visits

Pre-study Site Visits (typically conducted for sites previously not in HPTN)			
Type of Visit	Purpose	Timing/Requirements	Responsible Group(s)
Pre-study assessment (Section 10.3.1)	To assess site infrastructure, operations, and staffing	Prior to acceptance as a participating site, and prior to finalization of protocol	LOC, SDMC, LC, and/or DAIDS
Pre-study operations (Section 10.3.2)	To obtain site input on day-to-day study implementation and content of study CRFs;	Following finalization of protocol, when draft CRFs and SSP manual are available, and prior to study-specific training	LOC, SDMC, LC

Pre-study Site Visits (typically conducted for sites previously not in HPTN)			
Type of Visit	Purpose	Timing/Requirements	Responsible Group(s)
	to review source document requirements for each procedure		
Special assignment study-specific initiation (Section 10.3)	To be specified in advance by DAIDS/Clinical Site Monitor	Following IRB/EC approval of protocol and prior to study training. See the table in Section 11.4.2	Lab and/ or Clinical Site Monitor
Protocol Training (Section 11)	To participate, as trainers and representatives of the central operations components, in study-specific training	Following Clinical Site Monitor initiation visit. See the table in Section 11.4.2 for a list of specific requirements	LOC, SDMC, LC and any experts/ consultants as applicable

10.3.1 Pre-study Site Assessment Visits

Prior to site-specific study activation, staff from the LOC, SDMC, LC, and/or DAIDS may conduct one or more pre-study site assessment visits. The purpose of these visits is to assess site readiness and assist the site to prepare to undertake a specific HPTN study. 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 LOC CRM, SDMC PM, 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 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.

The pre-study assessment visits may be conducted anytime between the identification of the site as a participant in the protocol and finalization of the protocol. Dependent on the complexity of the protocol and the site development and infrastructure, the LOC, SDMC, LC and/or DAIDS may make multiple visits. Timing and activities for visits will be planned in conjunction with the site staff.

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 PM, 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).

10.3.2 Pre-study Operations Visit

On a study-by-study basis, a pre-study operations visit may take place. Following the pre-study site assessment visit, and after a study protocol is finalized and draft study CRFs have been approved by the protocol team, the LOC CRM, LC and SDMC PM may conduct pre-study operations visits with at least one participating study site. This is part of the process for finalizing the study CRFs and SSP Manual (described in Section 10.5 and 10.7, respectively). Depending on the needs of the study, multiple visits may be conducted. Every effort will be made to involve key study implementation staff from sites in the visits. For some studies, visits may be conducted at each participating study site. For other studies, a single visit may be conducted, and key staff from other sites asked to attend the visit.

The purpose of pre-study operations visits is to obtain detailed site input on both day-to-day study implementation tasks and activities and the content of the study CRFs. The visits take place over several days and may include a step-by-step “walkthrough” (time permitting) of the protocol specifications for each study visit and the CRFs completed at each visit. Source documentation requirements associated with each study procedure also are discussed. Input received from site staff is incorporated by the LOC CRM and SDMC PM into the draft study SSP manual and the study CRFs set, such that a form set reflecting all required site input can be finalized prior to conduct of study-specific training.

Following the visit, the LOC, LC and SDMC staff member will generate a visit report and distributes it to the site investigators, DAIDS, and the other Network entities, as appropriate. The LOC CRM, LC representative and SDMC PM will work with the site staff to address any issues raised by the visit(s) and documented in the visit report(s).

10.3.3 Study-specific Training Visit

LOC, SDMC, and LC staff members collaborate with site staff to plan and implement study-specific training. This training is described in Section 11.4.

10.4 Site-specific Study Activation Notification

When a site has completed all study activation requirements (see Table 10-1), the LOC CRM will send the completed activation checklist to the DAIDS Medical Officer (or DAIDS Branch Chief) for approval for study activation. After approval from DAIDS, 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).

10.5 CRF Development

The SDMC is responsible for developing CRFs for each protocol. CRFs are designed to collect the data used to address protocol-specified study objectives. The HPTN CRF development process is outlined as follows:

- CRF development 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. Scientific expertise (e.g., behavioral scientists, clinicians) is sought externally, as appropriate

- A draft set of protocol CRFs is developed
- The SDMC will convene a conference call or in-person meeting of a subset of the protocol team in order to obtain the team's input on CRF content. The subset should include representatives from the LOC, LC, DAIDS, investigators, community representatives, and other site staff as appropriate. The draft form set and relevant study materials (e.g., Schedule of Forms) are comprehensively reviewed during the call or meeting. Approved changes are incorporated into the CRFs and other study materials. The SDMC, LOC, and LC determine if CRFs and related study materials should be part of any planned operational "walkthrough" at a pre-study operations visit to a study site
- As needed, finalized CRFs are translated by the study sites or contractor (ideally before any planned operational walkthrough or pre-study operations visit). The translation process is initiated and coordinated by the SDMC. Back-translations, especially for behavioral questionnaires, will be reviewed by the SDMC and LOC for approval
- Study-specific training is conducted (see Section 11.4)
- After study-specific training is conducted (see Section 11.4) final CRFs are distributed by the SDMC to study sites prior to or upon activation (see Section 12.3.2)

10.6 Electronic Data Capture

Some types of studies may require methods of data collection in addition to, or instead of, CRFs. For example, questions about a study participant's sexual behavior or drug use may best be collected using a computerized questionnaire methodology such as an "[Audio]-Computer Assisted Self-Interview" ([A]CASI). The protocol team and SDMC 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 CRFs.

10.7 Study-specific Procedures (SSP) Manual

10.7.1 SSP Manual Development

In addition to study protocols, an SSP manual is prepared as an instructional and reference resource to guide conduct of HPTN studies at each site. SSP manuals contain links to applicable DAIDS policies and manuals (such as 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 CRF development beginning when a protocol is nearly finalized. The LOC CRM is responsible for assembling the manual in close cooperation with the SDMC and LC, as well as other key protocol team members. All manuals follow a common [template table of contents](#) that is tailored to the needs of each study.

The LOC CRM is responsible for coordinating the development of the SSP manual; however, other protocol team members are assigned authorship and review responsibilities for certain sections. For example:

- The SDMC PM is responsible for sections of 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 sections of the manual related to laboratory processing, testing, etc.
- The DAIDS Medical Officer and other clinically-trained team members often are required to develop and/or carefully review sections of the manual related to clinical procedures
- The DAIDS PAB protocol pharmacist is responsible for sections of the manual related to investigational product management by the site pharmacist. The PAB protocol pharmacist also provides significant input on other sections of the SSP Manual related to participant study product use

Regardless of primary authorship assignments, the LOC CRM is responsible for coordinating the development of all sections, reviewing all sections, and incorporating all sections into the manual. As the manual is developed, the LOC CRM will forward it for review by other team members as needed, collect comments, and incorporate these into revised draft versions of each section. Input may also be sought from site staff prior to finalization of the manual, both by requesting review and comment on draft versions of the document and through conduct of the pre-study operations visits described in Section 10.3.2.

After incorporating all team and site input as needed, the LOC CRM will issue the first final implementation version of the SSP Manual, labeled with version 1.0 and the version date. This electronic copy of the manual will also be posted on the HPTN website's collaboration portal once final. Release of version 1.0 of the SSP Manual typically closely follows conduct of study-specific training and usually precedes study activation at the first participating site.

10.7.2 SSP Manual Amendment

If a need for additions or modifications to the SSP Manual is identified after distribution of the first final implementation version, the LOC CRM will draft or obtain the new text and obtain review and comment from protocol team members as needed/applicable. The LOC CRM also will update an SSP Manual version control log to document the change. After review comments are incorporated, the new text and the version control log will be considered final and ready for distribution. Electronic file(s) containing the revised sections and version control log will be posted on the HPTN website's collaboration portal. The LOC CRM will inform the study team and site staff that the electronic file(s) containing the revised section(s) (with new version number and version date) and version control log have been posted on the HPTN website's collaboration portal and instruct the site staff to add the revised section(s) to the SSP Manual filed with the site's administrative and regulatory documents for the study and to replace the existing sections with the new sections in all other working copies of the SSP Manual.

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.

10.8 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, and filing requirements are specified in the DAIDS policy: [Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS funded and/or Sponsored Clinical Trials](#). 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. Guidance is provided in the DAIDS policy on essential documents.

10.9 IRB/EC Approval

Section 8.4 of this manual details the study-related documents that must be submitted to and approved by all IRBs/ECs responsible for oversight of research involving human subjects at each study site. All required approvals by all responsible IRBs/ECs must be obtained and documented prior to study initiation.

The DAIDS-approved version of the study protocol will be provided by the LOC CRM to each site for submission to the IRBs/ECs. If specific IRB/EC requirements make it difficult to adhere to the procedures described in the following sections, site staff must notify the LOC CRM.

10.9.1 Site-specific Informed Consent Forms: English Version

The protocol will include sample informed consent forms as appendices. Site staff will adapt the sample informed consent forms appended to the protocol to reflect local procedures and IRB/EC requirements, site-specific information (e.g., amount of participant reimbursement in local currency), and local contact information. As outlined in the DAIDS Protocol Registration Manual, the site-specific informed consent forms must be labeled with the exact protocol number and title listed on the cover page of the protocol, the protocol version number, and protocol version date. Pages must be numbered 1 of x, 2 of x, 3 of x, etc., with “x” representing the total number of pages in the individual informed consent form. Version control conventions (e.g., labeling all forms with both the protocol version number and date and the informed consent form version number and date) must be implemented at each site to avoid confusion and inadvertent use of an outdated form. Each informed consent form also should be labeled (e.g., English Language Informed Consent; Back-translation of Local Language Screening Consent, etc.). Figure 10-1 presents examples of the recommended label format for all informed consent forms. Note that a site may elect to submit one version of the consent form to the IRB/EC first (e.g., English site-specific version), before finalizing the others (translation, back-translation) for submission; however, all versions must be provided to the IRBs/ECs.

Figure 10-1 Examples of Informed Consent Footers

Site-specific English consent

HPTN OXX Protocol Version 1.0 Dated 10 October 2015	page 1 of X English Language Enrollment Consent Informed Consent Version 1.0 Dated 12 March 2016
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Local Language Consent

HPTN OXX Consent Protocol Version 1.0 Dated 10 October 2015	page 1 of X Chinese Language Enrolment Informed Consent Version 1.0 Dated 12 March 2016
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Back-translation of Local Language Consent

HPTN OXX

page 1 of X Back translation of Chinese Enrollment

Consent

Protocol Version 1.0

Informed Consent Version 1.0

Dated 10 October 2015

Dated 12 March 2016

Site staff are allowed to add information to their site-specific informed consent forms in order to help explain study concepts to participants or to comply with IRB/EC requirements. However, if site staff delete or make any substantive change to the risk or alternative treatment information presented in the sample informed consent forms, written justification must be provided for the deletion or change. The justification must be approved by the site IRBs/ECs, and documentation of IRB/EC approval must be submitted for review and approval by the [DAIDS Protocol Registration Office](#) (PRO) at the RSC. Similarly, if non-US laws or regulations result in the deletion or substantive change to any of the required information in the sample forms, written justification must be submitted to the DAIDS PRO for review and approval. Refer to the [DAIDS Protocol Registration Policy and Procedure Manual](#) for further details.

Site staff may submit their locally adapted English informed consent forms to the LOC CRM before submission to all responsible IRBs/ECs and before the forms are translated and back-translated (if back-translations are required).

10.9.2 Site-specific Informed Consent Forms: Translations

Site staff will translate the informed consent forms into all applicable local languages (note that the DAIDS RSC will create Spanish translations of the sample informed consent if requested by the LOC, but cannot do so for other languages) and, if applicable, arrange for an independent back-translation of each informed consent form. Back-translations are *NOT* required if a clinical research site (CRS) has an English site-specific informed consent.

If informed consent discussions will only be conducted in Spanish, site-specific Spanish language informed consent forms must be submitted to the PRO. No back-translations are required by DAIDS.

Note: CRSs are required to complete the [DAIDS Protocol Registration Translation Confirmation Document](#) (which can be found on the [RSC website](#)) for any protocol registration documents in Spanish.

If informed consent discussions will be conducted in English and another local language, including Spanish, the site-specific English and local language informed consent forms must be submitted to the PRO. No back-translations are required by DAIDS.

If informed consent discussions will be conducted only in a local language other than English or Spanish, site-specific local language informed consent forms must be submitted to the PRO. Back-translations of the site-specific local language informed consent forms (into English) also must be submitted to the PRO.

10.9.3 Submission to IRBs/ECs

Site staff will submit the protocol, site-specific informed consent forms, and other required documents (see Section 8.4) to all responsible IRBs/ECs. The cover letter provided to the IRBs/ECs with the required documents should include:

- DAIDS ES and/or Network protocol ID number
- Full protocol title

- Protocol version number from the final version of the protocol approved by DAIDS and/or the final version date of the protocol document approved by DAIDS
- List (title and date) of all documents submitted, including informed consent forms

Note: For sites with multiple responsible IRBs/ECs, it is likely that all IRBs/ECs will provide comments on the submitted study documents. It is the responsibility of the IoR to incorporate all such comments into a single final version of the study informed consent forms and obtain approval of this final version from all responsible IRBs/ECs. This may require multiple submissions to the responsible IRBs/ECs.

10.9.4 Obtain IRBs/ECs Approval Documentation

In order to link the IRB/EC approval letter(s) to the current DAIDS-approved version of the protocol, documentation from each IRB/EC of approval must reference the following:

- DAIDS ES and/or Network protocol ID number
- Full protocol title
- Protocol version number and/or date
- The approved informed consent forms, version number and date
- Risk/benefit category if research involves pregnant women, children or adolescents (see Section 8.5.6 for more information)
- Effective date of IRB/EC approval
- Signature of the IRB/EC Chair or designee
- Title of the person signing for the IRB/EC

It is recommended, but not required, that the expiration date of the approval also be included. If the approval documentation is provided in a language other than English, the document must also be translated into English.

10.10 Site-specific Protocol Registration

After obtaining approval from all responsible IRBs/ECs, HPTN study sites must complete protocol registration procedures with the DAIDS PRO. Complete details of the site-specific protocol registration are included in the DAIDS Protocol Registration Manual. Protocol registration is completed for each HPTN study on a site-by-site basis. The registration submission is done by the site directly to the PRO via the [DAIDS Protocol Registration System](#) (DPRS). The purpose of these procedures is for DAIDS to confirm regulatory compliance and completeness of site informed consent forms and IRB/EC approval documentation prior to study initiation. If a site encounters problems when submitting protocol registration materials through the DPRS, a CRS can submit protocol registration materials via email to the DAIDS Electronic Protocol Registration (EPR) mailbox at EPR@tech-res.com. The DAIDS Protocol Registration Checklist must accompany EVERY submission made to the DAIDS PRO through the EPR mailbox.

Upon obtaining all required IRB/EC approvals, site staff will submit the following documents to the PRO:

- A copy of the signed and dated [FDA Form 1572](#) or [DAIDS Investigator of Record Form](#) (the original must remain at the site)
- Signed and dated current CV of the IoR, in English (current within two years)
- Documentation of approval from all relevant IRBs/ECs and RE, if applicable, of the study protocol, informed consent forms, and other required material such as recruitment material. This documentation must reference the protocol number, title, version number, and date as it appears on the cover page of the protocol. If the approval documentation provided by the IRB/EC is in a language other than

English, both the non-English version and a translation into English must be submitted

- Copy of the approved site-specific informed consent forms(English and any local language); the approved informed consent forms must include the protocol number, title, version number, and date as they appear on the cover page of the protocol
- Back-translations of the local language site-specific informed consent forms (if applicable) See Figure 10-1
- A local language [DAIDS Protocol Registration Translation Confirmation Document](#). Only one Translation Confirmation Document that attests to the accuracy of the translation of each language for all of the protocol registration documents is required with each protocol registration submission

PRO staff will review all materials including a careful review of the site-specific informed consent document(s) if applicable (see Section 10.2.3). Sites will receive an Initial Registration Notification from the PRO that indicates whether or not the registration was completed successfully. The site must place a copy of all final protocol registration notifications from the PRO in the site's regulatory files.

PRO staff try to complete their reviews of submitted materials within 10 working days of receipt; however, more time may be required if there are multiple informed consent forms to be reviewed. If modifications to the informed consent forms are required, the site will need to address these and submit revisions to their IRB/EC for approval. The site will provide any further documentation or resubmissions to the PRO.

10.11 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* provided to HPTN study investigators and pharmacists by the DAIDS PAB. All sites conducting studies with drugs or other investigational 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 return. The manual also details the responsibilities of the Pharmacist of Record. The pharmacist at each CRS 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 SSP manual and/or in a separate study-specific pharmacy procedures document developed by the DAIDS PAB in conjunction with the LOC and other team members as necessary.

Questions regarding the management of study products should be directed to the DAIDS PAB protocol pharmacist.

10.12 Pharmacy Establishment Plans

A Pharmacy Establishment Plan is required for each site conducting an HPTN study involving investigational 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 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 DAIDS PAB will provide an initial response to the Pharmacist of Record within 10 to 12 working days; revisions and review will continue until PAB has approved the Plan.

The Pharmacist of Record is encouraged to work with study investigators and other local staff members to complete the DAIDS Standard Pharmacy Establishment Plan. For sites conducting multiple studies using different types of products with different storage and dispensing requirements (e.g., topical microbicides and systemic antiretrovirals), DAIDS PAB may require that a separate Pharmacy Establishment Plan be completed for each study.

Questions regarding the completion and review of Pharmacy Establishment Plans should be directed to the DAIDS PAB.

10.13 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, 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 HTPN LOC, LC and/or SDMC.

To avoid repetitive cycles of translation, translations are completed after the English versions are finalized. Translated informed consent forms and CRFs must be back-translated into English by a translator not involved in the original translation, as described in Section 10.5. Other materials also may require back-translations at the discretion of the Protocol Chair(s), statistician, LC representative, LOC CRM, or SDMC PM.

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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 must complete Human Subjects Protection (HSP) training (Section 11.1) as well as Good Clinical Practice (GCP) training (Section 11.2). 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 Program Officer and/or other designated DAIDS staff upon request. The DAIDS Policy: Requirements for Human Subjects Protections (HSP) and Good Clinical Practice (GCP) Training for Clinical Research Site Personnel gives further detail
- 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 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 continuing training for current staff (Section 11.5)

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	All key CTU/CRS staff (refer to DAIDS SOP)	Prior to awards being made for clinical research and every three years thereafter	<ul style="list-style-type: none"> • DAIDS-sponsored HSP training sessions • Online training course provided by HIV/AIDS Network Coordination (HANC) • Other online training programs e.g., NIH GCP learning center; online university-based training modules • Commercial training programs
GCP and FDA training requirements	All key CTU/CRS staff (refer to DAIDS SOP)	Prior to study initiation and every three years thereafter	<ul style="list-style-type: none"> • DAIDS-sponsored GCP training session • Online training course provided by HANC • Online training course

HPTN Training Requirements			
Training	Required Personnel	Timing/Frequency	Sources for Training
			provided by NIAID <ul style="list-style-type: none"> 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 substances 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 a 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	<ul style="list-style-type: none"> GCLP courses provided by the DAIDS contractor (at annual and/or regional meetings) or online Courses available from private training companies NOTE: these may not cover the appropriate DAIDS related regulations
Study-specific training	Applicable CTU/CRS study staff	Prior to initiation of study and for new staff within three months of joining the study staff	<ul style="list-style-type: none"> Leadership and Operations Center (LOC) Clinical Research Manager (CRM), Statistical and Data Management Center (SDMC) Project Manager (PM), HPTN Laboratory Center (LC)

HPTN Training Requirements			
Training	Required Personnel	Timing/Frequency	Sources for Training
			representative <ul style="list-style-type: none"> • IoR for new staff

11.1 Human Subjects Protection Training

All key personnel must receive HSP training prior to awards being made for clinical research and every three years thereafter. New clinical research site personnel (hired after study initiation) must receive HSP training within 90 days of assignment to the study project or prior to functioning without direct supervision.

The [National Institutes of Health](#) (NIH) provides an online education module on the protection of human subjects, [Protecting Human Research Participants](#), which is specifically designed for extramural researchers. Completion of this module fulfills the HSP training requirement. The HPTN may also provide training at annual meetings to fulfill this requirement. In addition, many universities and research institutions provide training which, when documented, fulfills this requirement.

11.2 Good Clinical Practice Training

All key personnel must receive GCP training that meets [International Conference on Harmonisation \(ICH\) E6](#) standards prior to study initiation and every three years thereafter. New clinical research site personnel (hired after study initiation) must receive GCP training within 90 days of assignment to the study project or prior to functioning without direct supervision. One course that may be completed is located online at [NIH GCP learning center](#).

Training of all HPTN site study staff is encouraged and facilitated through the provision of onsite GCP training to the extent possible. The Clinical Site Monitor provides GCP training to site study staff at the direction of DAIDS. Other opportunities, such as special GCP training sessions at annual meetings or at regional workshops, may also be offered. 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 key laboratory personnel receive GCLP training prior to involvement in a HPTN study. 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. FSTRF may also provide refresher training at the regional DAIDS training sessions. 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 13.7.2 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 for 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://www.dangerousgoods.com/profile.htm>

<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>

Laboratory Related Issues

Relevant HPTN laboratory issues and developments may be discussed at the annual meetings.

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, and LC collaborate with the 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.

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 must be maintained in each site's Essential Documents files.

Responsibilities for HPTN Study-Specific Training	
Task	Lead Group/Individual
Scheduling training	LOC CRM, LC representatives, SDMC PM, site investigator
Arranging logistics	LOC CRM, SDMC PM, LC, designated site study staff member
Developing the agenda	LOC CRM, SDMC PM, LC representative, site investigator and site study staff members
Compiling, producing, and providing training materials	LOC CRM, SDMC PM, LC representative, site investigator and designated staff
Arranging for translation of study and training materials and activities, as needed	Site investigator and designated site staff
Arranging for standardized clinical training (if applicable)	LOC CRM with site investigator
Conducting training	LOC CRM, SDMC PM, LC representative or designee, site investigator, designated site study staff members, and others as appropriate such as clinical experts
Document participation	Designated site staff
Maintaining training documentation	Designated site staff members

11.4.1 Scheduling Study-Specific Site Training

Scheduled study-specific training should be coordinated between LOC, SDMC, LC, and IoR or designee at each site. Training is conducted as closely as possible to the actual study start date at each site. Specified study specific site activation requirements should be met (or be close to completion) prior to conducting training of a site (see the table in Section 11.4.2).

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 will:

- 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, case report forms (CRFs), training materials, other study implementation materials, 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

Guidelines for Scheduling HPTN Study-Specific Training (based on Study Site Activation Requirements)	
To be completed prior to scheduling study-specific training:	
1	Current Federal Wide Assurance number in place for the study site institution(s)
2	Completion of US FDA 30-day review period/safe to proceed notice (if applicable)
3	Local regulatory authority approval of the study protocol (if applicable)
4	Signed Clinical Trials Agreement (CTA) (if applicable)
5	Hiring of adequate staff prior to training (as determined by CRM)
6	Completion of HSP training for all key site personnel
7	Completion of GCP training by all key site personnel
8	Pharmacy Establishment Plan and approval from DAIDS Pharmacy Affairs Branch (PAB) (if applicable) <ul style="list-style-type: none"> • Well-developed draft SOP for product management and accountability • Pharmacist training as deemed required by PAB and team • Draft plan or SOP for specific requirements for particular study agent • Draft plan for regimens and administration • Draft product prescriptions
9	All import approvals for study products (if applicable)
10	All export approvals for study products, (if applicable)
11	SDMC confirmation of adequate preparation for training based on the following: <ul style="list-style-type: none"> • Installation of required data transfer equipment, including testing of the system

Guidelines for Scheduling HPTN Study-Specific Training (based on Study Site Activation Requirements)	
	<ul style="list-style-type: none"> Well-developed draft SOP for data management, including data QA/QC procedures (final version required before activation, a well-developed draft must be available before training) Well-developed draft SOP for randomization, if applicable Availability of SDMC-provided materials (e.g., DataFax forms) onsite, well-developed draft translated versions, if required
12	<p>LC confirmation of adequate local laboratory readiness based on the following:</p> <ul style="list-style-type: none"> Proficiency in performing protocol-required tests Draft specimen management plan and draft chain of custody of study samples Well-developed QC/QA procedures Protocol-specified test validation Well-developed protocol-specified SOPs (final versions required before activation) Local laboratory backup arrangements LDMS set-up and internet connectivity to FSTRF IATA specimen shipping certification, if applicable GCLP training for appropriate laboratory staff Clinical Laboratory Improvement Amendments (CLIA) accreditation for US laboratories
13	Clinical Site Monitor study initiation visit
14	<p>Draft SOPs for the following:</p> <ul style="list-style-type: none"> Communication with responsible Institutional Review Board/Ethics Committee (IRB/EC) Source documentation Obtaining informed consent from potential study participants Participant eligibility determination Participant safety monitoring and Adverse Event (AE)/Serious Adverse Event (SAE) reporting (if applicable) Participant accrual plan (SOP or plan) Participant retention plan (SOP or plan) Communication with affiliated sub-sites, if applicable <p><i>Note: Final versions of these SOPs are required for site activation. Well-developed draft SOPs (as determined by the LOC CRM) must be in place prior to study-specific training. Finalization may occur shortly after study-specific training.</i></p>
15	Other documents and approvals as needed (site- and study-specific) including site-specific SOPs
16	<p>Study staff signature sheet, roster, and delegation of duties</p> <p><i>Must be reasonably complete; finalization may occur shortly after study-specific training.</i></p>
17	<p>Complete protocol registration package including:</p> <ul style="list-style-type: none"> US and in-country IRB/EC approvals of protocol and approved informed consent forms (local language and back-translation, where applicable) Signed FDA Form 1572 or DAIDS Investigator of Record Agreement Curriculum vitae of the IoR
18	<p>Study specific procedures (SSP) manual or draft SSP manual for use as a reference during training emailed to the site.</p> <p><i>Note: Each section of the SSP must be well-developed for this training version.</i></p>
19	<p>Resolution of action items identified during Clinical Site Monitor's site initiation visit</p> <p><i>Note: Acknowledgment from DAIDS of resolution of any significant action items identified during the Clinical Site Monitor's site initiation visit.</i></p>

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

- Work with LOC CRM/SDMC PM/LC to plan training and finalize agenda
- Work with LOC CRM to identify and meet translation and interpreter needs
- Work with SDMC PM 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

Onsite training conducted with representatives of the LOC, SDMC, and/or LC present as trainers is the standard for pre-study training. However, other alternatives (i.e., teleconferencing, video conferencing, working closely with the site staff to present the training) are possible in cases where circumstances (limited resources, travel difficulty, or experienced local staff) make onsite presence impractical. Regardless of the training strategies employed, the LOC, SDMC, and LC are responsible for providing the agenda (developed with input from study staff at 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	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 DataFax	SDMC	Relevant staff and supervisors
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 CRFs	LOC, SDMC, site designee	All staff
Interviewing and behavioral data collection strategies	SDMC or designee	Relevant staff and supervisors

Sample Agenda for HPTN Study-Specific Training		
Session/Module Topic	Suggested Presenter/Facilitator	Expected Site Staff Attendance (minimum)
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	LOC or designee (i.e., clinical expert)	IoR, the study coordinator, clinical staff (physicians, clinicians, nurses)
Investigational product management and accountability	LOC, site pharmacist or designee	Relevant staff and supervisors
Documenting and reporting AEs/SAEs	LOC, SDMC	All staff
Study-specific and/or local counseling procedures	LOC, site designee	All staff
Participant accrual and retention plans, participant-tracking database	Site designee, LOC	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
Research ethics/human subjects protection	LOC, Site PI/IoR or designee	All staff
CRF Tracking System	SDMC	Relevant staff and supervisors
Data Request and Transfer System	SDMC	Relevant staff and supervisors

During training, site study staff are expected to:

- Present training modules as agreed upon with the training team
 - Present local plans, SOPs, requirements, etc.
 - Attend all required training sessions
 - All site study staff are invited to and encouraged to attend all sessions/modules
 - All site study staff are expected to attend sessions designated for "all staff"
 - Site study staff members must attend relevant role-specific sessions
- Note: Failure of study staff to attend required training sessions typically will delay site-specific study activation, as additional training will be required before study activation can be approved. Therefore, every effort should be made to avoid absences from required sessions.*
- Fully engage in the training; ask questions; identify issues requiring additional clarification; identify best site-specific study implementation plans, materials, and tools

11.5 Continuing Study Training

LOC, SDMC, and LC staff will leave copies of all study-specific training materials at the site or post them on the study collaboration portal to be used to train study staff hired after the initial training.

It is the responsibility of the IoR to ensure 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 CRM and SDMC PM 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 will 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). Study staff will file such documents with other study implementation materials (e.g., in the SSP Manual) 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 them, as needed, and incorporating their content into day-to-day study operations. All issued content from the LOC, SDMC and the LC will be stored on 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). Methods such as videotapes of previous training sessions, or teleconference and/or web-based training may also be options for continuing training.

11.6 Research 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.

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12 STUDY IMPLEMENTATION

Once a site has completed study-specific training of site study staff and 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) Manual for each study (see Section 10.7).

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 and site-specific participant accrual targets are specified in HPTN protocols and/or SSP Manuals, based on the scientific objectives and statistical considerations of each study. 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. For multi-site studies, 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 Chair(s) and biostatistician will take the lead in making this determination with the protocol team and work with the LOC Clinical Research Manager (CRM) and Statistical and Data Management Center (SDMC) Project Manager (PM) to ensure that the determination is operationalized in the SSP Manual as needed. In studies for which enrollment targets are shifted across sites, sites will inform their Institutional Review Boards/Ethics Committees (IRBs/ECs) of increases or decreases in their enrollment targets in accordance with IRB/EC requirements. At a minimum, updates are provided to IRBs/ECs 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 Chair(s) and biostatistician should take the lead in making this determination with the protocol team, and work with the LOC CRM and SDMC PM to ensure that the determination is specified in the study protocol and operationalized in the SSP Manual as needed.

The LOC CRM and SDMC PM 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 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 that is applicable to all HPTN studies 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 manual. 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 treatment 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 IoR and designated staff to establish study-specific participant recruitment plans or Standard Operating Procedures (SOPs) for each HPTN study, and also plans to ensure that only persons who meet study eligibility criteria are enrolled in HPTN studies. See Table 10-1 for further guidance on the content of such SOPs.

The [Division of AIDS \(DAIDS\)](#) policy on essential documents ([Requirements for Essential Documents at Clinical Research Sites Conduction DAIDS Funded and/or Sponsored Clinical Trials](#)) 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 provide participating study sites with a list of participant identification numbers (commonly referred to as “PTIDs”) to be used for purposes of study data management. Detailed information on the 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 policy on essential documents specifies that participant initials be recorded on screening and enrollment logs, in addition to PTIDs. Per HPTN policy, in agreement with DAIDS, participant initials need not be recorded on screening and enrollment logs if doing so presents a potential threat to participant confidentiality. However, in such cases, a separate document must be available to document the link between a participant’s name and PTID.

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 Chair(s) and biostatistician, together with the LOC CRM and SDMC PM, are responsible for proactively addressing potential over-enrollment and under-enrollment issues. Accrual and over-enrollment/under-enrollment issues are discussed during routine protocol team conference calls, meetings, etc. Toward the end of the accrual period the Protocol Chair(s) and biostatistician take the lead in determining with the protocol team 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 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 and should seek approval from the HPTN EC and local regulatory authorities. The LOC CRM maintains documentation of this consultation in the LOC study implementation files.

Over-enrollment is not permitted as a means to “make up for” participant loss-to-follow-up, unless specifically directed by the SMC, EC or the DAIDS 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 Follow-up Visits

For each HPTN study, the expected duration of participant follow-up, as well as the number and type of follow-up study visits or contacts that are scheduled to take place during the course of the study, are specified in the study protocol. For each protocol-specified follow-up visit, a target date for when the visit should be conducted is also defined in the SSP Manual.

In addition to specifying target visit dates, the SSP Manuals also specify allowable visit “windows” for certain follow-up visits.

Interim visits are those that are not expected per protocol and are in addition to regular study visits. Interim visits or contacts may take place for a variety of reasons, e.g., a participant may be sick, need additional study product, additional laboratory tests, etc. The handling of interim visits is specified in each SSP Manual.

12.1.5 Participant Transfer between HPTN Research Sites

Participant transfer between HPTN research sites participating in the same study is allowed in some, but not all, HPTN studies. Transfer procedures, including the handling of study product-related documentation for each study, will be detailed in the SSP Manual. The study coordinators at both the originating research site and the receiving site must coordinate the participant transfer to ensure that all transfer procedures are followed and documented.

12.1.6 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 investigational 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 investigational product or intervention.

In all studies, protocols and SSP Manuals will specify requirements for monitoring medical and/or social harms to participants and will delineate when participants should be terminated for medical or social harms. Study staff will follow these requirements to monitor and respond to participant safety issues.

In all cases, prior to terminating a participant from an HPTN study, the IoR will seek approval of members of the protocol team designated in the study protocol; at a minimum, the Protocol Chair, DAIDS Medical Officer, LOC CRM and protocol statistician must be consulted. 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.

12.1.7 Participant Unblinding

12.1.7.1 Unblinding of Individual Participants during the Conduct of a Blinded Clinical Trial

Whether unblinding of individual participants is allowed during the conduct of a clinical trial must be stated in the protocol. In general, unblinding of participants during conduct of a clinical trial is not allowed unless there are compelling medical or safety reasons to do so, e.g., knowledge of the blinded information is necessary for treatment of severe adverse events.

If participant unblinding is allowed during conduct of a clinical trial, the protocol must state procedures for obtaining permission to unblind.

If a participant is unblinded for medical reasons, if at all possible, the random assignment should be given by the SDMC directly to the participant's health care provider and should not be revealed to study site staff or other HPTN staff unless absolutely necessary.

If a participant has been unblinded to HPTN site staff, the participant should be encouraged to remain on study and if at all possible on study product unless medically contraindicated.

12.1.7.2 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 or that have been terminated before completion due to DSMB or sponsor decision may unblind participants after all participants have completed their final data collection visit and before database lock. This decision is the responsibility of the protocol team, in consultation with the DSMB when applicable.

The protocol team should 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) in order to determine the most appropriate method of unblinding participants and in developing participant letters or counseling materials. The protocol team 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, by participant and by study arm, for each site. The lists will be sent to the study site via secure courier or password protected electronic file.

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 policy: [Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials](#)*, the DAIDS SOP for Clinical Site Data Collection and Reporting and study specific SSPs.

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 policy: [Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Research](#).

12.2.1 Participant Research Records

The United States (US) Code of Federal Regulations (CFR) and [International Conference on Harmonisation \(ICH\) Good Clinical Practice \(GCP\) E6 guidance](#) 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 random assignment (if applicable)
- A record of the participant’s exposure to investigational 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 case report forms (CRFs) 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)

In addition to the above, the [DAIDS policy for 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 policy: [Requirements for Source Documentation in DAIDS Funded and/or Sponsored Trials](#). 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 of the following:

- Narrative chart notes
- Visit checklists or flow sheets
- Laboratory reports
- Medical records or clinic charts
- DataFax CRFs
- Randomization log or other documentation (when applicable)
- Investigational product dispensing and accountability records (when applicable)
- Other source documents and non-DataFax 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 DataFax and non-DataFax forms as source documents is provided below. Also provided below is information related to investigational 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 used as source documentation must document the PTID of the study participant to whom they pertain, 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.

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 PM, Laboratory Center (LC), and the sites. Study sites are allowed to develop site-specific versions of these checklists in order to best reflect local staffing plans, logistics, and procedures. 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 CRFs and non-DataFax Forms Provided by the SDMC

The CRFs developed for each HPTN study are designed for use with the DataFax data management system described in Section 12.3. Before the beginning of each protocol, the SDMC develops a CRF production plan with each site depending on their printing capabilities. For some studies, the SDMC also will provide non-DataFax forms to each participating site.

The SOP for source documentation requires that a site must document which CRFs, if any, will be used as source documents. 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, 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 CRF
- Recording a chart note stating the reason why an alternate source document was used

12.2.1.6 Laboratory Specimen Labels Provided by the SDMC

Blank label-stock and a computer program for printing labels, or in some circumstances pre-printed labels, may be provided by the SDMC. These labels include PTID and a space to

write the specimen collection date and visit code for the visit at which the specimen was collected. The labels are only intended to be used on original specimen “containers” (such as vacutainers, slides, etc.). If a specimen is to be stored, then the Laboratory Data Management System (LDMS) labeling system will be used to generate other labels once the information has been entered into the LDMS and the samples have been processed.

12.2.1.7 LDMS Specimen Tracking Sheets Provided by the SDMC

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 SDMC with the CRFs for the study, but sites may elect to use their own laboratory requisition forms instead.

12.2.1.8 Product Dispensing and Accountability Records

As indicated in Section 10.11, the receipt, dispensing, and final disposition of all investigational 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* as well as any supplemental instructions provided in the study protocol and/or SSP Manual.

12.2.1.9 Document Organization

All participant study records must be stored securely at the study site in accordance with the specifications of the study protocol and SSP Manual. See Section 8.9 for additional considerations related to participant confidentiality.

12.2.1.10 Record Retention Requirements

For studies under an Investigational New Drug Application (IND), investigators must retain study records for a period of at least two years following the date a marketing application is approved for the drug for the indication for which it is being investigated and for at least 3 years after the completion of research; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the United States [Food and Drug Administration](#) (FDA) is notified ([21 CFR 312.62](#)), or longer if needed to comply with local regulations. For studies not under an IND, investigators must retain study records for a minimum of three years, or longer if needed to comply with local regulations. The three-year time period begins when all of the following are completed:

- All research-related interventions or interactions with human subjects (e.g., when all subjects are off study)
- All protocol-required data collection and 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 Storage and Retention of Clinical Research Records](#). 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 [RSC website page for CRF management](#).

12.3 The DataFax System and CRFs

For HPTN studies for which the SDMC manages study data, CRFs are transmitted to the SDMC, and data are entered and cleaned using the DataFax data management system.

DataFax is a data management system that integrates fax and computer technologies for processing CRFs. The study site retains the original CRF hard copy and transmits an electronic image to the SDMC. All data transmissions are stored as electronic images at the SDMC.

Electronic transmission is accomplished by a standard fax machine via phone lines or via the Internet using an Internet-ready fax machine. The SDMC's Information Technology (IT) staff can work with each study site to determine the best method for their data transmission or assist with problem solving.

Study sites must transmit completed forms to the SDMC as soon as possible after completion (generally within 5 days after the participant's visit, with safety information such as adverse events (AEs) sent within 24-48 hours) and respond promptly to SDMC Quality control (QC) reports, clinical queries, and requests for clarifications and corrections. Site data management performance, including number of QC notes, the percentage of resolved QCs, and the time it takes the site to transmit the completed CRFs to the SDMC, is tracked by the SDMC on a regular basis and reported to the protocol team and other HPTN study oversight and leadership groups, as specified in the study reporting plan.

12.3.1 Processing of CRFs at the SDMC

Each DataFax CRF is identified by a barcode denoting the protocol number and type of form. Pages do not need to be faxed in sequence. DataFax processes images by separating a fax into individual pages, adjusting each page to correct for proper alignment and rotation, and identifying each page based on the barcode information in addition to key items such as PTID and visit code. DataFax stores each image of a CRF that has been received and tracks all versions of each CRF received, along with all associated QC notes.

DataFax uses Intelligent Character Recognition (ICR) to read data from checkboxes and numbers from numerical fields and enter it into the study database. The SDMC staff review each CRF at least twice, comparing the data entered by the ICR process with the actual data image and correcting any discrepancies. Data in specified text and comment fields are entered manually as appropriate.

Data fields requiring clarification or correction (e.g., missing data or out-of-range values) or clinical data on CRFs needing verification or clarification (e.g., a severity grading on an adverse event log) are flagged with QC notes that are included in QC reports regularly emailed to the Clinical Research Sites (CRSs) for review. Corrections or clarifications in response to QC notes are made on the original CRF and re-faxed to the SDMC. The QC reporting schedule is determined by the size and progress of the study and is documented in the protocol reporting plan (see Section 12.5).

12.3.2 CRF Distribution and Duplication

The SDMC will distribute CRFs to CRSs in a format that is determined by the SDMC PM with input from the study sites. The formats may be:

- Bulk CRFs: preprinted CRFs bundled by form or visit type
- Electronic CRFs: PDF versions of the CRFs are furnished to the site and the site is responsible for printing them

12.3.3 CRF Completion

Site staff are trained to enter data on the CRF correctly, usually during protocol-specific training. Form-specific instructions are, in most cases, printed on the back of each CRF.

12.3.3.1 Standard CRF Elements and Forms

All HPTN DataFax CRFs have been designed using standards and conventions developed by DataFax and the SDMC. The standard elements include: participant ID format, page numbers, visit codes, and staff initial/date fields. Instructions for study staff on correct completion of each of these CRF elements on DataFax CRFs are included in SSP Manuals.

Certain CRFs have been standardized within the HPTN to ensure that all required data is collected and to create as much consistency as possible between protocols. To date, the following CRFs are considered standard in the HPTN:

- Adverse Event
- Social Impact
- Select Components of Laboratory Results CRFs
- Concomitant Medications
- Pre-existing Conditions
- Pregnancy History and Report
- Pregnancy Outcome
- Missed Visit
- Participant Transfer
- Participant Receipt
- Termination

12.3.3.2 CRF Revisions

The need for revisions to study-specific CRFs during the conduct of a study is identified by the protocol team or SDMC. The SDMC is responsible for revising and reissuing CRFs. Revised CRFs are sent to the protocol team for approval, as appropriate, prior to printing and reissuing to study sites. Revised CRF pages are given a revision date and code. If IRB/EC approval is required for new or revised CRFs, the study site staff are responsible for seeking the approval and communicating it to the SDMC PM and LOC CRM. Once approval has been obtained, the site staff are further responsible for removing and destroying all previous versions and implementing new versions according to instructions provided by the SDMC.

12.3.3.3 Storing DataFax Forms

DataFax forms are designed for storage in a standard two- or three-ring binder with the holes punched down the left side of the form. They may also be placed in ordinary file folders.

Storage of blank CRF supplies should be done in an organized fashion, enabling a site to inventory current supply at any time during the course of a protocol.

12.3.3.4 CRF Transmission Maintenance

The SDMC IT staff are responsible for maintaining the CRF data transmission processes between the CRSs and the SDMC. Maintenance responsibilities include:

- Assisting CRSs with troubleshooting data transmission problems if they occur and developing alternate data transfer methods, if necessary

- Providing support and supplies, as appropriate, for the maintenance and operation of data transmission systems
- Maintaining a tracking system for the transmission of CRFs to the SDMC

12.4 Study Team Communications

After initial release of a study protocol and SSP Manual, 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
- *SSP Manual updates:* These updates are developed and issued as described in Section 10.7. Like the initial version of an SSP Manual, development of the updates is coordinated by the LOC CRM, and final versions are posted on the HPTN website.
- *Data Communiqués:* These documents are developed and issued by the SDMC PM to clarify issues related to study data collection. Final versions are distributed to all study sites for filing in the SSP Manual and are posted on the HPTN website. They are considered an official part of the SSP Manual
- *Laboratory Communiqués:* These documents are developed and issued by the LC representative to clarify issues related to laboratory procedure. Final versions are distributed to all study sites for filing in the SSP Manual and are posted on the HPTN website. 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)
- *Study implementation questions:* Site questions about study implementation should be directed to the LC, LOC CRM and the SDMC PM. 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 PM 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 update, 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 a standardized reporting and QC system for tracking study progress and site performance.

A study reporting plan is prepared by the SDMC PM in conjunction with the study statisticians and is reviewed by the protocol team prior to the start of the study. The reporting plan lists the types and frequencies of reports to be produced for a given protocol. The approved reporting plan is included in the study SSP Manual. Reports that may be included are:

- Enrollment and retention reports
- Adherence reports
- QC reports
- Clinical query reports
- Data management quality summary reports
- Laboratory performance reports
- SMC reports
- DSMB reports

12.5.1 Confidentiality of Study Data

The disclosure of study end points 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 Accrual Reports

To track accrual (i.e., recruitment, screening, and enrollment) in HPTN studies as closely as possible to “real time”, study site staff report relevant accrual information to the LOC CRM throughout the study accrual period. The LOC CRM will compile information received from each study site into a cross-site report and distribute the report to the protocol team.

Working with the Protocol Team Chair and SDMC, the LOC CRM determines the relevant accrual information to be reported and the frequency for site reporting and report distribution. In addition to using the report to assess accrual performance at all sites, the LOC CRM and SDMC PM will review the report to identify significant discrepancies between site- and SDMC-reported enrollment information, since such discrepancies may indicate data submission problems at the sites, data receipt or entry problems at the SDMC, or both. In general, SDMC-generated enrollment and retention reports will lag behind real-time accrual reports due to the time required to transmit and enter data into the study database.

12.5.3 Enrollment, Visit Completion, Loss to Follow-Up and Retention Reports

During the protocol accrual period, the SDMC routinely generates protocol-specific enrollment reports showing projected and actual participant enrollments. The SDMC also generates protocol-specific reports on participant visit completion, retention and loss to follow-up rates for each scheduled study visit. Details of these reports are included in the reporting plan included in the SSP Manual.

12.5.4 Clinical Management Committee

For each study with a biomedical intervention, a Clinical Management Committee (CMC) will be instituted, composed of appropriate protocol team clinicians (and external clinicians as appropriate), who would provide support to site clinicians regarding individual participant clinical management (toxicity management, clinical holds of study drug, study drug re-challenge, permanent discontinuations). No aggregate data is to be provided to this Committee and blinding will be maintained with regards to the individual participant discussion(s).

12.5.5 SDMC Clinical Query Reports

SDMC clinical safety staff review clinical data submitted on CRFs. Using the DataFax system, they attach a query to any data items that need verification or clarification from the CRS site clinician. On a regular basis outlined in each protocol's SSP, the SDMC clinical staff generate a clinical query report that is sent to the site's clinical staff on a regular basis. Site clinical staff review these reports and correct, verify, or clarify the items in question. These reports are considered to be of high priority.

12.5.6 QC Reports

On a regular basis as determined by the internal SDMC protocol operations team, the SDMC Data Coordinator sends protocol-specific DataFax QC reports to CRSs. The reports identify data items submitted on CRFs that are inconsistent, missing, contain out-of-range values, and/or are illegible. CRS data management staff members review the reports, correct or clarify the CRF items in question, and re-transmit the CRF to the SDMC. If flagged items are correct as shown on the CRF, the staff member should verify with a brief note on the CRF next to the item in question and re-transmit the CRF. If the site has questions about any flagged items that show up repeatedly on QC reports, they should contact the Data Coordinator and SDMC PM for further explanation of the QC.

The CRS data management staff should respond to QC reports as soon as possible, generally within 7 to 10 working days of receipt. To ensure that the SDMC has adequate time to resolve QC notes, revised CRF pages should be re-transmitted by CRS data management staff no less than five days prior to the next scheduled QC report.

12.5.7 Data Management Quality Summary Reports

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

- Total number of CRF pages faxed during the report period
- Total number of items identified for QC
- QC rate (the number of QC items per 100 CRF pages)
- Percentage of QCs resolved
- Mean number of days from the visit date to the date the CRF page was received at the SDMC

If the SDMC PM or LOC CRM is aware of any technical or site issues that have affected the information in this report (e.g., loss of Internet connectivity, electrical power loss to the site, or misunderstanding of documentation requirements), an explanation will be provided in the email message provided to the protocol team at the time the report is posted. If there are concerns about a site's data management quality, the SDMC PM will work with the site to help develop strategies for improving performance.

12.5.8 SMC Reports

The SMC reviews all protocols at a minimum of 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 (blinded if necessary) 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 retention
- Laboratory performance, specimen storage and quality assurance (QA) testing (with input from the LC)
- Data quality and timeliness
- Review of aggregate safety data as a closed review for all studies with a biomedical intervention. The SMC composition for these studies would include clinicians experienced in the review of safety data, who are not affiliated with the protocol team or HPTN. For studies not monitored by a DSMB, the SMC should be comprised of individuals who are non-study team members and who are not affiliated with the HPTN apart from the unblinded statistician. The SMC will review safety data only during a closed session with no study team or HPTN members or sponsors present.
- Endpoint summary

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.

12.5.9 Data and Safety Monitoring Board (DSMB) Reports

A DAIDS 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, blinded or unblinded. 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
- SMC review summary

Closed report (data reported by arm — blinded or unblinded):

- 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.

12.5.10 Modification of Study Recommended by DSMB

When the DSMB recommends modification to a study, this information will be immediately communicated to National Institute of Allergy and Infectious Diseases (NIAID) and 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.

12.5.11 Reporting of Protocol Deviations

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 sponsor (DAIDS), particularly those that might otherwise not be evident in the study data or reported otherwise. Reportable protocol deviations are defined by the HPTN as individual incidents, trends or omissions that result in:

- Significant added risk to the participant
- Non-adherence to significant protocol requirements
- Significant non-adherence to GCP

Examples of reportable protocol deviations are:

- Enrollment of an ineligible patient

- Informed consent not obtained prior to performing protocol-specified procedures
- Non-compliance with study randomization and blinding procedures
- Protocol-specified procedures not followed by site staff
- Breach of participant confidentiality
- A protocol-specified laboratory assay consistently not being performed (a single missed assay during one participant visit would not be considered a reportable protocol deviation)
- A site-specific laboratory assay is deliberately added to protocol requirements by the investigator to be conducted for all participants

Participant non-compliance with the study protocol, including treatment specifications, is not considered to be a reportable protocol deviation, but should be discussed by the protocol team.

After consultation with LOC, SDMC, and LC representatives, all deviations that meet the above criteria will be recorded on the Protocol Deviation case report form, submitted to DataFax and entered into the study database.

One Protocol Deviation CRF should be completed for each participant affected by the deviation. If more than 5 participants are involved in the same protocol deviation, or if the deviation does not involve specific participants, enter a special Participant ID number (PTID) as instructed on the Protocol Deviation CRF. If the deviation occurred over a period of time, the date the deviation first started and when it ended or if it is ongoing at the time this report is completed should be indicated on the form.

Full documentation of all protocol deviations for each study should be maintained at the site and reported as needed to the local IRB/EC. In addition to submitting the CRF to DataFax, it should also be scanned and 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 an investigational product, the DAIDS Protocol Pharmacist. 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.

12.6 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.

12.6.1 Release of Data during the Conduct of a Study

No data on study participants beyond baseline data will be available to site, protocol team or any other body, other than to the DSMB and to the SMC based on criteria cited above in Sections 12.5.8 and 12.5.9. Exceptions to this rule require approval by the Leadership Group/Executive Committee and/or the DSMB, as appropriate.

Site-specific data should only be shared with those responsible for monitoring the safety or conduct of the trial (DSMB and/or SMC). Publication or presentation of site-specific data during the trial is not approved under the HPTN Publications Policy (Section 21) and should not occur unless authorized by the HPTN Leadership group and/or Executive Committee. It is the responsibility of the site Principal Investigator (PI) and the IoR to ensure that inappropriate dissemination or analysis of data does not occur.

Return of data to the sites by the SDMC after the completion of the study is achieved by making files available to the site where the site's individual participant identified data are listed in a computer-readable format. In some cases, sites may directly access their own site CRF data using protected data return systems developed by the SDMC.

12.6.1.1 Early Safety Trials

In Phase I and Phase IIa trials in which the primary objective is to provide an early assessment of participant safety, most data submitted from a site can be made available to the site by the SDMC. The following data will not be made available to the site:

- 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., sent directly to the SDMC from the LC or other central laboratory)
- For blinded trials, the participant's random assignment.

12.6.1.2 Clinical Efficacy Trials

In Phase IIb and III trials, the primary objective is typically to extend insights about safety and to assess effects on clinical efficacy endpoints or on surrogates relating to biologic or behavioral plausibility of an intervention. In such trials, most data collected from the participants prior to randomization can be made available to the site during the trial by the SDMC. In general, data collected post-randomization is not made available. The following data are almost never available:

- Data that constitute primary or secondary endpoints
- PTID identified data from Computer-Assisted Self-Interviews (ACASI or CASI)
- Coding (e.g., by MedDRA) of AEs
- Laboratory data sent directly to the SDMC from the LC or a central laboratory
- For blinded trials, the participant's random assignment

12.6.1.3 Other Types of Studies

In "non-comparative" cohort, vanguard, demonstration projects and studies with retrospective data collection (e.g., case-control), all data submitted to the SDMC can be made available to the sites during the conduct of the study with the exception of:

- Coding (e.g., by MedDRA) of AEs
- PTID identified data from Computer-Assisted Self-Interviews (ACASI or CASI)
- Laboratory data sent directly to the SDMC from the LC or a central laboratory

12.6.2 Release of Data after Completion of a Study

12.6.2.1 Final Release of Site-specific Data to Site Investigators After the Completion of the Study

Final site-specific study data can be requested by the site investigators once the database is cleaned and locked and all intended manuscripts reporting primary results of the protocol objectives have been approved by the Manuscript Review Committee (MRC) for publication. The Protocol Chair will communicate to the SDMC, LC and HPTN PI the protocol team's decision that the team has completed all intended publication of protocol objectives, and request that the site-specific data may be released to site investigators if requested. All manuscripts based on HPTN study data, with the exception of Public Use datasets, must be reviewed by the MRC (see Section 21). The HPTN LC will inform the MRC of laboratory-related publications that do not report primary or secondary protocol results. The SDMC will not check or validate the accuracy of data summaries and analysis computations completed outside the SDMC.

12.6.2.2 Final Release of Data to HPTN Investigators after the Completion of the Trial

The complete study database can be released to all HPTN investigators once the manuscripts reporting the results of the protocol objectives have been approved by the MRC for publication. The Protocol Chair will communicate to the SDMC and HPTN PI the study team decision that the team has completed all intended publication of protocol objectives, and may request that the data be released to all Network investigators. The HPTN LC must approve the decision to lock data sets that include laboratory results, and must approve the final release of data sets that include laboratory data. Data may be released to HPTN investigators within one year of this decision, providing the SDMC has completed the procedures required to lock the dataset. The study database must be locked prior to release, and unless otherwise requested, the datasets will be de-identified. All manuscripts based on HPTN study data, with the exception of Public Use datasets (see Section 21), must be reviewed by the MRC. The HPTN LC will inform the MRC of laboratory-related publications that do not report primary or secondary protocol results. The SDMC will not check or validate the accuracy of data summaries and analysis computations completed outside the SDMC.

12.6.3 Limited Release of Data to Non-HPTN Investigators

For pre-specified purposes, e.g., ancillary studies involving data external to the HPTN, 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 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 protocol statistician.
- Release of baseline data after completion of enrollment requires only approval of the Protocol Chair(s), LC PI, and the protocol statistician(s).
- 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.

12.6.4 Release of Data from a Study Conducted Under an IND

The Clinical Trials Agreement (CTA) governs the release of data to the manufacturer. The guidelines in this policy will hold for IND studies unless otherwise specified by the CTA. Data cannot be released unless it is in agreement with the terms of the CTA.

12.6.5 Public Use Datasets

Federal research sponsors often require that data be made available to the public in the form of "Public Use" datasets that have been prepared by the SDMC for wide scale dissemination. Data from HPTN studies may be released as a Public Use dataset after all analyses and publications of study results by the protocol team are considered complete by the protocol team and public release is approved by the Protocol Chair(s), the relevant Scientific Committee, the HPTN Executive Committee and NIH as the study sponsor. See Section 21 regarding publications based on an HPTN study Public Use data set.

12.6.6 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.

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13 LABORATORY COMPONENT

The following section applies to any site laboratory performing a study under the guidance of the HPTN Laboratory Center (LC). These laboratories will be referred to as Clinical Trials Unit (CTU)/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) Good Clinical Laboratory Practice (GCLP), the HPTN Quality Assessment and Quality Control Policies, and local Standard Operating Procedures (SOPs) for proper handling and storage of laboratory specimens. The CTU/CRS laboratories should also have in place a well-defined quality management plan that comprehensively covers specimen management issues including specimen collection/acquisition, tracking, processing, testing and storage, as well as back-up plans, assay validations, and procedures for quality assessment and quality control (QC).

The documents, [HPTN Quality Assessment](#) and [Quality Control Policies](#), outline specific requirements for laboratory Quality Assessment procedures and QC activities. These policies cover required Quality Assessment activities for the laboratory, including handling of reagents and conducting of assays. References for applicable United States (US) federal and non-US regulations are also included.

In addition to this Network-level set of SOPs, the Study Specific Procedures (SSP) Manual developed for each protocol contains a section on laboratory procedures that includes detailed instructions for the specific study.

13.1 HPTN Laboratory Program

13.1.1 HPTN Laboratory Quality Assessment Policy

The HPTN LC has developed and implemented a generic LC Quality Assessment policy that is the basis for a range of quality assurance (QA) activities carried out by the LC and CTU/CRS laboratories. This laboratory Quality Assessment policy applies to all CTU/CRS laboratories and CTUs and is designed to monitor, evaluate, and improve the quality of laboratory data, ensure the reliability of test data, and evaluate the competency of the site laboratory and appropriate clinical staff; this includes personnel (laboratory and clinical) involved in phlebotomy, collection of other samples and performing tests in site clinics/laboratories. The Principal Investigator (PI) of each CTU/CRS is responsible for assuring the implementation of the quality assessment policy at the laboratories and clinics that support their CTU/CRS.

The objectives of HPTN laboratory Quality Assessment Policy (and related programs) are to:

- Ensure that the quality assessment activities are comprehensive and coordinated, and that appropriate information is reviewed and reported.
- Establish, maintain, support, and document an ongoing Quality Assessment program that includes effective and systematic mechanisms for monitoring, collecting, and evaluating information about important aspects of laboratory procedures, in order to identify opportunities for improving data quality and participant care.
- Assist in improving care and identifying problems through the use of ongoing monitors by focusing on identification, assessment, correction, and follow-up of problems that affect laboratory performance.
- Implement corrective action when problems are identified.
- Follow-up on identified problems to assure improvement and resolution.

See [HPTN Laboratory Quality Assurance Policy Version 5.0, Quality Assessment Policy Version 3](#).

13.1.2 HPTN Laboratory Quality Control Policy

The HPTN policy on laboratory QC contributes to the laboratory Quality Assessment. The institution of appropriate QC practices will maximize the accuracy of reported results and will provide mechanisms for early identification of potential problems. As part of the laboratory Quality Assessment program, each site is expected to develop its own internal QC procedures. Required components of a QC program are included below in Section 13.2, and described more fully in [HPTN Laboratory Quality Control Policy Version 6.0](#).

CTU/CRS laboratories are evaluated by the HPTN LC and other monitoring groups to ensure that they meet an established standard for data quality, participant care, and laboratory compliance. Key performance areas (listed in Section 13.2.1) are monitored through collection, recording, and investigation of data pertaining to the laboratory area; findings are evaluated to detect trends and overall compliance with the laboratory Quality Assessment program. When indicated, corrective action will be implemented and documented. Monitoring is on-going to assure appropriate action is taken and that those actions result in correction of any problems. In addition to complying with monitoring and oversight by the HPTN LC, DAIDS contractors, and the DAIDS Clinical Site Monitor, sites are required to develop and implement internal QC plans for laboratory procedures. Site-specific Quality Assessment/QC procedures are a requirement for site activation for HPTN protocols; these procedures may be adapted from the HPTN generic program with additional input from DAIDS contractor programs, or may be developed by the site. Documents related to the site's Quality Assessment/QC program must be submitted to the HPTN LC for review, comment, and approval. Key areas covered in the Quality Assessment Policy, which guide Quality Assessment/QC procedures at study sites, are described below.

13.2 HPTN Laboratory Quality Assessment and QC Program

13.2.1 CTU/CRS Laboratory Quality Assessment

The HPTN policy on laboratory quality assessment provides guidelines for components of a laboratory quality assessment program. Components are listed below with a fuller description of each item in [HPTN Laboratory Quality Assurance Policy Version 5.0, Quality Assessment Policy Version 3](#).

Key components of laboratory performance termed Quality Assessment Monitors are monitored to ensure consistency and accuracy of laboratory data. These include:

- Proficiency testing. Proficiency programs are used as an external check on the QC and Quality Assessment of a test system. Any deficiencies cited by any accrediting organization and/or DAIDS-sponsored program in which the laboratory participates must be reviewed by the laboratory supervisor and/or director and/or designee. An appropriate investigative report (IR) must be completed and submitted to the DAIDS contractor, and also to the Primary Network Laboratory (PNL) assigned to the CTU/CRS. It is possible that the HPTN LC may not be the PNL.
- Specimen management. Specimens sent to the laboratory are monitored to determine the effectiveness of the collection procedures outlined in the site-specific Specimen Management Plan and in the protocol-specific "chain of custody" SOP, and also to ensure the integrity of the specimens received.
- Reporting of results. Results that are released to clinic or study staff are monitored to determine the effectiveness of the laboratory review, reporting system, and chain of custody.

- Technical delays. Technical delays are monitored to help evaluate the overall effectiveness of the laboratory. Any time there is a delay in reporting participant test results due to a technical problem in the laboratory, the problem must be documented; clinic and HPTN LC staff must be notified
- Performance improvement monitoring. The laboratory will identify potential problems and potential areas for improvement within the laboratory. Problems and potential problems will be monitored for frequency, possible causes, corrective action, and improvement. This should also include a review of safety incidents for staff and study participants, as well as any protocol deviations
- Staff development, training, and performance are assessed through:
 - Training documentation
 - Continuing education records
 - Annual competency assessments of employees that may include: blinded specimen analysis, proficiency testing (PT) sample analysis, written exams, observation of a technique, and safety review
- Quality control (see Section 13.2.2)
- Technical procedures are monitored for:
 - Maintenance of equipment
 - Procedure review
 - Storage of laboratory records
 - Result modification/amendment
 - Result reporting change
 - Reference intervals (age/gender appropriate)
 - Instrument validation
 - Assay validation
 - Assay comparisons

13.2.2 Laboratory QC Procedures

CTU/CRS laboratory QC activities are an integral part of the laboratory Quality Assessment program. CTU/CRS QC programs are divided into the main areas of focus listed below:

- Internal QC (testing of known materials)
- Parallel testing — validation of new controls and reagent lots as well as back-up instruments
- Blinded or split-sample testing
- Proficiency (external) testing programs
- QC monitoring — corrective action logs
- Quality assessment program feedback
- Preventative maintenance program
- Result comparisons with back-up instruments/methods

Further guidance on development of a site QC program incorporating these components is contained in [HPTN Laboratory Quality Control Program Version 6.0](#)

13.3 CTU/CRS Site Laboratory Quality Assessment/QC Plan

Each site that participates in HPTN protocols is expected to expand on the generic HPTN Laboratory Quality Assessment Policy and HPTN Laboratory Quality Control Policy implemented by the HPTN LC through the development of a site-specific laboratory Quality Assessment and QC plan. The HPTN Laboratory Quality Assessment policy, generic SOPs, and the HPTN Laboratory Quality Control Policy, all of which provide guidance on development of a site laboratory Quality Assessment and QC plan, are available on the HPTN LC website. The site-specific Quality Assessment/QC plan is designed to ensure

accurate, timely, and reliable test results by providing routine monitoring of the overall laboratory operation.

13.4 CTU/CRS Laboratory Performance Assessment

13.4.1 Non-US CTU/CRS Laboratories

DAIDS has arranged for existing laboratories outside of the US that participate in DAIDS-funded research to receive proficiency panels from the College of American Pathologists (CAP), OneWorld (Digital PT), the United Kingdom National External Quality Assessment Service (UK NEQAS) and other approved proficiency providers - through DAIDS-funded contractors/partners for protocol-related analytes. When a new CTU/CRS is included in a new HPTN protocol, the HPTN LC will work with the site and DAIDS contractors to ensure coverage of protocol analytes; costs related to participation in these PT programs may need to be paid for by the site, unless another arrangement can be made. Each year, the appropriate DAIDS contractor will re-enroll sites based on the assays that are or will be done at that specific site for DAIDS-sponsored protocols; the assay list will be prepared with input from the LC, the CTU/CRS, and other networks affiliated with the CTU/CRS. To facilitate communication between the LCs of different networks and CTUs/CRSs outside of the US, the leadership of five of the clinical trials networks has assigned a PNL to each non-US site. A list of the PNL assignments can be found on the HIV/AIDS Network Coordination HANC website (see Section 13.15 for URL). The appropriate DAIDS contractor and the LC personnel monitor the results of PT and communicate directly with the sites and the HPTN LC, as well as the PNL (if HPTN is not the PNL), regarding any issues or problems with the results, and work with the sites and the PNL to identify appropriate investigational responses and/or corrective actions.

DAIDS staff and/or DAIDS contractors may conduct laboratory-specific audit visits to determine laboratory readiness to participate in clinical trials. These audits are conducted annually at sites outside of the US, unless the laboratory has been certified by CAP and/or has been deemed in good standing by the DAIDS Clinical Laboratory Oversight Team (DCLOT). GCLP compliance will ensure that consistent, reproducible, auditable, and reliable laboratory results will be produced. DAIDS reserves the rights to conduct for cause or ad-hoc audits at any laboratory in the US that is participating in DAIDS-sponsored clinical trials. After an audit, an audit report will be distributed to the laboratory. The laboratory is responsible for working with DAIDS, their contractors, and the HPTN LC to resolve the audit report findings. Audit report findings must be adequately addressed by the CTU/CRS laboratory to maintain a satisfactory performance standard. The types of audits performed and process for resolution of audit findings are described GCLP Lab Audit Information document. Information regarding this process can be found on the HANC website.

In addition to the annual assessments described above, the CTU/CRS may undergo an annual visit (protocol training or protocol-related assessment visit) by HPTN LC staff. At these visits, the HPTN LC staff will provide the CTU/CRS with any recommendations or corrective actions deemed necessary, and will send this information to the appropriate site representatives, LOC, SDMC and the DAIDS HPTN LC program officer. If deemed necessary, trip reports will be written to document these actions. The HPTN LC routinely reports on site performance related to protocol testing to the HPTN Executive Committee (EC).

13.4.2 Non-affiliated External Laboratories Outside the U.S.

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. To ensure the safety of study

participants and the quality of data produced using back-up equipment and/or laboratories, the primary testing laboratory must be able to demonstrate acceptable equivalency between the primary and back-up instruments and/or laboratories for the relevant analyte(s) using tools such as laboratory audit reports, EQA history, instrument validations, regular specimen comparisons, and reference intervals.

The development and approval of a back-up plan that demonstrates equivalency between back-up instruments and/or laboratories is the responsibility of the director of the primary testing laboratory.

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

13.4.2.1 Specific Responsibilities of CTUs for Quality Assessment for External Laboratories

CTU/CRS that support the HPTN who wish to contract with outside laboratories for specimen testing must work with the HPTN LC and the external laboratories to ensure, as far as possible, the integrity of the results and correct handling of specimens. To fulfill this requirement, each CTU/CRS using an external laboratory must:

- Consult with HPTN LC staff to determine which assays being performed at external laboratories require inclusion of EQA, and to determine what materials should be used as controls and frequency of testing.
- Document inclusion of known controls with groups of samples submitted to external laboratories
- Maintain archival records that document the results of assays done on control samples and participant samples.
- Consult with HPTN LC staff immediately when results are unacceptable, to formulate a plan for assessing performance of the external laboratory in greater detail and to discuss possible plans for corrective action

13.4.3 Proficiency Testing

Each site will be enrolled in PT programs as appropriate for each HPTN protocol. Prior to protocol activation, the laboratory must be in good standing for the required EQA as determined by the HPTN Network Laboratory 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 passing scores. 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 that a panel has not been received, 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 will 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 may decide that they will determine if grading is applicable.
- When a site receives a score <80% for any analyte, the PNL will trigger a report to the site. The HPTN LC will work with the CTU/CRS lab to determine what actions should be taken with participant samples.
- For CTU/CRS laboratories that receive unsatisfactory results (failures) on two out of three consecutive panels or three panels in a row for the same analyte, the HPTN LC

will provide instructions to the laboratory on what additional measures 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) through the PNL. Determinations will be on a case by case basis, depending on the reason for the PT failure.

DAIDS contractors that provide PT support to CTU/CRS laboratories currently include:

- pSMILE (safety laboratory tests; each CTU/CRS will have a main contact)
- Virology Quality Assurance (VQA; HIV viral load, HIV DNA PCR, HIV genotyping)
- Immunology Quality Assurance (IQA; CD4/CD8, Viable PBMC)
- Pharmacology Quality Assurance (PQA)
- Microbicides Quality Assurance (MQA)

13.4.4 US CTU Laboratory Certification

CTU/CRS laboratories within the US that participate in HPTN protocols are required to have Clinical Laboratory Improvement Amendments (CLIA) certification and to provide documentation of this certification to the HPTN LC. Recertification is required every two years. Renewals must be provided to the HPTN LC.

HPTN LCs performing diagnostic assays for the HPTN protocols are required to be CLIA-certified. Other testing performed at the HPTN LC may not fall under the CLIA or GCLP guidelines because they fall under research or developmental testing.

13.5 HPTN LC Oversight of CTU/CRS Laboratories

HPTN LC staff conduct periodic site visits to assess the implementation of laboratory QC procedures, including proper maintenance of laboratory testing equipment and appropriate use of reagents as they relate to HPTN protocol testing. Each site is visited approximately annually by one of the QA/QC coordinators or Deputy Director, or more often if necessary. Annual visits for each HPTN protocol are not required. During these visits, laboratories are assessed using the [HPTN Laboratory Assessment Checklists](#), or if a quality assessment visit is more focused, a shorter report may be generated [Study Visit Assessment Report Template](#). The purpose and scope of the visit are discussed with site personnel prior to the visit. In addition, the HPTN LC may place an HPTN LC staff member onsite. HPTN LC staff work directly with the on-site QA/QC coordinator 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.

13.6 Laboratory Monitoring by the Clinical Site Monitor

DAIDS Clinical Site Monitors will periodically conduct a complete laboratory audit prior to or during the conduct of an HPTN protocol. Peripheral blood mononuclear cell (PBMC) specimens should NOT be disturbed during such laboratory audits.

13.7 Specimen Handling and Processing

Each CTU/CRS laboratory should have documented procedures for handling and processing of specimens to be used in DAIDS-sponsored clinical trials. In addition, each laboratory is required to utilize the Laboratory Data Management System (LDMS) for collection, testing (specific to HIV RNA), storage, and labeling of certain biological samples identified by the HPTN LC for each HPTN protocol, as described below.

13.7.1 Laboratory Data Management System

Each CTU/CRS is required to utilize the LDMS. LDMS training may be provided at annual meetings, regional meetings, at the Frontier Science and Technology Research Foundation (FSTRF), or onsite. 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 their LDMS system, including hardware and software upgrades. HPTN LC staff will provide LDMS codes for each protocol so that specimens are entered correctly into the system. Additional details are included in the SSP Manual for each HPTN protocol and on the FSTRF website.

All sites 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.

On a periodic basis (at a minimum, monthly), the SDMC will send each CTU/CRS laboratory that is storing samples for an HPTN protocol a missing sample report. This report is an Excel file that lists samples that were indicated as collected on the Case Report Form (CRF) and are missing from the LDMS. This could include samples that are logged in incorrectly, not stored, or not received by the laboratory.

13.7.2 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 on-site, 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. Study staff who transport, ship or receive infectious substances and diagnostic samples must receive adequate and appropriate training to ensure compliance with guidelines and regulations. Documentation of the appropriate training must be filed onsite, and a copy must be sent to the HANC.

IATA regulates the safe transportation of dangerous goods by air in accordance with the legal requirements of the International Civil Aviation Organization. IATA requires training and certification for those involved with shipping Class 6.2 infectious substances and diagnostic specimens. IATA regulations define infectious substances, cultures and stocks, biologic products, and diagnostic specimens and specify the requirements for the handling and shipping of each. Diagnostic specimens and infectious substances are further separated into risk groups based on the organism that is known or suspected to be present within the sample.

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. Specimens sent from the sites to other locations within the US are not covered under this importation permit.

Useful websites with information concerning specimen handling and shipment are provided in Section 13.15

13.8 Laboratory-related Site-specific Protocol Activation Requirements

A specific set of protocol activation requirements will be created for each HPTN protocol. Requirements may vary between studies and sites. Examples of these requirements are:

- HPTN LC approval of PT for protocol-related testing
- Quality Assessment/QC procedures at the site
- Site SOP for establishing/maintaining reference intervals
- Appropriate validation for protocol-specified tests
- Appropriate laboratory assay SOPs
- Appropriate HIV algorithm validation
- Local laboratory back-up arrangements, if necessary
- IATA specimen shipping certification
- Site Specimen Management Plan for the appropriate collection, processing and handling of protocol-related samples, as well as "chain of custody" for samples used for primary study endpoints
- Laboratory manager curriculum vitae
- LDMS utilization, provided by FSTRF, including training documentation

The HPTN LC notifies the LOC Clinical Research Manager (CRM) for the study when the site's laboratory-related procedures, facilities, and staff are deemed ready for study activation. This HPTN LC approval constitutes local laboratory certification for CTU/CRS laboratories outside of the US. The HPTN LC verifies annually that the laboratories are meeting the necessary protocol-specified laboratory requirements for each protocol. Certification can be rescinded at any time for failure to maintain key systems or requirements, such as failure to appropriately use the LDMS.

Prior to protocol activation, each site is required to establish a Specimen Management Plan for local specimen handling and maintenance of "chain of custody" related to testing for primary endpoints. This plan must be approved by the HPTN LC. The plan should specify:

- How a sample is obtained
- How a sample is transported from the clinic to the laboratory
- What documentation accompanies each sample
- How a sample's departure from one place and arrival at another is documented
- The temperature at which a sample is transported
- Any time requirements for the delivery of the sample
- How a sample is handled and processed once it reaches the laboratory
- How discrepancies and rejected samples are handled

Specific information that must accompany each specimen includes the participant identification number (PTID), collection date, and visit code. Specimen labels provided by the SDMC include this key information. Accountability for the samples must be maintained with requirements for signatures of each individual who handles the specimen. The site SOP should also detail:

- How the results are returned from the laboratory to the clinic
- How problem samples are reported back to the clinic
- How critical values are handled
- How to dispose of samples that arrive in unsuitable or unusable condition

13.9 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.

13.10 Centralized Testing

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.

13.11 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 this study, as currently recommended by the CDC SOP for post-exposure follow-up.

13.12 QA Testing

The HPTN LC will develop a plan for each protocol to verify the HIV infection status of clinical trial participants. This will 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 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 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 seroconversion 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 screening (to explain viral loads that are low or undetectable).

The SDMC is responsible for:

- Notifying the HPTN LC when QA testing is due for a protocol, if this testing is planned on a specific schedule, or is triggered by specific milestones, such as completion of site enrollment
- Generating a list of PTIDs for QA testing, with associated specimen-collection dates
- Providing QA testing list to the HPTN LC in standard format
- 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 and the need for further testing
- Creating and distributing a report of discrepancies for External Advisory Committee (EAC) review, if necessary

The HPTN LC is responsible for:

- Working with sites to ship samples to LC for retesting
- Conducting the QA testing
- Providing the SDMC with all QA test results
- Working with CTU/CRS laboratories to determine causes of any discrepancies
- Working with the SDMC to collate necessary material for an EAC, if necessary

13.13 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. Testing algorithms will be designed in consultation with the study team and will be described in the 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.

The HPTN LC performs QA and confirmatory HIV testing for HPTN studies as specified in HPTN protocol documents and/or the SSP Manual. 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 PI and HPTN LC QA/QC Core Director. 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.

13.14 External Advisory Committee (EAC)

In some cases, the HPTN LC may choose to convene a protocol-specific External Advisory Committee (EAC) to review cases where there are incomplete HIV test data (e.g., due to missed testing or loss-to-follow up at study sites) or where results from 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

The EAC is typically composed of the HPTN LC PI, the HPTN LC QA/QC Core Director and three or four additional virologists who are not HPTN LC investigators and have experience and expertise in HIV testing. For each study, the external EAC members will have no scientific affiliation with the study (e.g., protocol team members may not serve as committee members). Protocol team members including DAIDS Prevention Sciences Program (PSP) representatives and study operations staff from the LOC, SDMC, and LC may take part in EAC meetings as non-voting discussants or observers. Decisions of the EAC are considered final for purposes of primary analyses of HIV endpoints.

If an EAC is convened, the SDMC statistician for each study (or designee) will provide data reports to the EAC as needed to support review and decision-making. For blinded studies, data provided to the EAC will not include participants' treatment assignments.

It is not necessary or expected that an EAC will be convened for all HPTN protocols, or that an EAC will review all HIV endpoints for a specific protocol. If the HPTN LC deems that it is necessary to have the EAC review all HIV endpoint determinations for a specific protocol, the EAC will develop written "terms of reference" to guide their review and decision-making. The terms of reference will specify, for example, considerations related to deviations from protocol-specified testing algorithms and discordance between results obtained at the HPTN LC and the local laboratories. The terms of reference will also specify the membership of the EAC for the protocol, procedures for communication with the protocol team, and the format and frequency of EAC meetings. In these cases, terms of reference must be finalized for before undertaking any data reviews and decision-making for that protocol.

If an EAC is convened, designated staff from the SDMC will provide administrative support to the EAC. Ideally, the SDMC staff will arrange and convene EAC meetings and will document EAC decisions. It may be necessary to convene the meetings through email. SDMC statisticians will incorporate EAC decisions into HPTN study databases for purposes of HIV endpoint analyses.

13.15 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 required testing as mandated by the respective protocols. Each study should address short- and long-term storage of specimens before study initiation. At the completion of 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 PI(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 long-term specimens. 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 executive 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.

13.16 Referenced or Useful Web Links

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

Resources:

HIV/AIDS Network Coordination	https://www.hanc.info/Pages/default.aspx
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Specimen Shipping, Shipping Materials and Information:

CDC Shipping Regulations	http://www.cdc.gov/od/ohs/biosfty/shipregs.htm
Code of Federal Regulations	http://www.gpoaccess.gov/cfr/index.html
US Postal Service	http://www.usps.com
Saf-T-Pak	http://www.saftpak.com
CDC Office of Health and Safety - Biosafety	http://www.cdc.gov/biosafety/
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.dangerousgoods.com/profile.htm
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	http://www.phmsa.dot.gov/staticfiles/PHMSA/Hazmat/digipak/pdfs/presentation/Infectious_Substances(04_07).pdf

Risk Group Assessments:

Risk Group Classification for Infectious Agents	http://www.absa.org/riskgroups/index.html
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	http://www.aphis.usda.gov/wps/portal/footer/topicsofinterest/applyingforpermit

HIV Antibody Testing Algorithm:

HPTN Requirements, Frequently Asked Questions (FAQs)	http://www.hptn.org/hptn_structure/NetworkLab/HIVABTestQA.htm
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14 SAFETY CONSIDERATIONS

Ensuring participant safety is critical to all HPTN trials. Close cooperation between the study investigators, site staff, [Division of AIDS](#) (DAIDS) Medical Officers, Leadership and Operations Center (LOC) Clinical Research Manager (CRM), Statistical and Data Management Center (SDMC) Project Manager (PM), SDMC Clinical Affairs Safety Associate and other members of the study team is necessary to closely monitor participant safety and to respond to occurrences of toxicity or social harm in a timely manner.

The specific 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) Manual. 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.

The study protocol for biomedical 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 investigational in the 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 [Regulatory Support Center](#) (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 biomedical clinical trials 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 that are relevant to biomedical trials, 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) Data and Safety Monitoring Board (see Section 15.8). Safety

documents are usually distributed via email; however, some information, such as IBs, may be distributed to investigators and study coordinators in hard copy through express mail.

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.

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 Clinical and Laboratory Data Safety Review 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 data safety 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 DataFax case report forms (CRFs) to the SDMC as well as the reporting of AEs that meet the criteria for expedited reporting to the RSC.

The SDMC clinical affairs 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 affairs staff members apply AE coding and clinical data queries to data requiring confirmation, clarification, or follow-up. These queries are sent to the sites on a regular basis for resolution.

For studies with pause criteria or rules, SDMC clinical staff are also responsible for working with SDMC programmers to create computer programs that alert SDMC clinical staff when criteria for pausing the study are met and the protocol team must be notified. Pause criteria must be in specified in the study protocol.

14.2.2 Tier Two

Unless otherwise determined, a sub-group of the Protocol Team, including the Protocol Chair, DAIDS Medical Officer, site clinicians, and the SDMC Clinical Affairs Safety Associate will serve as members of the Clinical Management Committee (CMC). The CMC provides support to site clinicians regarding individual participant clinical management (toxicity management, clinical holds of study drug, study drug re-challenge, permanent discontinuations, etc.).

In addition, for trials with no DSMB oversight, the HPTN Study Monitoring Committee (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.

14.2.3 Tier 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 are considered to be social impacts. 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.

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15 STUDY OVERSIGHT

Study oversight within the HPTN takes place at a number of levels. 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. For each study, the Protocol Chair monitors performance across sites to identify emerging issues and address them within the protocol team. The HPTN also has established oversight procedures by 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). 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 and organizing and convening the Prevention Data and Safety Monitoring Board (DSMB) where applicable, DAIDS staff provide guidance and oversight to HPTN studies. DAIDS groups involved in study oversight include: the Prevention Sciences Program (PSP), Regulatory Affairs Branch (RAB), and Pharmaceutical Affairs Branch (PAB).

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, the 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 Monitor and noted in the monitor’s site visit report.

The requirements for CQMPs are detailed in the DAIDS policy [Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Sponsored Clinical Research Sites](#).

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 made by the DAIDS monitors, but are intended to identify systematic issues and address them. The following types of visits may be made throughout the course of the study:

- *Periodic Visits:* Conducted throughout course of the protocol
- *Close-out Visits:* Conducted after the last participant visit is completed
- *“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 or other reasons

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, or case report forms), as well as observe the performance of study procedures. Site staff are encouraged to share with 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 a 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 Conference on Harmonisation \(ICH\) Guidelines E6](#).

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

- The rights and well-being of human subjects are protected
- The reported trial data are attributable, legible, contemporaneous, original, accurate, and verifiable from source documents
- 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 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 the Clinical Site Monitor are to perform periodic onsite monitoring visits to all sites conducting HPTN clinical research and report findings by:

- 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 DAIDS–Enterprise System (ES) database (DAIDS-ES) to view the status of the Clinical Site Monitor’s report.

15.3.2 Onsite Clinical Monitoring Visits

DAIDS will determine the frequency of onsite 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 and/or PSP Program Officer representative, as well as the OCSO representative be present (in person or by teleconference) 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. A written summary of the debriefing will be transmitted by fax or email to the PSP/OCSO staff within two days of the debriefing.

PSP/OCSO staff may initiate follow-up discussions with the site based on this summary information.

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 CSM module within 20 working days of the visit. The system will notify all appropriate persons that the report is available. The Program Officer will review the report and enter any identified issues 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 DAIDS-ES (CSM module) and the DAIDS-ES 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 DAIDS-ES 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

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. Issues identified in site visit monitoring reports are brought to the protocol team during routine protocol team conference calls. 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 scientific committee (SC), working group (WG), or SMC for further deliberation and guidance.

15.5 Study Monitoring Committee (SMC) Oversight

The voting members of the SMC will include individuals independent of the study team, the HPTN leadership or NIH. The SMC is responsible for reviewing study data, with an emphasis on participant accrual, participant retention, protocol and intervention adherence, and other key performance indicators. In addition, for Phase I or II 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 will also monitor the rate of required endpoints for continued feasibility of the trial.

The SMC (voting members) is composed of representatives of the LOC, SDMC, and LC (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 via DataFax 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, such as screening numbers, from sites. The LOC queries the SMC voting 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. Other representatives from the protocol team and the NIH (SMC Observers) are invited to join the call at this time.

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 Executive Committee (EC) and any other appropriate HPTN organization(s) are informed of 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 protocol team may refer the issue to the EC.

At the discretion of the SDMC PI, 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 review, the SMC reviews the open portion of the DSMB report and rate of endpoints 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 DAIDS DSMB as appropriate. 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.

15.6 HPTN Leadership

The EC monitors HPTN studies with regard to protocol development, implementation, analysis, and reporting. The HPTN PIs receive the SMC open reports and summaries.

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.

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/Program 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 the interim and final reports. Protocols sponsored by a collaborating institution or research group (i.e., National Institute of Child Health and Human Development (NICHD), 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. The details for suspending enrollment at a particular site or study are in the OCSO SOP for [Temporary Suspension of Clinical Research Site Activities](#).

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. 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 12.5.9). 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 in person or via telephone the open session of the DSMB review to discuss study progress and respond to questions.

15.9 Data and Safety Monitoring Board Summary

The DSMB provides written summary of all reviews to DAIDS and NIAID. The written reports are communicated to the protocol team. The EC and any other appropriate HPTN organization(s) are informed of 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 DSMB, the protocol team may refer the issue to the EC.

A subset of the protocol team (i.e., Protocol Chair, Statistician, Medical Officer) will provide a written response to the DSMB written report as soon as possible.

15.9.1 DSMB Recommendations for Study Modification

Based on DSMB recommendations, NIAID may find it necessary to terminate 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

When the DSMB recommends modification to a study, this information will be immediately communicated by the study Protocol Chair to HPTN leadership. This leadership team includes:

- Network 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.

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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 the following minimum requirements prior to receiving Division of AIDS Site Approval (see [Office of Clinical Site Oversight](#) (OCSO) SOP entitled [Clinical Research Site Approval Process for Network Sites](#)). This approval is different from study specific site activation approval. As such, 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) and DAIDS staff to ensure Network and protocol-specific requirements are met. The OCSO Program Officer (PO) will: (1) communicate site approval requirements to the site; (2) identify issues; (3) facilitate issue resolution in order to efficiently complete the site approval process. Requirements and SOPs are reviewed and verified by OCSO (see the [OCSO SOP on Activation](#) and [OCSO requirements](#)).

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 Conference of Harmonisation \(ICH\) Good Clinical Practice E6 Guidelines](#) and United States [Food and Drug Administration](#) (US FDA) 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 also see DAIDS policy: [Requirements for Manual of Operational Procedures](#)).

SOPs describe and document a research site's approach to conducting research and serve to ensure standard, uniform performance of site- and study-related tasks. SOPs identify who is responsible for a task and describe actions to be conducted by responsible staff. SOPs also may serve as useful training tools for new staff. The same format should be used for all SOPs at a research site. In general, it is recommended that the SOP format include, at a minimum, the following elements:

- SOP number and title
- Purpose
- Scope (to whom the SOP applies)
- Staff responsibilities/roles
- Procedure listing/description
- Reference to relevant regulations and guidelines
- Version number and approval and effective date
- Revision history (when the SOP was revised and why)
- Approval signature(s)

Additional, optional elements that may be included in site SOPs include responsibilities, materials and equipment, and definitions.

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 are able to carry out the DAIDS research.

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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 completed [Ancillary Study Application](#) is assigned a number in the order that it was received (e.g., HPTN 074-01, HPTN 074-02, etc.) that relates the application to a primary HPTN study. The application provides 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, 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 Statistical and Data Management Center (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 via the [SDMC Resources Form](#). 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 HPTN LC 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 HPTN LC 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

If investigators are interested in obtaining stored specimens for an ancillary study, they must also submit an [Ancillary Study Application](#). Processes for review and approval of ancillary studies are described below.

If an ancillary study 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 funding is required for LC activities the [LC Resources Form](#) must be completed. Funding issues must be resolved before the ancillary study is approved. There may also be additional costs at the HPTN Leadership and Operations Center (LOC) and SDMC related to the study. If this is the case, those funding issues must be resolved before the ancillary study is approved. If an ancillary study is approved, non-HPTN investigators must also complete an HPTN [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 ([SDMC Resources Form](#), [LC Resources Form](#) and [LOC Resources Form](#)) and budgets are required to complete the proposed ancillary study. Examples of operational elements could include processing of samples or data, scheduling conference calls, case report form (CRF) development, protocol development, etc.

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

17.2 Ancillary Study Approval Process

The investigator proposing the ancillary study is responsible for ensuring that all necessary reviews and approvals are obtained and that all relevant HPTN and Division of AIDS (DAIDS) procedures are followed. All ancillary studies are subject to HPTN Network approval and, if applicable, DAIDS approval. 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](#).

17.3 Network Approval of Ancillary Studies

A summary of the Network approval process for ancillary studies includes approval by the following sequentially:

- Approval by the Protocol Chair in consultation with the Protocol Team
- Approval by the PIs of the HPTN LOC, LC, and SDMC
- Approval by the HPTN EC, as appropriate

17.3.1 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
- The protocol team, including protocol representatives of the Central Resources (SDMC, LC and LOC), and DAIDS Medical or Program Officer for the primary HPTN study.
- The PI of each study site to be involved in or affected by the ancillary study
- 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.

17.3.2 Central Resources (LOC, LC and SDMC) Approval

Once approval has been obtained by the Protocol Chair and Protocol Team, the proposing Investigator will email the ancillary study application form to the Central Resources leadership group at centralresourcesancillary@hptn.org. The PIs of the Central Resources, with input from the Central Resources liaisons working on the affiliated primary study, will evaluate the proposal, taking into account such considerations as the cost of the proposed ancillary study, the strength of the study design, the demands it would place on Central Resources, etc. The Central Resources leadership group will provide one of the following responses:

- Reject
- Return with comments for revision or clarification and the option to resubmit
- Approve
- Referral to the HPTN Executive Committee (EC) for further review

17.3.3 Executive Committee (EC) Approval

If referred by the Central Resources leadership group, the Ancillary Study Application will be reviewed for approval by the HPTN EC.

17.4 DAIDS Approval of Ancillary Studies

Ancillary studies may be subject to additional DAIDS 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. Pursuit of the DAIDS review steps may begin after Network approval as outlined above has been obtained.

- **DAIDS Prevention Science Review Committee (PSRC) Review:** Approval by the DAIDS Protocol Safety Review Committee (PSRC) may be needed depending on the nature and scope of the ancillary study. The DAIDS Medical Officer for the primary study will work with the 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.
- **Informed Consent:** Ancillary studies may or may not require separate informed consent depending 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 separate written informed consent is needed. 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. Once the RSC has approved the sample informed consent form, site-specific versions must be prepared including, where applicable, translation into the local language(s) and independent back-translation for submission to the IRBs/ECs. Further details of this process are provided in MOP Section 10.9.
- **Documentation of IRB/EC Approval or Exemption:** Documentation of submission to and opinion of all responsible IRBs/ECs must be submitted to the proposing Investigator or designee prior to ancillary study implementation, whether this be approval of the investigation or determination that the activity/study is exempt from IRB/EC review under 45 CFR 46. The IRBs/ECs of each individual institution where research is being conducted or from where the retrospective samples will be analyzed may need to be consulted. It is the responsibility of the principal investigator of the ancillary study to ensure all approvals or exemptions are documented.
- **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.

17.5 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 an appendix to the application. If HPTN funding 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.

17.6 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.

17.7 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.

17.8 Documentation of Ancillary Study Approval

Copies of all HPTN, regulatory, and IRB/EC approvals (if applicable) must be maintained on file by the study site and the lead Investigator or designee.

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18 CLINICAL RESEARCH SITE STUDY SPECIFIC CLOSE-OUT

The term “close-out” refers to procedures undertaken to fulfill administrative, regulatory, and human participant requirements after participant follow-up in an HPTN study has been completed at a Clinical Research Site (CRS). For the purposes of a [Division of AIDS \(DAIDS\)](#) Network, study close-out may be defined as the time 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 Responsibilities for CRS Study Specific Close-out

Study specific close-out 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 close-out.

To facilitate planning for CRS study specific close-out, the Statistical and Data Management Center (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 protocol team will begin planning for CRS study specific close-out prior to completion of participant follow-up at each participating study site. As part of this planning, the protocol team will:

- Provide input to the Leadership and Operations Center (LOC) Clinical Research Manager (CRM) regarding content of the study-specific close-out checklist
- If applicable, develop plans, procedures, and materials for unblinding the protocol team, study staff, and participants (see Section 12.1.7 for participant unblinding)
- Develop 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)
- Develop plans for data analysis, manuscript preparation, and publication, taking into account that the primary manuscript must be submitted within eight months of the last participant scheduled follow-up visit

In addition to taking part in the above-listed activities, designated protocol team members from the LOC, SDMC, Laboratory Center (LC), and DAIDS will facilitate planning for CRS study specific close-out as follows:

- The LOC CRM will develop a study specific closeout checklist
- The SDMC Protocol Statistician and Project Manager (PM) will develop a plan for final study data submission, cleaning, database lock and analysis. For information about publications, see Section 21
- The SDMC PM will provide technical assistance as needed to study sites wishing to access data maintained at the SDMC to fulfill IRB/EC study close-out reporting requirements
- If applicable, the SDMC PM will provide study sites with a listing of study participants who did not provide informed consent for post-study specimen storage and possible future research testing
- 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
- If applicable, the DAIDS Pharmaceutical Affairs Branch (PAB) Protocol Pharmacist will develop written instructions for final disposition of investigational study drugs/products and associated documentation
- As an HPTN study draws to a close, the SDMC staff will determine whether the number of outstanding quality control queries, particularly ones essential to analysis of protocol objectives, warrant a data quality control visit. When appropriate, the SDMC PM 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
- 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 close-out 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.

- 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 Storage and Retention of Clinical Research Records.

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 any labeling change for this licensed product and at least three years after the completion of research. 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 Storage and Retention of Clinical Research Records](#). 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 may be 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 PM will provide study sites with a listing of study participants who did not provide informed consent for post-study specimen storage and possible future research testing. Study staff must obtain permission from the LC before destroying specimens.

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19 NETWORK EVALUATION

The HPTN is committed to excellence in all aspects of its research as well as Network governance. The Performance Evaluation Committee (PEC) is charged with directing the internal Network evaluation. The evaluation documents the success of the Network and its components in meeting evaluation standards developed by the PEC.

The PEC is responsible for overseeing a continuous, comprehensive evaluation of the HPTN. This includes the Clinical Trials Units (CTUs) and Clinical Research Sites (CRSs) as well as other grantee organizations and entities that are also part of the HPTN—Leadership and Operations Center (LOC), Laboratory Center (LC), Statistical and Data Management Center (SDMC), and standing committees. Performance evaluation serves primarily to ensure that groups are contributing effectively to those protocols they have undertaken and to elicit closer scrutiny and corrective action where successful and timely completion of studies is in jeopardy. The goal of the evaluation is to provide data to assist in leadership decisions about changes necessary within the Network to improve overall functioning.

The PEC reviews evaluation reports and data, adjusts performance measures as needed, and reports evaluation findings to the Executive Committee (EC) for review and action.

Membership

The PEC Chair is appointed by the EC and reports the results of the Network Performance Evaluation at an in-person meeting. The membership of the PEC should include the PEC Chair, Evaluation Coordinator from the LOC, representatives from the SDMC, LC, LOC, HPTN investigators and study coordinators, community and the [Division of AIDS](#) (DAIDS).

19.1 Network Evaluation Plan and Performance Measures

To develop the evaluation plan for each component of the HPTN, the PEC uses the following approach for each area. This plan is reviewed and revised by the PEC on an annual basis.

- Objectives, and the activities necessary to achieve them, are identified to fully describe the function of each component of the HPTN being evaluated. These are based on the Network approved processes
- For each activity, the PEC identifies an indicator (or indicators) to be used to determine if objectives are being satisfactorily met. These measures are re-evaluated each year to determine their appropriateness and relevance to the performance of the Network
- The performance indicators are disseminated to the Network members before the start of the evaluation period
- A web-based questionnaire is sent annually to a representative sample of Network members. Results of this evaluation are used by the PEC to assess perceptions of Network functioning across groups and committees. The data collected from this exercise yields important information about the various functions of the Network
- The PEC submits an evaluation report to the EC at in-person meetings with recommendations for improvement
- Results of the evaluation are also sent to CTU Principal Investigators (PIs), protocol teams and committee chairs as well as the PIs of the LOC, SDMC and LC
- Network entities are requested to respond to findings and recommendations of the PEC

19.2 Performance Criteria for CRSs

The PEC reviews performance both by site per protocol and by protocol across sites. Performance measures for the CRSs include the following:

- *Study implementation:* Accrual rate, retention, adherence to protocol/protocol violations, data management, specimen results reporting
- *Community participation:* Development of and adherence to a site-specific community involvement plan, evidence of Community Advisory Board (CAB) participation and input, participation of site community representatives and community educators in HPTN activities as well as at regional and national conferences and meetings
- *General site/research management:* Adequate site and study staffing (coverage and experience); staff training (for physicians, nurses, quality assurance/quality control (QA/QC) coordinators, laboratory personnel, etc.)

19.3 Performance Indicators

The LOC is responsible for providing leadership and coordination of various functions of the Network, including the protocol development and implementation, Network's Scientific Committees (SCs), Working Groups, Network Communications, Community program and community involvement within the Network, and Network Evaluation. Specifically, the LOC provides technical expertise and administrative support through personnel and resources.

The SDMC and the LC are charged with providing statistical, data management, and laboratory support and expertise to the Network's Scientific Committees, Protocol Teams, and CRSs. Their specific activities, although varied, are all conducted to ensure that statistical and laboratory activities of the Network support the aims of the studies and are timely, reliable, and valid.

The performance indicators used for the evaluation include:

Activity	Measure	Standard	Source
Executive Committee (EC)			
EC meeting attendance	Percentage of voting EC members at each meeting	90% of voting members in attendance	Meeting minutes
Individual attendance at EC meetings for voting members	Proportion of EC members who attended 75% of meetings	100% of members attend 75% of meetings	Meeting minutes
Concept activity	Number of concepts reviewed and approved by the EC	1 annually	LOC (PRISM)
Concept review activity	Timeliness of concept review	Timely review with full feedback within 4 weeks of concept submission	LOC (PRISM)
Concept to protocol	Timeliness to SRC	16 weeks to SRC	LOC (PRISM)
Manuscript Review			

Activity	Measure	Standard	Source
Committee (MRC)			
Manuscript review timeliness	Average number of days for manuscript review	5 working days	Manuscript tracking system (in development)
	Abstract	1 working day	
	Poster	2 working days	
	Presentations	1 working day	
Science Review Committee (SRC)			
Review cycle of protocols	Average number of days	5 working days	SRC/LOC
Protocol approval	Number of protocols approved	No standard but tracked	LOC (PRISM)
Protocol review timeliness	Average number of days for feedback to team	5 working days	SRC summary
Leadership and Operations Center (LOC)			
Science Generation	Concept to protocol version 0.1 to SRC	16 weeks	LOC
Science Generation	Response to SRC review	15 working days	LOC
Science Generation	Response to PSRC review	15 working days	LOC
Publications	Number of manuscripts / presentations that have coauthors from LOC	No standard but tracked	LOC
Protocol implementation	Time from protocol version 1.0 to site activation	120 days (domestic) 240 days (international)	LOC (PRISM)
Trainings at Site	Number of trainings conducted at sites	No standard but tracked	LOC
Assessment Visits	Number of assessment visits at sites	At least once per site for each study	LOC
Laboratory Center			

Activity	Measure	Standard	Source
(LC)			
Concept development	Percentage of concept reviews provided	100%	LOC
Concept to Protocol (first draft) version 0.1 to SRC	Timeliness of concept to protocol version 0.1 to SRC	16 weeks Extensions may be granted	LOC
Protocol design and implementation expertise	% of protocols with an HPTN LC QC representative on the protocol team	100%	LOC
Protocol design and implementation expertise	% protocol teams with additional HPTN LC investigators on the protocol team (e.g. virologist)	No standard but tracked	LOC
Response to SRC review	Timeliness of response to SRC	15 working days	LOC
Response to Prevention Science Review Committee (PSRC) review	Timeliness of response to PSRC	15 working days	LOC
Site monitoring	Number of sites / External Quality Assurance (EQA) panels monitored	No standard but tracked	LC
Coordinator support	Number of QA/QC coordinators onsite	No standard but tracked	LC
Assay development	Number of new assays developed and evaluated for use in HPTN trials	No standard but tracked	LC
Publications	Number of manuscripts / presentations related to new assay development/ evaluation and pathogenesis- or transmission-based studies	No standard but tracked	LC

Activity	Measure	Standard	Source
QC testing volume	Approximate number of QC tests performed (e.g. duplicate testing of enrollment and endpoint samples)	No standard but tracked	LC
Protocol testing at the LC	% of HPTN protocols supported by testing at the LC	No standard but tracked	LC
Participation in cross-network committees	Number of committees with HPTN LC members	No standard but tracked	LC
Statistical and Data Management Center (SDMC)			
Statistical leadership	Percentage of leadership calls and meetings with SDMC representation	100% of leadership calls and meetings	Meeting Minutes
Science Generation	Concept to protocol version 0.1 to SRC	16 weeks	LOC
Science Generation	Response to SRC review	15 working days	LOC
Science Generation	Response to PSRC review	15 working days	LOC
Protocol development support	Number of protocols input provided	No standard but tracked	SDMC
Protocol development support	Number of protocol Case Report Forms (CRFs) developed	No standard but tracked	SDMC
Protocol development support	Time to completion of additional data collection tools (i.e., ACASI)	≤120 days	SDMC
Protocol development support	Time from final protocol version 1.0 to protocol activation (i.e., English database readiness)	≤120 days	SDMC
Sites			
Enrollment	Percentage of expected participants enrolled during evaluation period	Meet the protocol specified goal	SDMC/LOC

Activity	Measure	Standard	Source
Retention	Percentage of protocol expected retention rate during evaluation period	Meet the protocol specified goal	SDMC/LOC
Adherence	Percentage of treatment schedules adhered to by site	The site should adhere to 100% to treatment schedules	SDMC
Case Report Forms (CRF) faxed to SDMC	Average number of days to fax CRF to SDMC	Average of 5 days to fax CRF to SDMC	SDMC
QC resolved within 28 days	Percentage of QC reports resolved in 29 days	% of QC resolved in 28 days are compared per site within each protocol	SDMC

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20 SELECTION OF SITES

Once the concept for a new study has been approved by the Executive Committee (EC) and a first draft of the protocol is available, a Site Selection Committee (SSC) will be formed. The SSC will be composed of the following voting members (one vote per group):

- Protocol Chair and 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)
- Statistical and Data Management Center (SDMC)
- Leadership and Operations Center (LOC)

Additional individuals, for example, a [National Institutes of Health](#) (NIH) representative and/or [Office of Clinical Site Oversight](#) (OCSO) representative, will be invited to participate as non-voting discussants. It will be the responsibility of LC, SDMC, LOC and [Division of AIDS](#) (DAIDS) to assign representatives to the SSC.

After the SSC is assembled, an introductory call is held and the LOC Clinical Research Manager (CRM) will chair the call and will explain the process of site selection to the SSC.

20.1 Site Selection Process and Site Selection Questionnaire

Unless otherwise directed by the EC, the SSC will create a questionnaire that will be submitted to all potential Clinical Trials Units (CTUs) and Clinical Research Sites (CRSs) in the HPTN unless the protocol requirements are unique. This may involve a two-step process of soliciting initial information from all sites and then a follow-up questionnaire to those sites that the SSC determines best fit the needs of the study.

The questionnaire will solicit information pertinent to the Clinical Research Site's (CRS)/CTU's (hereto referred to as site) ability to execute the protocol, and will vary according to the requirements of the study. However, some topics that might be covered include:

- Prior experience in HIV prevention research
- Population studied and demographics
- Experience working with/recruiting the population sought for the study
- HIV prevalence in the site's surrounding area
- HIV incidence including annualized incidence overall, incidence during most recent year, and number of seroconversions (if available) during a specified period of time
- Duration of follow-up and loss to follow-up from previous or ongoing studies
- Experience in performing similar clinical studies
- Anticipated ease/difficulty in meeting recruitment/retention targets within the allocated timeframe
- Site capacity including staff experience, workload, education and other studies ongoing or planned at the site that would compete for staff, infrastructure (clinic space, staff and laboratories) and participant population
- Infrastructure for regulatory support
- Internet access, information technology (IT) infrastructure and adherence to IT best practices
- Additional resources (human, clinical and laboratory equipment, etc.) needed to undertake the study as planned
- Experience in collaborating with Community Advisory Boards (CABs) and the community
- Staff experience, workload, education
- Laboratory facilities and expertise

- Location and type of rooms
- Clinical Laboratory Improvement Amendments (CLIA) or the College of American Pathologists (CAP) certification for United States (US) sites
- Participation in DAIDS External Quality Assurance (EQA) for non-US sites
- Proficiency programs
- Laboratory Data Management System (LDMS) capabilities
- Freezer storage capacity
- Shipping capabilities
- Pharmacy facilities and capabilities
- Other study-specific requirements

Prior to distribution of the questionnaire, the SSC will agree upon a set of criteria and scoring process for ranking each site. Here are examples of [site selection criteria](#) and [scoring process](#).

The LOC will distribute the questionnaire to the Principal Investigators (PIs) of the CTUs and CRSs affiliated with the HPTN Network. If CRSs attached to the CTUs currently affiliated with the HPTN do not meet the criteria outlined by the team, the questionnaires will be sent in the following order:

- Other DAIDS Network-funded sites
- Sites that were proposed in existing CTUs, but not funded
- “New to DAIDS” sites

A deadline for responding to the questionnaire will be included with this communication. Sites that do not return a questionnaire will not be considered for the study. Sites that submit late questionnaires may be considered for the study at the discretion of the SSC.

The LOC CRM will distribute the sites’ responses to the SSC for review. After an initial review, the SSC will communicate by teleconference or email if additional data or clarification is needed from a site. Requests for additional information will be compiled by the LOC CRM and forwarded to the sites with a deadline for response. The SSC will discuss whether, beyond the content of a questionnaire, a pre-study site visit will be necessary for a potential site in order for the SSC to consider that site for participation in the study (see Section 10.3.2 for details concerning pre-study visits).

Once clarifying explanations have been received from sites and forwarded to the SSC by the LOC CRM, a teleconference or in-person meeting of the SSC (chaired by the LOC CRM) will be held to discuss the sites’ appropriateness for the protocol. The SSC will evaluate each site based upon topics covered in the site selection questionnaire and score each site based on predefined scoring criteria. The SSC will also consider and discuss any additional factors that are relevant to a site’s consideration for the study.

At the end of this meeting, the LOC CRM will summarize the comments made regarding each site and request that the voting entities score/rank assigned categories for each site (i.e., SDMC will rank the data management section, the LC representative will rank the laboratory sections, etc.). The LOC CRM will tally the section scores into one total score for each site. Upon completion, the LOC CRM will send the call summary and complete site rankings to the members of the SSC for review and approval.

Once approved by all members of the SSC, the LOC CRM will send a letter detailing the site rankings, categories discussed and background materials, such as completed questionnaires, to the EC prior to their next meeting. 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 voting. 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 HPTN PI will communicate the selection of sites to NIH in a letter with supporting information regarding approved sites.

All interested sites will be notified by email whether or not they have received approval to participate in the study. For sites that are not selected, the email will provide the reasoning for why others sites were chosen instead.

20.2 Addition of New Sites 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, 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 as stated above in 20.1:
 - First, evaluate funded sites for the HPTN
 - Then, evaluate all DAIDS Network funded sites
 - Then, evaluate sites that were proposed in existing CTUs, but not funded
 - Lastly, consider "New to DAIDS" sites
- No core funding 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. The SSC will evaluate each site based upon topics covered in the site selection questionnaire and score each site based on predefined scoring criteria. The decision of the SSC will be communicated to the EC. The HPTN PI will communicate the selection of sites on behalf of the EC to NIH. In addition, a new site (not currently approved HPTN site) will require approval by DAIDS based on the application process through the Network. Refer to OCSO Policy OCS-01: [Clinical Research Site Approval Process for Network Sites](#).

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21 PUBLICATIONS 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 policy is designed to be flexible and to facilitate rapid and accurate dissemination of HPTN study results. 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 analysis 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 CTAs
- Meet criteria for authorship, disclosure, scientific integrity, and other requirements of peer-reviewed scientific journals
- Ensure accurate acknowledgment of HPTN resources

Note: Procedures for HPTN SDMC and HPTN LC publications are described in Section 21.10.

21.1 RESPONSIBILITIES

The Protocol Chair and Protocol Biostatistician are responsible for generating the first draft of the primary manuscript and distributing the draft to the protocol writing group for review and comment. Outside of the primary manuscript, the protocol team is responsible for prioritizing all potential manuscripts related to an HPTN study including those that use HPTN-study related data, study specimens or are supported by HPTN resources relevant to a study. The protocol team is also responsible for developing or reviewing manuscript timelines, identifying writing teams, prioritizing manuscript development, monitoring timelines, and adhering to manuscript review procedures outlined in this policy. In addition, the Protocol Biostatistician is responsible for providing analyses for inclusion in manuscripts, abstracts, posters, or presentations within the specified time.

For each concept, the Lead Author is responsible for drafting manuscripts, abstracts, posters or presentations within the specified timeline. The Lead Author is responsible for establishing a writing team consisting of protocol team members for HPTN initiated concepts and of potentially non-protocol team members for non-HPTN initiated concepts with assistance from the LOC Clinical Research Managers (CRMs).

The Protocol Publications Committee (PPC), a subset of and specific to each Protocol Team, is responsible for reviewing and approving submitted draft manuscripts, abstracts, posters and presentations that relate to particular study or studies. 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.

The Manuscript Review Committee (MRC) is responsible for reviewing and approving manuscripts, abstracts, posters and presentations and ensuring that all Network Central

Resources (Leadership and Operations Center (LOC), Statistical and Data Management Center (SDMC), Laboratory Center (LC)) review the documents as appropriate, within the specified time. The composition of the MRC is described in Section 4.3.3.

The LOC CRMs are responsible for facilitating the PPC review, ensuring that authors are aware of the HPTN Publication Policy. The LOC CRM will draft a Publication Guideline document to be approved and followed by the protocol team. A template/example can be found on the HPTN website.

The LOC Manuscript Coordinator is responsible for tracking manuscripts, abstracts, posters and presentations as received from LOC CRMs.

21.2 DEFINITIONS

21.2.1 Tier 1 Priorities

Tier 1 Priorities are those that are publications in peer-reviewed journals or are abstracts, posters or presentations at scientific meetings or conferences that report the findings of primary and secondary study objectives as described in the study protocol. These are developed by HPTN Protocol Team members.

21.2.2 Tier 2 Priorities

Tier 2 Priorities are those that are publications in peer-reviewed journals or are abstracts, posters, and or presentations at scientific meetings or conferences that report findings that use HPTN data, specimens or resources where the analysis is focused beyond the primary or secondary study objectives; these may include findings from baseline data, ancillary studies or from more than one HPTN study. These may also include manuscripts/abstracts initiated by the Central Resource groups.

21.3 PUBLIC USE DATA SETS

Federal research sponsors 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 is released by the HPTN SDMC as a public use data set, 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 Protocol Publications Committee, Scientific Committee (SC) or MRC.

In general, all identifying information is stripped out of Public Use data sets so that they may be used without consulting the relevant Institutional Review Boards/Ethics Committees (IRBs/ECs). Data released to HPTN investigators per Section 12.6 of the HPTN Manual of Operations does not constitute public use data.

21.4 PROCEDURES

21.4.1 Publication Planning Process

A publication plan (contained within the Publication Guidance) and timeline should minimally contain the following information:

- Membership in Protocol Publications Committee
- Process for review, approval, and prioritization of manuscript or presentation concepts
- Expected date of last participant follow-up visit, if applicable
- Date data expected to be locked
- 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

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.

Publications based on screening and baseline data are typically permitted prior to the completion of the study. 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 21.14.2.) Publication of secondary outcomes typically follows the completion of the primary manuscript. Permission for exceptions may be sought from the HPTN Leadership.

21.4.2 Proposal Submission

Investigators and writing teams with a proposal for a manuscript or presentation should complete a Publication Proposal Form (see Publication Guidance) that outlines the planned analyses for the manuscript or presentation for Protocol Publication Committee (PPC) consideration and prioritization in addition to 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 submission.

21.4.3 Tier 1 Proposals

The Protocol Chair(s) is responsible for the development of all Tier 1 manuscripts.

Queries regarding the publishing of data, other than baseline data, prior to the release of the primary manuscript should be directed to the HPTN EC.

21.4.4 Tier 2 Proposals

Any investigator irrespective of affiliation may develop a Tier 2 Analysis Proposal. Investigators proposing manuscripts or abstracts that include findings from more than one HPTN study or use HPTN resources, specimens or data should submit a Publication Proposal Form to the appropriate PPC (or to the HPTN Leadership when it is not clear which protocol publications committee to submit) for review and approval.

All Tier 2 manuscripts or abstracts must be vetted through the MRC for approval prior to submission to meeting or journal.

If study data has been released by the SDMC as a Public Use data set (see Section 21.3), 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 funding of the HPTN.

21.4.5 Single-site Study Data

Proposals using data or information from a single site may be developed into manuscripts, abstracts, posters or presentations following receipt of approval from the Protocol Publications Committee. Single site manuscripts, abstracts, posters and presentations follow the same approval process as described above.

21.4.6 Multi-study Proposals

Proposals using data from more than one HPTN study must be sent for approval to each relevant Protocol Publications Committee (at a minimum the Protocol Chair and Statistician if the PPC is no longer active), and upon approval, then submitted to the HPTN EC for approval. A lead point of contact will be selected by the EC to track 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.

21.4.7 Monitoring publication progress

The PPC and the LOC are responsible for tracking the progress of proposals through publication or presentation for each protocol. In addition, updates by LOC CRMs on the progress of manuscript and presentation development are included in the Monthly Study Operations Reports and publication progress across protocols will be made to Network Leadership by the MRC Chair on a regular basis.

21.5 MANUSCRIPT REVIEW PROCESS

The lead author submits the manuscript, abstract, poster or presentation to the LOC CRM who coordinates the review processes.

21.5.1 Publication Committee Review

The LOC CRM firstly sends the draft to the PPC, sponsor(s) and product manufacturer (if applicable) for review and comment. If there are some Tier 2 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 approves, the LOC CRM submits for MRC review and to the LOC Manuscript Coordinator.

21.5.2 MRC Review of Manuscripts

The MRC receives the proposed document after PPC approval. The MRC Chair designates a primary and secondary reviewer to provide comments, one of whom is from the SDMC. An *ad hoc* reviewer may be appointed if additional expertise is required. The MRC reviews manuscripts within 5 working days of receipt, and it is recommended that any comments designated by the MRC as "Major" be addressed by the manuscript authors. Those designated as "Minor" are for consideration only and do not need to be addressed. Following review, the MRC sends the comments and outcome back to lead author, copying the LOC CRM and Manuscript Coordinator. The possible MRC review outcomes are:

- Endorse for publication
- Endorse with recommended modifications to be reviewed by the MRC Chair

- Recommend a second MRC review after modifications are made to obtain HPTN support

Prior to submission of manuscripts for publication or abstracts, posters or presentations to conferences, a final copy is provided by the lead author to the LOC CRM for tracking purposes.

If a manuscript or abstract is not accepted and reviewer feedback indicates a need to reformulate the essential components before it can be resubmitted or submitted to another journal or conference, it must be reviewed again by the MRC.

If any of the following occur the lead author, in consultation with the writing committee, may respond to the editor without MRC review:

- A manuscript is accepted for publication provisionally with required or recommended changes/additions
- A journal invites a revised draft of the same article
- An article is being submitted to another journal with minimal changes

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.

MRC review primarily focusses on original research manuscripts presenting data from the HPTN. Opinion pieces written by HPTN researchers must acknowledge support received from the HPTN, should be reviewed by the MRC, but do not need to be approved by the MRC. However, all such documents must provide a disclaimer that the opinions of the authors do not necessarily reflect the views of the HPTN.

21.5.3 MRC Review of Abstract and Presentation Review

All abstracts, posters and presentations should seek an expedited MRC review. After approval by the PPC or the HPTN leadership (for those that are not study-specific), the LOC will coordinate the review process. The MRC Chair will triage abstracts as necessary to the SDMC, LC, or to the Study Monitoring Committee (SMC) for review to determine that the analyses are appropriate and the data reported accurately. All abstracts will be reviewed by the MRC chair and a designated member statistician within three working days.

If study data has been released by the SDMC as a Public Use data set (see Section 21.3), presentations may be developed independent of Network oversight and do not require review of the PPC or MRC.

21.6 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.

21.7 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. 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.

21.8 RESOLUTION OF DISPUTES

Resolution of disputes with respect to the manuscript or presentation development and approval process will be managed by the MRC. If a dispute cannot be resolved by the MRC, the MRC Chair will refer it to the HPTN EC for final resolution.

21.9 THIRD PARTY AGREEMENTS

Third party agreements with product sponsors will include an agreement on publications policy and authorship in accordance with the guidelines set forth in the study's Clinical Trials Agreement (CTA).

21.10 HPTN LC AND SDMC MANUSCRIPTS

In addition to assisting with Tier 1 and Tier 2 publications initiated by the study team or other investigators, the HPTN LC or SDMC also publish work initiated in 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 or SDMC-related data analyses or statistical/analytic methods.

For work that includes use of data and/or specimens from 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. In some cases, 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.

21.11 RESPONSIBILITY OF THE SDMC IN HPTN DATA AND PUBLICATIONS

The central database for HPTN studies resides at the SDMC or designee. This includes Case Report Form (CRF) data, (A)CASI data (online questionnaires), results of protocol-specified laboratory analyses and ancillary study data. Section 12.6 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.

Analysis of HPTN data to address the primary and secondary objectives of an HPTN study (i.e. Tier 1 publications) is the responsibility of the SDMC, led by the designated protocol biostatistician. Analysis of Tier 2 publications 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. As a member of the Manuscript Review Committee (MRC), the SDMC PI or designee reviews all manuscripts, abstracts, posters and presentations describing data or results of HPTN studies.

21.12 RELEASE OF INFORMATION TO THE PUBLIC

21.12.1 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. These guidelines are in keeping with the policies and procedures of the DAIDS Office of Program Operations and Scientific Information (OPOSI), the NIAID Office of Communications and Government Relations (OCGR) and the NIAID News and Public Information Branch (NPIB).

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.

21.12.2 Disclosure of Study Results

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).

The release of study results at the end of the study provides an opportunity to share findings that could influence the standard of care in the communities where HPTN studies are conducted, or the design and/or conduct of ongoing or future HIV prevention trials. The protocol team should create a study results communications plan well before the end of the study. The plan should identify key members of the communication team (i.e., Protocol Chair, Protocol Biostatistician, designated spokespeople, etc.) and their roles, specify the timeline and activities planned for release of the study results within the team and externally, and identify the key stakeholders (protocol team members/site staff, sponsors, community advisory boards, host country officials, collaborating institutions, other US government and non-US public health agencies, and investigators/sponsors of other studies that may be impacted by the study results) to be informed of the results. Disclosure of study results, particularly of Phase IIb/III trials, by the protocol statisticians to study investigators, other protocol team members, HPTN leadership (Network PIs, LC PI, LOC Project Director, SDMC PI and others as necessary) and sponsors should be part of the study communications plan. Ideally, study results are revealed to the protocol team and sponsor at an in-person meeting that includes a review of the key analyses and planning for public release of results and coordination of future publications.

Results will be released to host country officials, 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.

Particular care is to be taken to coordinate release of results with officials in host countries and in the communities where the study was conducted.

21.12.3 Press and Public Announcements Related to Data and Safety Monitoring Board Reviews

A NIAID Data and Safety Monitoring Board (DSMB) typically oversees all HPTN Phase IIB or Phase III clinical trials. NIAID has overall responsibility for the public release of information following DSMB reviews of HPTN studies. When an NIAID press release or public statement related to a DSMB review is required, DAIDS and NIAID communications staff develop these materials in consultation with the DAIDS Medical/Program Officer, the HPTN PI, the Protocol Chair and others. The DAIDS Medical/Program Officer, Protocol Chair, HPTN LOC and SDMC will work together to ensure that each study site and investigator is adequately prepared in advance of DSMB reviews and, as needed, coordinate implementation of appropriate communication strategies, including dissemination of statements at the site level.

Prior to each DSMB review, the DAIDS Medical/Program Officer, in consultation with the DSMB Executive Secretary, key members of the study team and others, assesses the potential for clinically significant and/or newsworthy review outcomes and considers the most likely scenarios (e.g., study discontinuation or change of study design) and is responsible for communicating this internally at NIAID as appropriate (i.e., notifying the OPOSI which will in turn notify OCGR and NPIB) and with key members of the study team and Network leadership. As needed, a draft "schedule of events" – a timing and communications planning document for activities related to the DSMB review and its outcome - will be developed in advance of the review by the HPTN LOC, in consultation with

the DAIDS Medical/Program Officer, Protocol Chair, protocol statistician and DSMB Executive Secretary. The DAIDS Medical/Program Officer is responsible for seeking input from and coordinating communications with OPOSI, NPIB, and OCGR. If necessary, draft statements and Question & Answer documents for the press will be prepared by NPIB or OCGR, in consultation with OPOSI and the DAIDS Medical/Program Officer, the DSMB Executive Secretary, and key members of the study team. For scheduled reviews, draft documents are typically provided to study team representatives for review in advance of the DSMB review.

NIAID is under no obligation to provide study team members with draft press releases/statements in advance of their official release. However, in special circumstances, confidential drafts may be provided. Immediately following each DSMB review, the Board's recommendation is communicated to the Director of NIAID who decides whether to adopt the recommendation. NIAID and the HPTN then proceeds with the planned communications activities for the actual DSMB review outcome. Only NPIB may issue an official statement or press release on behalf of NIAID concerning a NIAID DSMB review of an HPTN study. All NIAID press releases and public statements must undergo standard review with clearance granted by the Office of the Director, NIAID; Office of the Director, NIH; and the US Department of Health and Human Services (DHHS).

Study sites and study co-sponsors may not issue their own press releases or public statements prior to the NIAID press release or public statement being released. When a co-sponsor is a publicly traded company on either a US or non-US exchange, NIAID and the co-sponsor will coordinate the release of statements in accordance with public disclosure requirements and in accordance with the terms of any applicable Clinical Trials Agreements (CTAs).

If a DSMB review of an HPTN study is being coordinated with review of another study, communications planning and strategies must also be coordinated. On communications matters, only NIAID, NPIB, or OCGR may serve as the primary point of contact with the counterpart at the other research organization.

When the DSMB recommends modification to a study, this information will be immediately communicated by the study Protocol Chair and HPTN leadership. This leadership team includes:

- Network PIs
- 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.

21.12.4 Public Communications Regarding Changes in Ongoing Studies Not Overseen by a NIAID DSMB

Significant changes (e.g., early closure, re-design) to ongoing Network studies that are not overseen by a DSMB (e.g., Phase I clinical trials, observational cohort studies) may need to be made, and communication of these changes will also need to be carefully planned to ensure that key stakeholders are adequately informed and understand the rationale for the changes. In such cases, the HPTN LOC, Protocol Chair and DAIDS Medical/Program Officer will work with other members of the protocol team to develop a communications plan including many of the same elements described above for release of study results. The DAIDS Medical/Program Officer is responsible for seeking input from and coordinating communications with OPOSI, NPIB, and OCGR, as needed.

21.12.5 Press Releases/Public Announcements

All Network related press releases and public statements will be developed or approved by NIAID and, as appropriate, by its co-sponsors. When such materials are developed by the sponsor(s), the DAIDS Medical/Program Officer and HPTN LOC will coordinate review by Network and/or study leaders as needed. When these materials are developed within the Network, the DAIDS Medical Officer/Program Officer and HPTN LOC will ensure that they are reviewed and approved by DAIDS program leadership, OPOSI, OCGR and NPIB (NIAID), and, as appropriate, by the NIMH and NIDA program leadership and their respective communications offices. 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 PIs. General HPTN press releases and materials must be approved by the HPTN PIs. The HPTN LOC sends draft materials to the DAIDS Medical/Program Officer for review (and ensures that copies are provided to OCGR, NPIB, and OPOSI) and, as appropriate, to the NIMH and NIDA Program Officers. Following DAIDS Medical Officer/Program Officer review, OPOSI and NPIB will review the drafts for messaging and terminology. OCGR or NPIB compiles NIAID's comments and edits for consideration and/or incorporation by the HPTN LOC.

To ensure accuracy of information and proper identification of the HPTN, NIAID, and other funding sources, all press releases generated by HPTN CRSSs, Core Resources, or study co-sponsors must be reviewed by the HPTN LOC, which will as necessary, coordinate additional review by the appropriate funding institutes. Investigators should allow sufficient time for this process.

When study results are to be published or presented at a scientific meeting, the HPTN LOC, DAIDS Medical Officer/Program Officer, OPOSI, OCGR, and NPIB 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 CTA with a product manufacturer, 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.

All press releases, statements, and public announcements must properly acknowledge that the activities of the HPTN are performed cooperatively with NIAID, NIMH, and NIDA.

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.

21.12.6 Press Releases/Public Announcements Regarding Openings of New Trials

The CTU is responsible for sending a draft of any press release or public statement regarding opening or initiation of a new trial to the DAIDS Medical Officer/Program Officer and HPTN LOC for review and approval by the appropriate Network and NIAID entities in advance of release.

Note: This excludes recruitment materials developed by a CRS.